

**JACC STATE-OF-THE-ART REVIEW**

# The Adipokine Hypothesis of Heart Failure With a Preserved Ejection Fraction

## A Novel Framework to Explain Pathogenesis and Guide Treatment

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**ABSTRACT**

**HYPOTHESIS** The paper proposes a novel unifying hypothesis—that heart failure with preserved ejection fraction (HFpEF) arises primarily from the expansion and dysfunctional transformation of visceral adipose tissue, leading to the secretion of altered suite of signaling molecules (adipokines), which causes systemic inflammation, plasma volume expansion, and cardiac hypertrophy and fibrosis.

**ELEMENTS OF THE FRAMEWORK** The framework groups adipokines into 3 domains. Domain I adipokines are cardioprotective molecules but are suppressed in patients with excess adiposity. Domain II adipokines are cardioprotective molecules that are up-regulated by adiposity as a compensatory response mechanism. Domain III adipokines, whose secretion is heightened in adiposity, have proinflammatory, prohypertrophic, profibrotic, and antinatriuretic effects. HFpEF results from an adiposity-driven imbalance that promotes Domain III adipokines but suppresses Domain I adipokines, with Domain II adipokines representing an inadequate counter-regulatory response.

**KEY LINES OF EVIDENCE** 1) Obesity and dietary nutrient excess are the major drivers of experimental HFpEF; 2) changes in visceral adiposity and circulating adipokines are observed years before and predict the diagnosis of HFpEF (but not heart failure with a reduced ejection fraction) in the general community; 3) central obesity or visceral adiposity is present in >95% of patients with HFpEF and tracks with disease severity; 4) obesity and HFpEF exhibit striking parallelism in their molecular, pathophysiological, and clinical features; 5) characteristic changes in the adipokine profile occur in parallel in central obesity and heart failure and are correlated with disease severity; 6) adipokines have established effects on cardiac structure and function that can lead to HFpEF; 7) bariatric surgery or drug treatments for HFpEF cause shrinkage of visceral fat depots (disproportionate to changes in body weight), while simultaneously increasing Domain I adipokines and decreasing Domain III adipokines; 8) excess adiposity appears to identify patients most likely to respond to current treatments for HFpEF; and 9) experimental interventions that target only adipose tissue to selectively increase or decrease its secretion of specific adipokines cause distant effects on the heart to modulate cardiac structure and the evolution of cardiomyopathy.

**CONCLUSIONS** The totality of evidence suggests that HFpEF evolves—not as a heterogenous disorder related to diverse comorbidities and not as a primary disorder of cardiomyocytes—but as an adipose-driven derangement that is disseminated (through endocrine-paracrine signaling) to the heart. (JACC. 2025;■:■-■) © 2025 The Author. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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**ABBREVIATIONS  
AND ACRONYMS****AMPK** = adenosine monophosphate protein kinase**GLP-1** = glucagon-like peptide-1**HFpEF** = heart failure with a preserved ejection fraction**MRA** = mineralocorticoid receptor antagonist**mTOR** = mechanistic target of rapamycin**NAD<sup>+</sup>** = nicotinamide adenine dinucleotide**PGC-1 $\alpha$**  = peroxisome proliferator-activated receptor-gamma coactivator-1alpha**PPAR $\alpha/\gamma$**  = peroxisome proliferator-activated receptor-alpha/gamma**SIRT1** = sirtuin-1**SGLT2** = sodium-glucose cotransporter 2**OUTLINE**

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For the past 3 decades, the neurohormonal hypothesis has represented a unifying framework to explain heart failure with a reduced ejection fraction (HFrEF).<sup>1</sup> That hypothesis postulated that the activation of neurohormonal mechanisms—rather than hemodynamic factors (such as cardiac contractility and systemic vasoconstriction)—was critical in promoting the evolution and progression of heart failure. The paradigm focused on signaling molecules that were released from peripheral nerves or the kidney (catecholamines and angiotensin II), which accelerated the evolution and progression of cardiomyopathy. Subsequent work has largely validated the hypothesis, ie, trials of hemodynamic interventions have yielded disappointing or deleterious results,<sup>2-4</sup> whereas trials with beta-blockers, mineralocorticoid

receptor antagonists (MRAs), and neprilysin inhibitors supported a role for neurohormonal mechanisms.<sup>5,6</sup> Although some approaches to neurohormonal inhibition did not represent favorable therapeutic targets,<sup>7,8</sup> the overarching framework reshaped our understanding and treatment of HFrEF.

In contrast with HFrEF, no unifying biological framework has been proposed to explain the pathogenesis of heart failure with a preserved ejection fraction (HFpEF), currently the most incident and prevalent heart failure phenotype. HFpEF is typically regarded as being exceptionally heterogeneous—described as the end result of numerous comorbidities that (acting individually or in concert) have been hypothesized to cause coronary microvascular endothelial dysfunction and myocardial remodeling, exacerbated by heightened arterial load, diverse metabolic derangements, and systemic inflammation—all coexisting phenomena but without a common driving mechanism.

Challenging this prevailing wisdom, this paper proposes that the diverse features of HFpEF are linked by a common pathway, ie, that HFpEF arises from a nutrient excess-driven expansion and biological transformation of visceral adipose tissue, which leads to the secretion of a dysfunctional suite of signaling molecules—known as adipokines. These molecules produce deleterious cardiac, vascular, renal, and systemic inflammatory effects that recapitulate all the pathophysiological and clinical features of HFpEF. Drawing from decades of experimental research and clinical observations, the proposed adipokine hypothesis provides a novel conceptual framework for understanding the development of both HFpEF and its associated comorbidities. As in the case of the neurohormonal hypothesis of HFrEF, the new hypothesis of HFpEF provides a coherent, testable, and falsifiable structure to guide current thinking and future research.

**PART I: EVOLUTION OF THE ADIPOKINE HYPOTHESIS FOR UNDERSTANDING HFpEF**

In 2017, Obokata et al. proposed that obesity might represent a distinct phenotype of HFpEF,<sup>9</sup> raising the possibility that an expansion of adipose tissue could be a primary driver of the disorder. However, obesity is conventionally defined by body mass index, a metric that is heavily influenced by bone and skeletal muscle mass and is not a reliable measure of fat mass, particularly in ethnically diverse populations. Furthermore, not all fat depots are

clinically important; ie, when compared with subcutaneous fat depots, visceral adipose tissue is more biologically active, exerts endocrine and paracrine effects on vital organs, and produces deleterious systemic and cardiometabolic effects.<sup>10</sup> Central adiposity, defined by waist-to-height ratio, represents the most reliable approach to the assessment of visceral fat mass on a population level.<sup>11</sup>

It is therefore noteworthy that, although obesity (defined as a body mass index  $\geq 30 \text{ kg/m}^2$ ) characterizes 60% to 70% of patients with HFpEF,<sup>9</sup> central adiposity (identified by a waist-to-height ratio  $\geq 0.5$ ) is present in >95% patients with HFpEF.<sup>12</sup> The near-universal prevalence of excess adiposity in HFpEF has been confirmed by quantification of fat mass.<sup>13</sup> Importantly, visceral adiposity (assessed by imaging) precedes and predicts the development of HFpEF (but not HFrEF) in the general population,<sup>14</sup> and the magnitude of visceral adiposity and obesity in HFpEF closely parallels with the hemodynamic and clinical severity of the disease.<sup>15,16</sup>

**IDENTIFYING A ROLE FOR ADIPOKINE SIGNALING IN THE PATHOGENESIS OF HFpEF.** In human obesity, adipose tissue comprises a very substantial proportion of body weight, and thus, it represents the body's largest secretory organ. As a result, it is responsible for the substantial synthesis and release of numerous biologically active molecules, which exert outsized effects on interorgan signaling.

The expansion of visceral fat mass transforms the adipocyte secretome so that adipocytes secrete an altered suite of molecules that (acting in an endocrine or paracrine manner) promote renal and splanchnic sympathetic activation, heightened signaling through angiotensin II and aldosterone, sodium retention and plasma volume expansion, and systemic and pulmonary hypertension.<sup>11,17</sup> At the same time, the shift in the adipokine profile triggers systemic and regional inflammation<sup>17</sup> (leading to destruction of the coronary microvasculature and myocardial fibrosis<sup>18,19</sup>) and promotes ventricular hypertrophy, all acting in concert to impair ventricular distensibility.

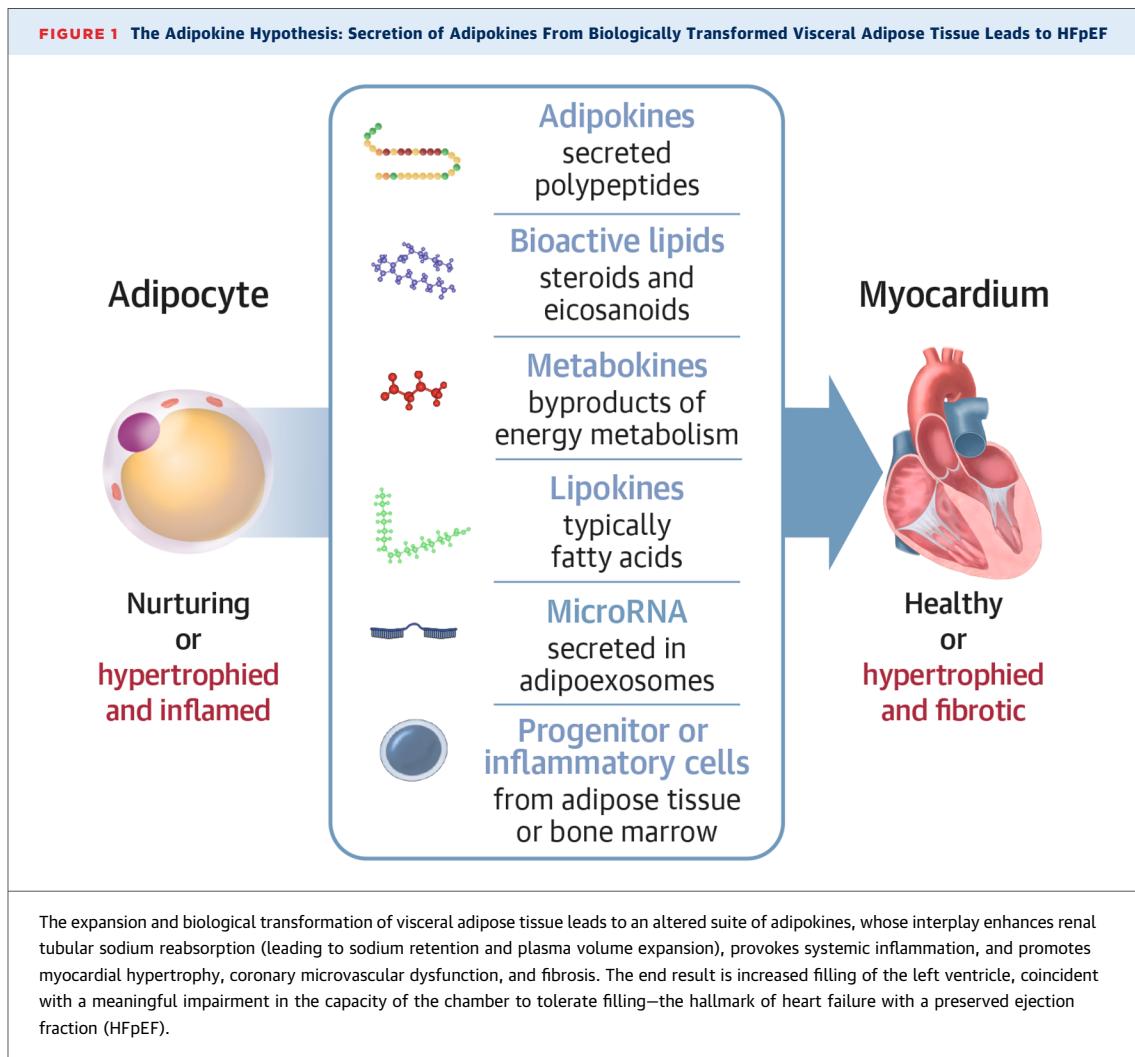
The end result is increased filling of the left ventricle, coincident with a meaningful impairment in the capacity of the chamber to tolerate filling. The fundamental abnormality in HFpEF is not a loss of cardiomyocytes, but it is the diminished ability of the left ventricle to tolerate the exaggerated

hemodynamic stresses imposed upon it. The secretion of prohypertrophic, proinflammatory and anti-natriuretic adipokines from dysfunctional visceral fat can explain the established pathophysiological features of HFpEF (Figure 1), and it can also account for its prevalent comorbidities.

**BUILDING BLOCKS OF THE ADIPOKINE HYPOTHESIS.** In 2018, the interplay of 3 adipocyte-derived hormonal signaling molecules—leptin, aldosterone, and neprilysin—was identified as central to the pathogenesis of HFpEF. Acting in concert, these adipokines could explain the occurrence of neurohormonal activation, sodium retention, hypertension, systemic inflammation, and end-organ fibrosis.<sup>20,21</sup> During the past 7 years, experimental studies have provided substantial support for the importance of the leptin-aldosterone-neprilysin axis. Notably, delineation of the axis anticipated the success of MRAs and neprilysin inhibitors in patients with HFpEF.<sup>22-27</sup> The adipocyte-centered framework also provided a foundational basis for the efficacy of drugs—sodium-glucose cotransporter 2 (SGLT2) inhibitors and incretin-based drugs—that act to shrink visceral fat depots or reverse their proinflammatory biological features, thereby emerging as functional adipokine modulators.<sup>22</sup>

In parallel with the description of the leptin-aldosterone-neprilysin axis, it was recognized that dysfunctional epicardial adipose tissue could secrete molecules that could exert paracrine effects on the heart.<sup>28</sup> The epicardium shares an unobstructed microcirculation with the adjoining myocardium, and thus, an expansion and biological transformation of epicardial adipose tissue would lead to the secretion of molecules that could cause inflammation and fibrosis directly in adjacent underlying cardiac tissue.

Viewed from this perspective, epicardial adipose tissue acts as a transducer that focuses the effects of system-wide adipocyte-driven inflammation onto the myocardium through the action of locally-secreted proinflammatory adipokines. This adipocyte-derived paracrine mechanism was considered to be particularly relevant to the development of HFpEF,<sup>28</sup> because epicardial fat expansion is a characteristic feature of patients with HFpEF, but not those with HFrEF.<sup>29</sup> An increased epicardial fat mass identifies patients with obesity who have underlying cardiac abnormalities and are likely to develop heart



failure<sup>30</sup> as well as patients with HFpEF who have an adverse prognosis, even after accommodating for body mass index.<sup>31</sup>

Over the past decade, dozens of both proinflammatory and cardioprotective adipokines have been shown to directly influence oxidative and organelar stress within cardiomyocytes, renal tubular sodium reabsorption, cardiac hypertrophy and fibrosis, and the development of cardiomyopathy. Changes in these adipokines have been shown to precede the onset of HFpEF and to track closely with the clinical severity and prognosis of established HFpEF. Interventions that selectively target adipose tissue have been shown experimentally to exert

distant effects on the structure and function of the heart.

Together, the totality of evidence points to an adiposity-induced shift in the balance of proinflammatory and cytoprotective adipokines, which promotes the evolution and progression of HFpEF. Accordingly, the current paper proposes the “adipokine hypothesis of HFpEF” as a coherent, mechanistically grounded and testable framework to guide the understanding and treatment of this disorder—a conceptual model that is likely to be applicable to vast majority of people with HFpEF (Box 1).

**FRUSTRATION WITH THE LACK OF A UNIFYING FRAMEWORK FOR HFpEF.** HFpEF is currently

**BOX 1. The Neurohormonal Hypothesis and the Adipokine Hypothesis: Conceptual Parallels****1. Neurohormonal Hypothesis of HFrEF**

This hypothesis describes the mechanisms that drive the evolution and progression of HFrEF. HFrEF progresses because of the enhanced and sustained release of cardiotoxic signaling molecules from peripheral nerves, the kidney, or the adrenal gland (eg, catecholamines, angiotensin II, and aldosterone) coupled with the attenuated signaling of cardioprotective molecules (eg, natriuretic peptides).

**2. Need for a New Framework for HFpEF**

A unifying explanatory model for HFpEF is needed. The prevailing view—that HFpEF is an exceptionally heterogeneous syndrome driven by multiple, loosely connected comorbidities—has provided limited insights and has not produced a clear foundation for research or therapeutic drug development.

**3. Adipokine Hypothesis of HFpEF**

This hypothesis proposes that the evolution and progression of HFpEF is driven by the enhanced sustained secretion of proinflammatory and profibrotic signaling molecules from adipose tissue (eg, leptin and others) coupled with suppressed synthesis and secretion of adipose-derived cardioprotective signaling molecules (eg, adiponectin and others). These biologically active molecules, collectively termed adipokines, act on the heart and vasculature through endocrine and paracrine mechanisms.

without a coherent unifying evidence-based framework. Systemic and pulmonary hypertension, diabetes, cardiac hypertrophy, vascular disease, and atrial myopathy are obvious features of the disease, but there is no evidence that these phenotypic characteristics represent distinct causal mechanisms or pathways. These comorbidities are also seen in patients with HFrEF, in whom they are not believed to carry any special mechanistic significance. Furthermore, the comorbidities of HFpEF have not identified a particular group of responders in clinical trials, and the treatment of these coexistent conditions has not influenced the clinical course of HFpEF. The convergence of comorbidities in HFpEF suggests a common origin, rather than distinct mechanisms.

The adipokine hypothesis offers an alternative perspective. Rather than considering hypertension, diabetes, chronic kidney disease, atrial myopathy, and systemic inflammation as representing individual candidate pathways, the “adipokine hypothesis of HFpEF” proposes that these coexisting disorders are the expected manifestations of a single underlying pathogenetic mechanism: the presence of an overabundant and dysfunctional mass of visceral adipose tissue, which secretes adipokines that increase blood volume and blood pressure and cause insulin resistance, systemic inflammation, atrial fibrosis and electrical instability, cardiac hypertrophy, and vascular and glomerular injury, with the aging heart being particularly vulnerable to the effects of adipokines.

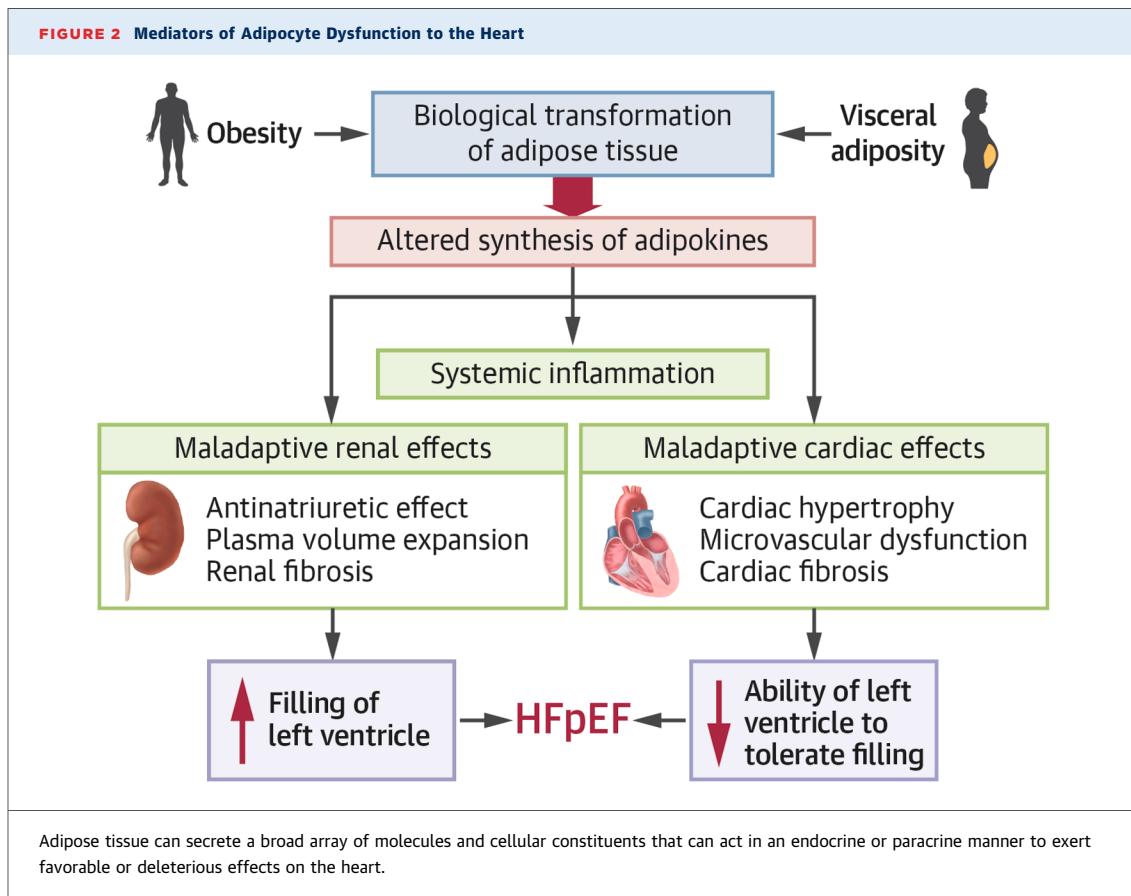
Epidemiologic observations support this reconceptualization. The emergence of HFpEF as a dominant clinical phenotype has coincided with a global epidemic of obesity and with the recognition that obesity acts as an accelerator for numerous disorders. Central obesity and adiposity precede HFpEF and are features of nearly every patient with HFpEF.<sup>12</sup> The expanded visceral adipose tissue mass in obesity is a secretory factory that manufactures numerous deleterious cardioactive molecules that have been implicated in experimental HFpEF. Accordingly, this paper puts forth a unifying hypothesis for HFpEF, proposing a single dominant pathway that applies to most patients, which explains both HFpEF and its comorbidities through one mechanism.

**TERMINOLOGY AND SCOPE FOR THIS INITIAL PRESENTATION OF THE ADIPOKINE HYPOTHESIS.**

In this paper, the term “adipokine” designates all molecules or cellular elements that are secreted by adipocytes and act in an endocrine or paracrine manner to exert effects on the heart and blood vessels. Adipokines may be secreted by any cell type within adipose tissue, including adipocytes,

regarded as a heterogenous disorder whose pathogenesis is driven in different cohorts by numerous independently acting comorbidities (eg, sedentary aging, systemic and pulmonary hypertension, diabetes, coronary artery disease, aortic stiffness, cardiac hypertrophy and fibrosis, atrial fibrillation with atrial myopathy, microvascular abnormalities, systemic inflammation, natriuretic peptide deficiency, and chronic pulmonary or kidney disease). For some, hypertension is the main driver of cardiac hypertrophy in HFpEF; for others, diabetes drives glucotoxicity in the heart; and for still others, the interplay of comorbid conditions triggers adverse changes in the coronary endothelium.<sup>19</sup> To many, impressed by its predilection to afflict elderly women, HFpEF has been regarded as the outcome of cardiac and vascular aging, exacerbated by atherosclerotic disease—even though large-vessel coronary artery disease is uncommon among patients with HFpEF. The presence of systemic inflammation in HFpEF is well recognized, but its origin has not been clearly defined.

The prevailing view that HFpEF arises from numerous independent mechanisms has left the field



endothelial cells, mesenchymal stem cells, macrophages, and fibroblasts—although adipocytes are playing the initiating role in states of nutrient excess.

As shown in **Figure 1**, adipokines can include a broad range of signals:

- Polypeptides and proteins (eg, leptin, adiponectin)
- Steroids and eicosanoids (eg, aldosterone, prostaglandin, and leukotrienes)<sup>31</sup>
- Lipokines (byproducts of lipolysis, eg, fatty acids)
- Metabokines (byproducts of cellular energy metabolism)<sup>32</sup>
- Adipoexosomes—nanosized extracellular vesicles that not only contain proteins, but also microRNAs that regulate gene transcription in distant tissues.<sup>33</sup> The quantity of adipoexosomes increases markedly when adipocytes assume a proinflammatory profile, as in patients with obesity or HFpEF.<sup>34</sup>
- Circulating inflammatory or mesenchymal stem cells derived from adipose tissue or adipose progenitor cells in the bone marrow, which are capable of homing to the heart to alter its biological characteristics.

For this initial presentation of an adipose tissue-centered framework for HFpEF (**Figure 2**), this paper focuses primarily on *polypeptides and proteins* secreted by adipose tissue, because they have been exceptionally well-characterized and been targeted by therapeutic innovations. However, studies of the role of bioactive lipids, lipokines, metabokines, microRNAs, and adipose- or bone marrow-derived cell constituents in adiposity-mediated HFpEF are emerging rapidly and warrant inclusion in the framework.

An essential dimension of HFpEF is its strong predilection to afflict women. Women show disproportionate increases in left ventricular filling pressures following increases in central blood volume and have greater ventricular and arterial stiffness than men. Importantly, adipose tissue comprises a larger proportion of total body weight in women, as compared with men. In fact, women are particularly predisposed to epicardial and intramyocardial fat expansion and to imbalances in adipocyte-associated proinflammatory mediators.<sup>35</sup> Hence, the adipokine hypothesis is positioned to integrate these

observations. The influence of sex—as well as race and ethnicity—on adipose tissue biology and adipokine signaling are important topics to be addressed in future work.

Finally, although the term “obesity” has commonly been used in both experimental and clinical research studies, in clinical practice, it is defined by body mass index. However, the mechanisms discussed in this paper are closely linked to excess and dysfunctional visceral fat, and not to changes in skeletal muscle or bone mass. Therefore, the adipokine hypothesis is applicable to the large number of people with *excess visceral adiposity*, many of whom do not meet the definition of “obesity.” The term “visceral fat” includes fat surrounding and residing within major organs as well as the abdomen.

## PART II: SUBSTANTIAL OVERLAP IN THE BIOLOGY, PATHOPHYSIOLOGY, AND CLINICAL FEATURES OF OBESITY AND HFpEF SUGGEST A COMMON MECHANISTIC LINK

Obesity, visceral adiposity, and HFpEF show substantial overlap in epidemiological studies and in the clinical setting,<sup>11–13</sup> and both obesity and HFpEF are characterized by exceptionally similar cardiac structural and functional abnormalities, neurohormonal and proinflammatory profiles, and similar molecular biosignatures of cardiomyocyte stress. The striking parallelism of the 2 disorders, depicted in Table 1 (and described in Parts II and III) suggests that obesity and HFpEF reflect a shared mechanistic origin (Box 2).

**HEMODYNAMIC, NEUROHORMONAL, AND CARDIAC ABNORMALITIES IN EXCESS ADIPOSITY.** Obesity is accompanied by augmented renal tubular sodium reabsorption, occurring along the entire span of the nephron.<sup>36</sup> Heightened renal sympathetic nerve activity together with elevated levels of angiotensin II, aldosterone, and leptin in obesity contribute to renal sodium retention, and both leptin and angiotensin II directly stimulate the release of aldosterone by the adrenal gland.<sup>37,38</sup> Hypertrophied adipocytes are an additional major source of aldosterone production (through a calcineurin-dependent pathway), and obesity is accompanied by aldosterone-independent activation of the mineralocorticoid receptors.<sup>38–40</sup> The additional effect of obesity to suppress circulating levels of natriuretic peptides—through enhanced expression of neprilysin or augmented clearance natriuretic peptides<sup>41,42</sup>—can promote further sodium retention, peripheral vasoconstriction, and hypertension. Due to the confluence of these factors, obesity is typically accompanied by

**TABLE 1** Pathophysiological and Mechanistic Overlap Between Obesity and HFpEF

	Obesity/ Visceral Adiposity	Heart Failure with Preserved Ejection Fraction
Central obesity (increased waist-to-height ratio)		Nearly universal.
Visceral adipose tissue		Increased epicardial and visceral fat. Molecular and cellular adipose tissue dysfunction.
Blood pressure		Hypertension in majority of patients.
Plasma volume		Expanded, with redistribution toward central compartment.
Left ventricular structure		Left ventricular hypertrophy with coronary microvascular endothelial dysfunction and rarefaction. Mild fibrosis in obesity, variable fibrosis in HFpEF.
Left ventricular volume and diastolic filling		Mild-to-moderate LV enlargement, with LV overfilling and abnormal diastolic filling dynamics.
Abnormalities of signal transduction and cellular homeostasis in cardiomyocytes and adipocytes		Activation of nutrient surplus signaling (mTOR) and suppression of nutrient deprivation signals (SIRT1/AMPK). Increased oxidative stress and proinflammatory signaling, leading to mitochondrial dysfunction and impaired calcium kinetics.
Myocardial injury		Mild increase in cardiac troponin, reduced by weight loss.
Renal tubular sodium reabsorption		Enhanced at multiple tubular sites because of activation of renal sympathetic nerves, renin-angiotensin system, aldosterone, and leptin.
Changes in renal structure and function		Glomerular hyperfiltration in obesity. Renal inflammation and fibrosis caused by angiotensin II, aldosterone, leptin, and other proinflammatory mediators.
Systemic inflammation		Large proportion of afflicted individuals have increased serum levels of high sensitivity C-reactive protein or other inflammatory mediators.
Sympathetic nervous system and renin-angiotensin system		Activated renal and mesenteric sympathetic nerves and angiotensin II contributing to sodium retention, blood volume expansion and redistribution, and LV hypertrophy.
Aldosterone and mineralocorticoid receptors		Angiotensin II- and leptin-dependent stimulation of aldosterone by adrenal gland, contributing to renal sodium retention and LV fibrosis. Secretion of aldosterone by adipocytes. Aldosterone-independent activation of mineralocorticoid receptors.
Natriuretic peptides		Disproportionately low circulating levels and diminished responsiveness to natriuretic peptides, leading to tissue cyclic GMP deficiency.
Leptin		Heightened circulating levels of leptin contribute to sodium retention, LV hypertrophy and myocardial fibrosis, and to renal inflammation and fibrosis.
Insulin sensitivity		Insulin-resistant state, often accompanied by type 2 diabetes.
Responsiveness to antihypertensive drugs		Excellent blood pressure lowering in patients with obesity in response to mineralocorticoid receptor antagonism and incretin-based drugs.

AMPK = adenosine monophosphate activated protein kinase; GMP = guanosine monophosphate; LV = left ventricular; mTOR = mechanistic target of rapamycin; SIRT1 = sirtuin-1.

volume-dependent hypertension, which is responsive not only to MRAs and neprilysin inhibitors, but also to incretin-based drugs.<sup>43–45</sup>

The neurohormonal derangements in obesity contribute directly to cardiomyocyte stress and derangements in cardiac structure and function. Increases in leptin, angiotensin II, and aldosterone together with diminished natriuretic peptide

**BOX 2. Reasons to Explore an Adipose-Centered Hypothesis for HFpEF**

1. The surge in the incidence and prevalence of HFpEF over the past 30 years has coincided with the global epidemic of obesity.
2. Visceral adiposity in the general community is a harbinger of the subsequent development of HFpEF (but not the development of HFrEF) across diverse populations.
3. Central adiposity is present in nearly all patients with HFpEF, and obesity (defined by a body mass index of  $\geq 30 \text{ kg/m}^2$ ) characterizes 60%-70% of patients with HFpEF. Conversely, a substantial proportion of people with obesity are likely to have mild (unrecognized) HFpEF as an explanation for their exercise intolerance.
4. Both obesity (visceral adiposity) and HFpEF share exceptionally similar and overlapping clinical presentations, cardiac structural and functional abnormalities, neurohormonal and proinflammatory profiles, and molecular biosignatures of adipocyte and cardiomyocyte stress.
5. In obesity, visceral fat undergoes hypertrophy, inflammation, and fibrosis, and in parallel, they secrete an altered suite of biologically active molecules that produce hypertrophy, inflammation, and fibrosis of the heart. The changes in adipokine profile seen in patients with visceral adiposity are strikingly similar to those seen in HFpEF.

signaling activate prohypertrophic and profibrotic pathways in the heart, leading to increased ventricular mass.<sup>20,21,46</sup> Leptin and aldosterone (along with the dysregulation of perivascular fat) also promote abnormalities in arterial stiffness.<sup>47</sup> Additionally, people with obesity but without clinical cardiovascular disease demonstrate markedly increased systemic inflammation (ameliorated by weight loss), leading to widespread endothelial dysfunction, particularly of the coronary microvasculature, often with mild subclinical fibrosis.<sup>48,49</sup>

In obesity, cardiomyocytes experience substantial increases in oxidative and other cellular stresses, which lead to mitochondrial dysfunction, impaired calcium handling, and potential loss of cardiomyocyte viability.<sup>50-52</sup> Cardiac troponin levels are increased in obesity and decline following marked weight loss.<sup>53,54</sup> In the absence of symptoms or a diagnosis of cardiovascular disease, obesity impairs ventricular distensibility as a result of myocardial hypertrophy, fibrosis, and oxidative stress.

When the constrained left ventricle is challenged by hypervolemia and by decreases in systemic

venous capacitance,<sup>15,55</sup> people with obesity exhibit heightened left ventricular filling pressures at rest or exercise, increased left atrial chamber dimensions, and abnormal diastolic filling dynamics.<sup>47,56,57</sup> These derangements may be clinically relevant, even if they do not meet current diagnostic thresholds for HFpEF. Patients with obesity also exhibit glomerular hyperfiltration, which (together with the profibrotic effects of angiotensin II, aldosterone, leptin and neprilysin, and perirenal fat) promotes the development of underappreciated chronic kidney disease.<sup>20,58</sup>

**HEMODYNAMIC AND NEUROHORMONAL ABNORMALITIES**

**IN HFpEF.** All pathophysiological mechanisms that are activated in people with obesity and visceral adiposity (described in the previous text) are also upregulated in patients with HFpEF.

Renal sodium retention, plasma volume expansion, and hypertension are seminal features of HFpEF. HFpEF impairs the ability of the kidney to excrete salt,<sup>59</sup> and nearly all patients with HFpEF have a history of hypertension. Those with concurrent obesity or visceral adiposity have an expanded plasma volume whose magnitude is proportional to the increase in left ventricular filling pressure.<sup>11,15,60</sup> Sympathetic nerve traffic is increased to both the kidneys and splanchnic bed, the latter leading to reduced systemic venous capacitance and increased stressed blood volume in HFpEF.<sup>16,61</sup> Renal and splanchnic denervation has been reported to produce favorable hemodynamic and clinical responses in patients with HFpEF.<sup>62,63</sup>

Increased serum aldosterone levels in patients with HFpEF are correlated with changes in ventricular geometry and have prognostic significance,<sup>64,65</sup> and mineralocorticoid receptors are activated in experimental models of HFpEF independent of aldosterone.<sup>66</sup> Patients with HFpEF have increased circulating levels of leptin and suppressed levels of natriuretic peptides,<sup>67</sup> and they show resistance to natriuretic peptide signaling, potentially related to increased circulating neprilysin.<sup>59,68,69</sup> The elevated blood pressure in patients with HFpEF is responsive to neprilysin inhibition, MRAs, and incretin-based drugs.<sup>70-72</sup>

The neurohormonal abnormalities that characterize HFpEF contribute to derangements in cardiac structure and function. Increases in leptin and aldosterone and diminished natriuretic peptide signaling in HFpEF promote the activation of prohypertrophic and profibrotic pathways in HFpEF.<sup>21,22,64</sup> In addition, most people with HFpEF demonstrate evidence of marked systemic inflammation (with or without obesity),<sup>73,74</sup> and coronary microvascular endothelial

inflammation leads to rarefaction and fibrosis, both contributing to impaired ventricular distensibility.<sup>18,19</sup> Furthermore, in experimental HFpEF, cardiomyocytes experience substantial increases in oxidative and nitrosative stresses, which lead to mitochondrial dysfunction, suppressed autophagic flux, and dysfunctional calcium handling.<sup>75-78</sup> Cardiac troponin is increased in patients with HFpEF, particularly during exercise and proportionally to the increase in left ventricular filling pressures.<sup>79</sup>

In patients with both HFpEF and obesity, incretin-based drugs ameliorate left ventricular hypertrophy and mitigate systemic inflammation and the release of troponin.<sup>72</sup> In experimental and clinical HFpEF, the action of natriuretic peptides to inhibit oxidative stress in the kidney and renal fibrosis is lost, but neprilysin inhibition can improve renal function and slow progression to end-stage kidney disease.<sup>80</sup>

**DECIPHERING THE SEQUENCE OF THE ADIPOSITY-HFpEF OVERLAP: VISCERAL ADIPOSITY AND CENTRAL OBESITY PRECEDES AND PREDICTS THE DEVELOPMENT OF HFpEF (BUT NOT HFrEF).** The available evidence indicates that both obesity and HFpEF result from the shared interplay of exceptionally similar pathophysiological mechanisms, which include sodium retention, neurohormonal activation, systemic inflammation and end-organ fibrosis, and enhanced signaling through the leptin-aldosterone-neprilysin axis. Yet, this parallelism (by itself) does not indicate whether one condition precedes the other.

Therefore, it is important to note that genetic obesity or dietary nutrient excess precedes and induces HFpEF (but not HFrEF) in experimental models.<sup>48,75-77</sup> More importantly, in the general community, both excess visceral adiposity and central obesity precedes and is a consistent harbinger of the subsequent development of HFpEF (but not the development of HFrEF)<sup>14,81,82</sup>—a finding that has been consistent across diverse populations. The ability of visceral fat to predict heart failure events follows a dose-response relationship and is particularly meaningful for fat depots surrounding the heart.<sup>30,83</sup> By the time that a formal clinical ascertainment of HFpEF has been made, nearly all patients with HFpEF have excess adiposity or central obesity,<sup>12,13</sup> and the severity of hemodynamic and clinical abnormalities parallels the degree of adiposity.<sup>9,15</sup> A substantial proportion of people with obesity (or visceral adiposity) are likely to have unrecognized HFpEF as an explanation for their exercise intolerance.<sup>84</sup>

The substantial mechanistic and clinical overlap of obesity and HFpEF—and the consistent finding that

an expanded fat mass presages the development of experimental and clinical HFpEF—points to visceral adiposity as the driving force in the pathogenesis of HFpEF. The adipokine hypothesis proposes that hypertrophied and inflamed visceral adipose tissue can disseminate its dysfunctional state of heightened cellular stress to the heart, vasculature, and kidneys—by virtue of the secretion and endocrine/paracrine delivery of an altered suite of biologically active molecules (ie, adipokines) (Figure 1). Surgical removal of visceral fat can ameliorate adverse systemic effects.<sup>85</sup>

#### ALTERNATIVE CONSIDERATIONS FOR A PATHOGENETIC

**ROLE OF VISCERAL ADIPOSE TISSUE.** Are there mechanisms—other than the secretion of adipokines—that might account for a causal relationship between excess visceral adiposity and HFpEF?

Both obesity and HFpEF are insulin-resistant states, and some have proposed that diminished responsiveness to insulin has adverse metabolic consequences. In contrast, others have proposed that such resistance is adaptive,<sup>86</sup> and it is the reactive hyperinsulinemia that promotes the development of HFpEF. However, there is little evidence that either insulin deficiency or hyperinsulinemia drive the cardiovascular abnormalities in either obesity or HFpEF, because drugs with strikingly different effects on insulin signaling (eg, incretin-based agents and SGLT2 inhibitors) demonstrate similar effects to reduce the risk of heart failure events in patients with HFpEF.<sup>24,26</sup> Furthermore, prolonged therapeutic elevation of circulating insulin levels neither increases nor decreases the risk of heart failure.<sup>87</sup>

Instead, insulin resistance appears to merely represent a biomarker of a shift in the expression of glucose transporter isoforms in skeletal muscle and adipose tissue. As a result of alterations in intracellular nutrient signaling, both obesity and heart failure induce a change in expression from an insulin-sensitive isoform (GLUT4) typically seen in healthy individuals to an insulin-insensitive isoform (GLUT1) typically seen during embryonic development. Downregulation of GLUT4 in adipocytes, as a result of visceral adiposity, is the primary cause of systemic insulin resistance.<sup>88</sup>

It is also possible that an expanded visceral adipose tissue mass might influence cardiac function because of physical forces. Specifically, an increase in fat mass might encroach onto the pericardial space to create a constraint on right and left ventricular filling,<sup>9</sup> a state that would be alleviated by pericardiectomy.<sup>89</sup> However, the importance of pericardial constraint as a mechanism of HFpEF in patients

with obesity remains a matter of debate, especially in light of evidence that a marked drug-induced shrinkage of pericardial fat results in a decrease—rather than an increase—in left ventricular volumes in patients with obesity and HFpEF.<sup>27</sup>

### PART III: PARALLELISM OF NUTRIENT SENSING PATHWAYS IN ADIPOSE TISSUE AND THE HEART POINTS TO INTERORGAN SIGNALING IN BOTH HEALTH AND DISEASE

In healthy people, adipose tissue typically exhibits nurturing functions, characterized by the storage and timely release of scarce fuel, the combustion of disruptive fatty acids, and the suppression of inflammation. However, in states of nutrient excess or HFpEF, the expansion of visceral white fat is accompanied by heightened adipocyte stress, a prerequisite for growth and replication. Nutrient-driven adipose tissue inflammation in obesity accelerates the endothelial-to-mesenchymal transition (thus promoting fibrosis), while causing mesenchymal stem cells to lose their regenerative capacity and to adopt a senescence profile.<sup>90</sup> These transformative changes in adipose tissue are mediated by the enhanced production of adipocyte-derived molecules that promote the local cellular oxidative and proinflammatory stresses that are essential for the proliferation of adipose tissue. However, once secreted, these molecules transmit the state of adipose tissue dysfunction, inflammation, and fibrosis to other organs, particularly the heart.

Adipocytes are capable of synthesizing >600 proteins,<sup>91,92</sup> and they can release countless nonprotein signaling molecules. The balance of adipokines favors a cytoprotective effect in healthy people, whereas a proinflammatory profile is dominant in states of adiposity and HFpEF. The effects of adipocyte-secreted polypeptides are mediated through well-defined intracellular signal transduction pathways, operating in both fat and cardiac tissue. There is a striking parallelism of nutrient deprivation and nutrient surplus signaling in adipose tissue and the heart, both in health and disease.

**IMBALANCE OF NUTRIENT-SENSITIVE SIGNAL TRANSDUCTION PATHWAYS IN HEART FAILURE.** In the healthy heart, cardiomyocyte stress is minimized by the dominance of nutrient deprivation signaling, which acts to enhance the oxidation of long-chain fatty acids, ATP production, and mitochondrial health, while promoting cellular housekeeping (ie, autophagy), and maintaining cellular viability. Nutrient deprivation signals are mediated by sirtuin-1 (SIRT1), adenosine monophosphate protein kinase

(AMPK) and peroxisome proliferator-activated receptor- $\gamma$  coactivator-1 $\alpha$  (PGC-1 $\alpha$ ).<sup>93,94</sup> However, the failing heart is characterized by a state of perceived intracellular nutrient excess, with enhanced uptake of glucose, the cytosolic accumulation of deleterious metabolic byproducts, impaired autophagic flux, and mitochondrial dysfunction.<sup>94,95</sup> This dysfunctional state is accompanied by increased oxidative and organellar stress and enhanced sustained signaling through proliferative, prohypertrophic, proinflammatory, and profibrotic pathways, eg, phosphoinositide-3 kinase-Akt-mechanistic target of rapamycin (PI3K-Akt-mTOR).<sup>93-95</sup> At the same time, the failing heart exhibits suppression of nutrient deprivation signals, ie, SIRT1, AMPK, and PGC-1 $\alpha$ —thereby limiting their ability to exert cytoprotective actions and oppose the action of nutrient surplus signals.

**IMBALANCE OF NUTRIENT-SENSITIVE SIGNAL TRANSDUCTION PATHWAYS IN OBESITY.** An expansion of visceral fat mass is also characterized by a dominance of nutrient surplus signaling (as evidenced by enhanced mTOR signaling) and a suppression of nutrient deprivation signaling (as evidenced by diminished AMPK/SIRT1 signaling) within hypertrophied and proliferating adipose tissue.<sup>96-98</sup> The shift in signal transduction pathways in inflamed adipocytes is strikingly parallel to that seen in the failing heart.

This parallelism does not appear to be coincidental; instead, it represents a coordinated interplay between the 2 organs, as evidenced by experimental adipose-specific interventions. Adipose-specific knockout of mTOR activity prevents obesity,<sup>99</sup> and mTOR inhibition ameliorates both adipose tissue inflammation and the features of HFpEF in obese (but not in lean) mice.<sup>100</sup> Additionally, selective SIRT1 up-regulation in adipose-derived stem cells alleviates diabetes-induced HFpEF,<sup>101</sup> and adipocyte-specific up-regulation of heme oxygenase-1 (which reinforces SIRT1 signaling<sup>102</sup>) improves the biological profile of cardiac and vascular tissues in experimental obesity.<sup>103</sup> Therefore, the parallel up-regulation of stress-enhancing intracellular signaling in adipocytes and cardiomyocytes appears to be driven by biological events in adipose tissue.

**OTHER INTRACELLULAR SIGNAL TRANSDUCTION PATHWAYS RELEVANT TO OBESITY AND HEART FAILURE.** Many other signal transduction pathways show parallel derangements in both the expanded fat depots and in the failing heart, and they act to modulate hypertrophy, inflammation, and fibrosis. For this review, the most relevant are as follows:

- Wnt signaling, either canonical signaling through Wnt/β-catenin or noncanonical Wnt signaling that is linked to Ca<sup>2+</sup> or to Jun N-terminal kinase (JNK);
- Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling;
- G-protein coupled receptors, which signal through cyclic AMP and phosphoinositol 4,5 bisphosphate;
- Activin receptors, which allow members of the transforming growth factor-β (TGF-β) superfamily to signal to the nucleus through intracellular Smad proteins.

#### PART IV: KEY LINES OF EVIDENCE SUPPORTING THE ADIPOKINE HYPOTHESIS OF HFpEF

Numerous independent and interdependent lines of evidence support the hypothesis that visceral adiposity is the preceding event and dominant feature of HFpEF and that adipokines are responsible for the transmission of the biological state of dysfunctional adipose tissue to influence the biological state of the heart, thus causing HFpEF (Box 3 and Central Illustration 1).

**A SUMMARY OF FINDINGS POINTING TO VISCERAL ADIPOSITY AND MALADAPTIVE SHIFTS IN ADIPOKINE SECRETION PROFILES AS THE KEY MEDIATORS IN THE PATHOGENESIS HFpEF. Excess adiposity as the preceding event and near-universal feature.** Obesity and adiposity from genetic causes or dietary excess represent the major mechanism that drives the development of HFpEF in experimental models. In the clinical setting, changes in visceral adiposity are observed years before the diagnosis of HFpEF and predict the development of HFpEF (but not the development of HFrEF). Central obesity (indicative of excess visceral adiposity) is nearly ubiquitous in patients with HFpEF, and the degree of adiposity is a major determinant of hemodynamic and clinical severity of HFpEF as well as its prognosis. Obesity and HFpEF exhibit striking similarities and parallelism and substantial overlap in their pathophysiological and clinical features and their molecular signatures. These findings are characterized in Parts II, III, and IV.

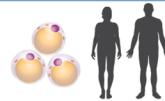
**Central role of adipokines in explaining experimental and clinical findings.** Adipocytes (but not cardiomyocytes) synthesize and secrete cardioactive adipokines. In people with visceral adiposity or obesity, the expanded adipose tissue mass emerges as the dominant source of proinflammatory adipokines. In the general community, changes in circulating levels of adipokines are observed years before the diagnosis of

**BOX 3. Lines of Evidence That Visceral Adiposity and Maladaptive Shifts in the Adipokine Secretion Profile Are the Principal Cause of HFpEF**

1. The heightened prevalence of HFpEF in clinical practice has coincided with the global epidemic of obesity.
2. Obesity and adiposity represent a major cause of HFpEF in experimental models.
3. Obesity and HFpEF exhibit striking similarities and parallelism and substantial overlap in their pathophysiological and clinical features and their molecular signatures.
4. Changes in visceral adiposity and in circulating levels of adipokines are observed years before the diagnosis of HFpEF and predict the development of HFpEF (but not the development of HFrEF) in the general community.
5. Central obesity (indicative of excess visceral adiposity) is nearly ubiquitous in patients with HFpEF, and the degree of adiposity is a major determinant of hemodynamic and clinical severity of HFpEF as well as its prognosis.
6. Adipocytes (but not cardiomyocytes) typically (and often uniquely) synthesize and secrete cardioactive adipokines. In people with visceral adiposity or obesity (where fat mass comprises as much as 50% of body weight), adipose tissue emerges as the dominant source of proinflammatory adipokines.
7. The pattern of changes in adipokines in experimental or clinical obesity closely parallels the pattern of changes in adipokines in experimental or clinical HFpEF. The magnitude of changes in circulating adipokine levels parallels the clinical severity and prognosis of HFpEF.
8. Adipokines have well-characterized effects on cardiac structure and function, and these actions have been implicated in the pathogenesis of cardiomyopathy and HFpEF in experimental studies.
9. Bariatric surgery or drug treatments for HFpEF cause shrinkage of visceral fat depots, to a degree that is disproportionately larger than the decline in body weight. Such shrinkage is accompanied by a simultaneous increase in circulating levels of adaptive adipokines and decrease in the circulating levels of maladaptive adipokines, leading to amelioration of HFpEF. The responses to bariatric surgery indicate that dietary nutrient deprivation is sufficient to produce a decisive shift in the balance of circulating adipokines to a cardioprotective profile.
10. An expanded adipose tissue mass is a primary driver of the upregulation of angiotensin II, aldosterone and neprilysin in HFpEF, explaining why excess adiposity has identified patients most likely to respond to current drugs for HFpEF in clinical trials.
11. Molecular interventions that target only adipose tissue so as to selectively increase or decrease its secretion of specific adipokines have been demonstrated to cause parallel effects on the heart through an endocrine mechanism, thereby modulating cardiac structure and the evolution of cardiomyopathy.

**CENTRAL ILLUSTRATION 1 Lines of Evidence Supporting the Adipokine Hypothesis of HFpEF****Lines of Evidence Supporting Adipokine Hypothesis**

Adiposity precedes and drives HFpEF experimentally



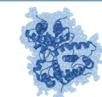
Adiposity changes precede/predict HFpEF clinically

Central adiposity nearly universal in HFpEF; associated with severity

**Excess adiposity as the preceding event and near-universal feature of HFpEF**

Obesity and HFpEF have very similar features

Expanded adipose mass is primary source of adipokines



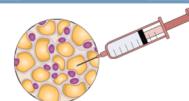
Adipokines change in parallel in obesity and HFpEF

Changes in adipokines precede/predict HFpEF; associated with severity

**Central role of adipokines in explaining experimental and clinical findings**

Adipokines have cardiac effects that replicate the changes in HFpEF

Bariatric surgery alleviates adipokine imbalance, HFpEF



HFpEF drugs improve adiposity and adipokine imbalance

Excess adiposity identifies patients most likely to benefit from HFpEF drugs

**Cardiovascular benefits of interventions that specifically target adipose tissue**

Adipose-specific interventions exert favorable cardiac effects

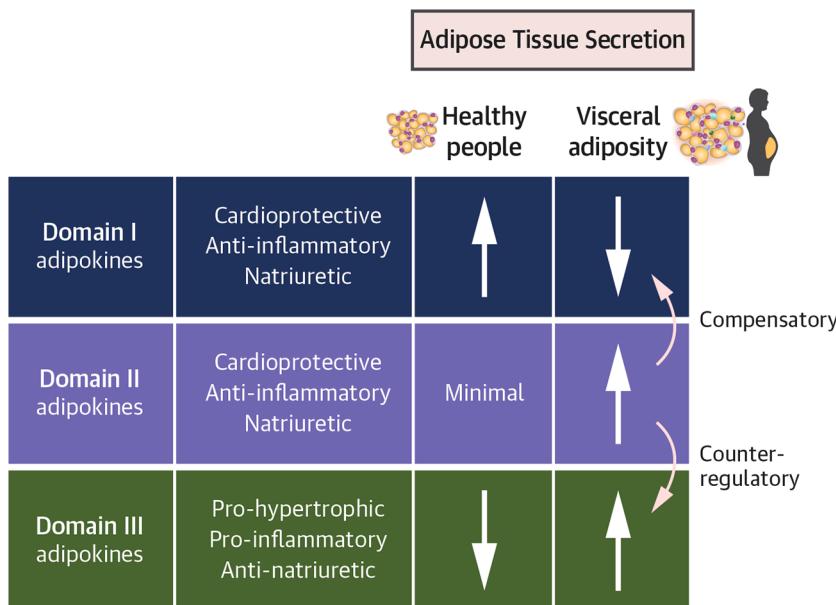
**Adipokine Hypothesis of HFpEF**

Packer M, JACC. 2025;■(■):■-■.

HFpEF = heart failure with preserved ejection fraction.

HFpEF and predict the development of HFpEF. The pattern of changes in adipokines seen in experimental or clinical obesity closely parallels the pattern of changes in adipokines seen in experimental or clinical HFpEF. The magnitude of changes in circulating adipokine levels parallels the clinical severity and prognosis of HFpEF. Adipokines have well-characterized effects on cardiac structure and function, and they have been implicated in the pathogenesis of cardiac stress, cardiomyopathy and HFpEF in experimental studies. These findings are characterized in Parts V, VI, and VII.

**Cardiovascular benefits of interventions that target adipose tissue and adipokines.** Bariatric surgery or drug treatments for HFpEF cause shrinkage of visceral fat depots to a degree that is disproportionately larger than the decline in body weight. Such shrinkage is accompanied by increases in circulating levels of cytoprotective adipokines and decreases in the levels of proinflammatory adipokines. These responses to bariatric surgery indicate that dietary nutrient deprivation is sufficient to produce a decisive shift in the balance of circulating adipokines to a cardioprotective profile. An expanded

**FIGURE 3 Characterization of Adipokine Domains**

In healthy people, adipocytes primarily secrete Domain I adipokines, with minimal secretion of Domain II adipokines and with suppression of Domain III adipokines. In people with visceral adiposity or obesity, adipose tissue secretes primarily Domain III adipokines, with suppression of Domain I adipokines. At the same time, adipocytes emerge as an important source of Domain II adipokines, acting as a compensatory response to the loss of Domain I adipocytes and as a counter-regulatory response to Domain III adipokines.

adipose tissue mass is the primary driver of the neurohormonal activation in HFP EF, explaining why excess adiposity may identify patients likely to benefit from current drugs for HFP EF. These findings are characterized in Part VIII.

Importantly, molecular interventions that target only adipose tissue so as to selectively increase or decrease its secretion of specific adipokines cause parallel effects on the heart, thereby modulating the evolution of cardiomyopathy. When HFP EF is produced experimentally in mice by transverse aortic constriction, the transplantation of bone marrow mesenchymal cells from HFP EF mice leads to recapitulation of the HFP EF phenotype in healthy recipient mice.<sup>104</sup> Similar cross-talk between adipocytes and the heart have been observed following the transplantation of adipose tissue.<sup>105</sup> In numerous studies, experimental overexpression or suppression of the secretion of specific adipokines—such that the effect occurs only in adipose tissue—exerts distant effects on the heart that are relevant to the pathogenesis of HFP EF. These findings are characterized in Part IX. Intriguingly, circulating adipokines may be capable of selectively targeting the heart as a result of cardiomyocyte-preferential expression of adipokine receptors.<sup>106</sup>

**A NOVEL CLASSIFICATION OF CARDIOACTIVE ADIPOKINES DESCRIBES FUNCTIONAL ALIGNMENTS THAT ARE RELEVANT TO HFP EF.** To promote an understanding of the mechanisms that underlie adipose-derived signaling in HFP EF, this paper introduces a novel, function-based classification of adiposity-relevant cardioactive adipokines, which groups adipokines into 3 domains (Figure 3 and Box 4):

1. **Domain I adipokines** are secreted by healthy adipocytes, being abundant in lean individuals and suppressed by obesity and visceral adiposity. They typically inhibit fat mass expansion and inflammation and exert adaptive and cytoprotective effects on the heart. In obesity and visceral adiposity, the diminished secretion of these molecules leads to deleterious effects on the heart, because it allows the effects of prohypertrophic and proinflammatory adipokines to be unopposed (Table 2).
2. **Domain II adipokines** are secreted by adipocytes in heightened quantities in states of obesity and visceral adiposity, acting as a compensatory response to the deficiency of Domain I proteins (described in the previous text) or as a counter-balancing mechanism to oppose the adverse

**BOX 4. Functional Classification of Adipokines Relevant to HFpEF**

**Domain I adipokines** are secreted by healthy adipose tissue, being typically dominant in lean individuals and suppressed by obesity and visceral adiposity. They alleviate stress and inhibit inflammation in adipose tissue and produce similar adaptive effects in the heart. An expansion of visceral fat causes the diminished secretion of these cardioprotective molecules, leading to HFpEF.

**Domain II adipokines** are secreted by adipose tissue in heightened quantities in states of obesity and visceral adiposity, acting as a compensatory mechanism in response to a deficiency of the Domain I proteins (described in the previous text) or as a counterbalancing mechanism to oppose the adverse biological consequences of the Domain III proteins (described in the following text). These adipokines exert cardioprotective effects, but in states of obesity and visceral adiposity, the enhanced secretion of these cardiac stress-mitigating proteins is insufficient to prevent HFpEF, often because of biological resistance.

**Domain III adipokines** are secreted by hypertrophied or hyperplastic inflamed adipocytes, and their secretion is dominant in people with visceral adiposity. These adipokines not only promote further adipose stress, but they also cause cardiomyocyte dysfunction; pathological cardiac and vascular hypertrophy, myocardial inflammation and fibrosis, coronary microvascular disease, renal sodium retention and plasma volume expansion, and systemic and pulmonary hypertension.

consequences of Domain III proteins (described in the following text). The cardioprotective effects of Domain II adipokines are insufficient to prevent HFpEF, often because sustained hyperactivation leads to biological resistance (frequently related to impaired receptor signaling), **Table 3**.

3. **Domain III adipokines** are secreted by hypertrophied, hyperplastic, or inflamed adipocytes, and their secretion is dominant in people with visceral adiposity. These adipokines promote pathological cardiac and vascular hypertrophy, inflammation, and fibrosis as well as coronary microvascular disease, renal sodium retention and plasma volume expansion, and systemic and pulmonary hypertension (**Table 4**).

Importantly, in health and across a broad range of disease states, adipokines that belong to the same domain typically change in an aligned manner, and in general, changes in Domain I adipokines are directionally opposite to changes in Domain III adipokines.

The molecules included in each domain (described in **Tables 2, 3, and 4** and Parts V, VI, and VII) represents a comprehensive, but not exhaustive, survey. This classification is intended as a working model,

subject to refinement, as new adipokines are identified and the biological functions of currently recognized adipokines are better understood.

#### PART V: DOMAIN I ADIPOKINES: CARDIOPROTECTIVE MOLECULES THAT ARE SUPPRESSED IN OBESITY/VISCERAL ADIPOSITY AND HEART FAILURE

Domain I adipokines are synthesized by adipocytes in healthy lean individuals and act to reduce both adipose tissue and cardiac stress. They inhibit myocardial and vascular hypertrophy, inflammation and fibrosis, thus preventing the development of HFpEF (**Figure 4**).

**DISTINCTIVE FEATURES OF DOMAIN I ADIPOKINES.** Domain I adipokines include adiponectin, C1q/tumor necrosis factor (TNF)-related proteins 3/9, omentin-1, secreted frizzled-related protein 5, extracellular nicotinamide phosphoribosyltransferase, zinc alpha 2-glycoprotein, and neuregulin-4.

Acting primarily in an endocrine manner, these adipokines can signal by up-regulation of nutrient deprivation pathways, eg, SIRT1, AMPK, and PGC-1 $\alpha$ , but they also act through G-protein coupled receptors, and they modulate Wnt signaling. Except under exceptional stress, cardiomyocytes are not a major site of synthesis for Domain I proteins, and their effects on the heart are primarily driven by adipocyte synthesis (**Box 5**).

#### ADIPONECTIN AND ADIPONECTIN-LIKE ADIPOKINES.

**Adiponectin.** In lean people, the dominant adipokine in the body is adiponectin, which is typically synthesized only by adipocytes, acting to enhance insulin sensitivity and encourage lipid storage, thereby preventing ectopic lipid accumulation.<sup>107</sup> Remarkably, circulating levels of adiponectin are several orders of magnitude higher than ordinary hormones, supporting a major systemic role for this adipokine. In lean individuals, adiponectin is a key component of adipocyte-derived extracellular vesicles.<sup>108</sup>

Once secreted, adiponectin acts in an endocrine manner to target the heart,<sup>106</sup> where it promotes up-regulation of nutrient-deprivation cytoprotective signals, ie, SIRT1, AMPK, PGC-1 $\alpha$ , and peroxisome proliferator-activated receptor-alpha/gamma (PPAR $\alpha$ ), thereby reducing oxidative stress and preserving mitochondrial health, while inhibiting myocardial hypertrophy, inflammation, and fibrosis.<sup>109</sup> Additionally, there exists a mutually antagonistic relationship between adiponectin and renal sympathetic nerve activity<sup>110,111</sup> and between adiponectin and aldosterone.<sup>112,113</sup> Adiponectin

<b>TABLE 2 Domain I Adipokines</b>			
Adipokine (Protein or Family)	Origin and Signaling Pathways	Biological Effects in Adipose Tissue and the Heart	Changes in Obesity, Visceral Adiposity, and Heart Failure
Adiponectin	Endocrine signaling, often as a component of adipoxosomes, also epicardial fat secretion. Signals through SIRT1/AMPK/PGC-1 $\alpha$ /PPAR $\alpha$ .	Cytoprotective effects in adipose tissue. Adiponectin reduces inflammation and cellular stress in cardiomyocytes and inhibits sympathetic nerve traffic and aldosterone.	Adiponectin signaling is deficient in both obesity and HFpEF.
C1q/TNF-related proteins, particularly CTRP3 and CTRP9	Adiponectin paralogs, mimicking adiponectin. Endocrine effects and epicardial fat secretion. These can act through AMPK and SIRT, and they inhibit Wnt/ $\beta$ -catenin signaling.	Adipocyte-derived CTRP3/CTRP9 exert anti-inflammatory and cardioprotective effects. Adipocyte secretion is important, because cardiac-specific CTRP3/CTRP9 overexpression exacerbates hypertrophy.	Serum CTRP3 and CTRP9 levels are decreased in obesity and heart failure.
Omentin-1	Endocrine signaling and epicardial fat secretion. Omentin-1 inhibits the activin type II receptor and suppresses Wnt5a/Ca $^{2+}$ signaling.	Omentin-1 reduces inflammation in adipose tissue. Adipocyte secretion inhibits maladaptive myocardial hypertrophy.	Omentin-1 is decreased in patients with visceral adiposity and heart failure, including HFpEF.
Secreted Frizzled-related protein 5 (SFRP5)	Endocrine or paracrine signaling, secreted by epicardial fat. SFRP5 acts as a soluble antagonist of Wnt5a.	SFRP5 inhibits ectopic fat accumulation. SFRP5 mitigates cardiac injury by reducing myocardial inflammation and fibrosis.	SFRP5 is suppressed in obesity and heart failure; correlated with diastolic filling abnormalities.
Extracellular nicotinamide phosphoribosyl-transferase (eNAMPT)	Endocrine action to promote synthesis of NAD $^{+}$ , the cofactor for SIRT1. eNAMPT antagonizes the receptor for C-C-chemokine ligand 5.	eNAMPT and NAD $^{+}$ deficiency has adverse effects on cardiac hypertrophy and remodeling and promotes cardiomyopathy. eNAMPT inhibitors cause cardiotoxicity.	Obesity suppresses adipocyte eNAMPT expression. Cardiac NAMPT is depleted in HFpEF.
Zinc alpha 2-glycoprotein (ZAG)	ZAG signals through $\beta$ 2- and $\beta$ 3-adrenergic receptors and protein kinase A to exert endocrine effects.	ZAG stimulates lipolysis, mitochondrial function, and biogenesis; activates adiponectin and inhibits leptin; and shrinks visceral fat depots and inhibits cardiac fibrosis.	ZAG is suppressed in obesity and in patients likely to have HFpEF.
Neuregulin-4 (NRG-4)	Secreted by brown adipose tissue, NRG-4 acts in endocrine manner, signaling through ErbB4.	NRG-4 reduces oxidative and proinflammatory stress in adipocytes, thus alleviating obesity. Therapeutic delivery of NRG-4 ameliorates cardiomyopathy and nephropathy.	Suppressed expression of NRG-4 in obesity and in pressure-overload cardiac hypertrophy.

CTRP = C1q/TNF-related proteins; HFpEF = heart failure with preserved ejection fraction; PGC-1 $\alpha$  = peroxisome proliferator-activated receptor-gamma coactivator-1 $\alpha$ ; PPAR $\alpha/g$  = peroxisome proliferator-activated receptor-alpha/gamma; other abbreviations as in Table 1.

antagonizes the actions of aldosterone to promote HFpEF.<sup>114,115</sup>

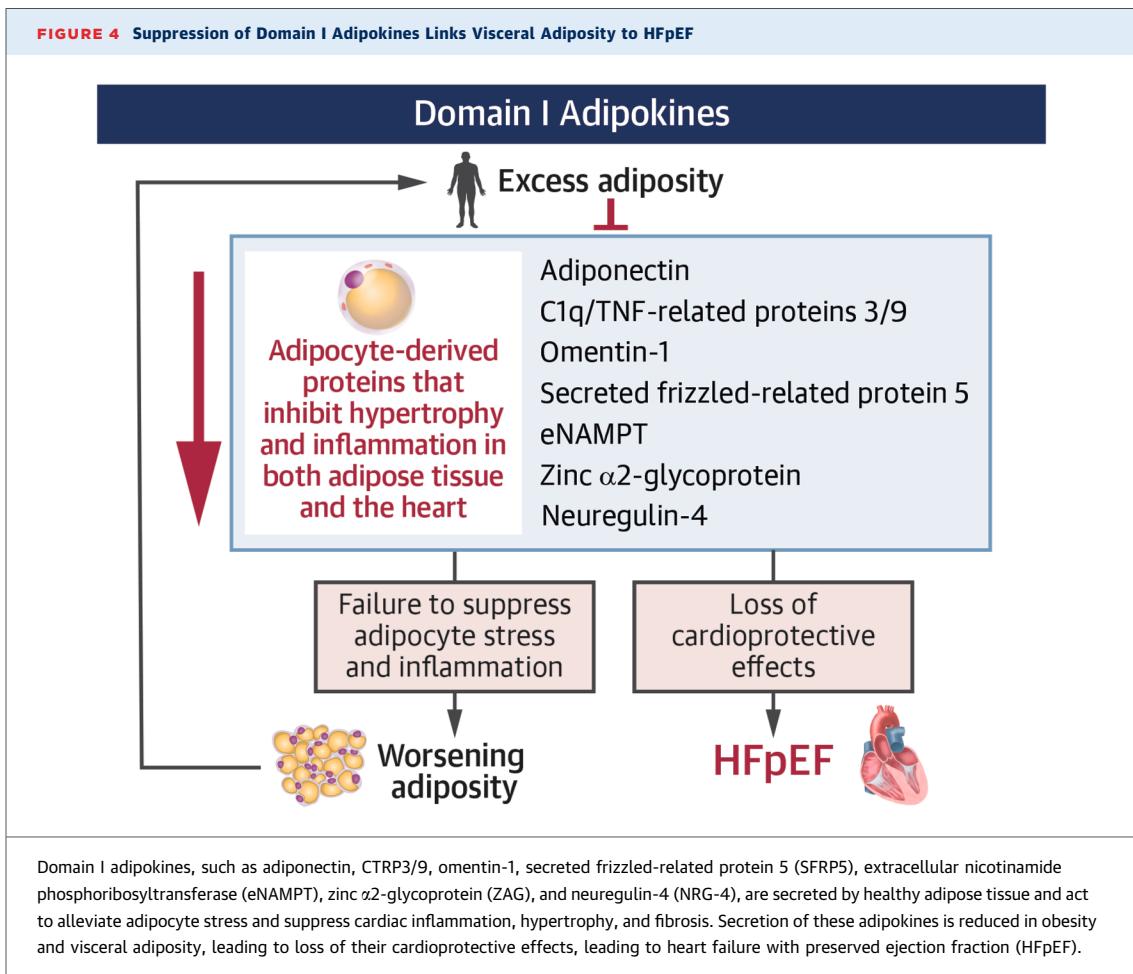
Obesity and visceral adiposity is accompanied by suppression of adiponectin,<sup>116</sup> and such suppression has been implicated in renal sodium retention and plasma volume expansion,<sup>117</sup> in the impaired tolerance of the heart to volume overload,<sup>118</sup> and in the pathogenesis of experimental cardiomyopathy and HFpEF.<sup>114,115,119-121</sup> In patients without overt heart failure, low serum adiponectin are associated with increased left atrial size and left ventricular mass, and they predict future cardiovascular events.<sup>122-124</sup> Serum levels of adiponectin are suppressed in patients with established HFpEF.<sup>125</sup>

Therapeutically, adiponectin adenoviral delivery ameliorates cardiomyopathy and heart failure,<sup>126</sup> and adiponectin receptor agonists produce favorable effects in HFpEF.<sup>127</sup> Although the stressed heart can secrete adiponectin as a paracrine mechanism,<sup>128</sup> as end-stage heart failure ensues, cardiac levels of adiponectin and its receptor become depleted, but

adipocyte-derived circulating levels increase, presumably as a compensatory response.<sup>129,130</sup> In patients with advanced heart failure, mechanical ventricular unloading leads to lowering of the adipocyte secretion of adiponectin, demonstrating the bidirectionality of crosstalk between fat depots and the heart.<sup>129</sup>

**C1q/TNF-related proteins (CTRP3 and CTRP9).** C1q/TNF-related proteins (CTRPs) comprise a family of 15 structurally related paralogs of adiponectin, which form heterotrimers (often involving adiponectin) and exert endocrine functions, often signaling through the adiponectin receptor.<sup>131</sup> Secreted primarily by adipocytes, CTRP3 and CTRP9 reduce adipocyte mass and improve insulin sensitivity, while exerting endocrine- and paracrine-mediated cardioprotective, anti-inflammatory, and vasodilator effects. They activate SIRT and AMPK and inhibit Wnt/ $\beta$ -catenin signaling.<sup>131-137</sup>

Circulating levels of CTRP3 and CTRP9 are decreased in individuals with visceral adiposity and



in patients with heart failure.<sup>138-140</sup> Experimental myocardial injury signals to fat depots to cause a decline in the adipocyte expression of both CTRP3 and CTRP9.<sup>141,142</sup> At the same time, the cardioprotective effect of adipose-derived stem cell-conditioned medium is blunted when CTRP3 is knocked down, whereas the measured delivery of CTRP9 systemically or via adipose-derived stem cells acts to mitigate cardiac injury.<sup>134,143</sup> These observations demonstrate bidirectional endocrine cross-talk between adipocyte-derived CTRP3 and CTRP9 and the myocardium.

Importantly, the benefits of CTRPs appear to be specifically related to their measured production by adipocytes, because coerced cardiac-specific overexpression of CTRP3 and CTRP9 (bypassing the influence of adipocytes) has deleterious effects on pressure-overload hypertrophy.<sup>144,145</sup> Glucagon-like peptide-1 (GLP-1) receptor agonists have been shown to alleviate the suppression of adipocyte

CTRP3 expression seen in experimental insulin resistance.<sup>146</sup>

**OTHER DOMAIN I ADIPOKINES. Omentin-1.** Omentin-1 is secreted by visceral fat, typically acting in an endocrine manner, with circulating levels that are typically correlated with adiponectin.<sup>147</sup> Omentin-1 interferes with the cellular pathways that mediate the action of Domain III adipokines by inhibiting the activin type II receptor and suppressing Wnt5a/Ca<sup>2+</sup> signaling, and it may also up-regulate AMPK.<sup>148-150</sup>

Experimentally, omentin-1 alleviates adipose tissue inflammation,<sup>151</sup> and it ameliorates myocardial ischemic injury and cardiac hypertrophy.<sup>152,153</sup> It also reduces oxidative and endoplasmic reticulum stress in endothelial cells<sup>148</sup> and promotes nitric oxide-mediated vasodilation, while alleviating hypertension.<sup>154</sup>

Clinically, circulating levels of omentin-1 are decreased in people with obesity and in patients with

**BOX 5. Key Features of Domain I Adipokines**

1. Adiponectin, the principal Domain I adipokine, is secreted almost exclusively by adipocytes and circulates in high concentrations in healthy adults. Adiponectin suppresses adipose tissue inflammation and maintains cardiomyocyte homeostasis. It antagonizes the activity of renal sympathetic nerves, the renin-angiotensin system and aldosterone, and it inhibits myocardial hypertrophy, inflammation, and fibrosis, thereby acting to prevent HFP EF. C1q/TNF-related proteins 3 and 9 are structural paralogs of adiponectin, with aligned actions.
2. Other Domain I adipokines—omentin-1, secreted frizzled-related protein 5, and extracellular NAMPT—exert effects on the heart that are similar to those of adiponectin, typically counteracting the actions of Domain III adipokines. Zinc alpha 2-glycoprotein is a major lipid mobilizing hormone that shrinks fat depots.
3. Domain I adipokines are suppressed in both obesity and in HFP EF in experimental models and in the clinical setting. In patients, this suppression is seen years before the onset of heart failure, and the magnitude of suppression is correlated with the severity of heart failure and prognosis.
4. Experimental overexpression or recombinant delivery of Domain I adipokines mitigates the development of cardiac hypertrophy and fibrosis and alleviates the evolution of cardiomyopathy and HFP EF.
5. Bariatric surgery, incretin receptor agonists, SGLT2 inhibitors, mineralocorticoid receptor antagonists, and angiotensin receptor neprilysin inhibitors enhance circulating levels of Domain I adipokines.

dilated cardiomyopathy and heart failure,<sup>155,156</sup> and those with the lowest levels have the most unfavorable prognosis.<sup>156,157</sup> Serum omentin-1 concentrations are also decreased in patients with HFP EF, being inversely related to biomarkers of inflammation,<sup>158</sup> but they increase following treatment with GLP-1 receptor agonists.<sup>159</sup>

**Secreted frizzled-related protein 5.** Secreted by adipocytes, secreted frizzled-related protein 5 (SFRP5) acts as a soluble decoy that antagonizes WNT5a, a Domain III adipokine, thereby inhibiting noncanonical Wnt/JNK signaling.<sup>160,161</sup> In adipose tissue, SFRP5 promotes insulin sensitivity, enhancing the storage of lipids and limits the formation of ectopic fat.<sup>162-164</sup> Additionally, SFPR5 exerts cardioprotective and renoprotective actions by improving mitochondrial function and reducing inflammation and fibrosis.<sup>165-167</sup>

Adipocyte expression of SFPR5 is suppressed in patients with obesity/visceral adiposity and inflammation,<sup>164</sup> and circulating levels of SFPR5 are reduced in obesity and in heart failure.<sup>168-170</sup> Patients with higher SFPR5 levels have better glycemic control, less systemic inflammation, and lower systolic blood pressures.<sup>169</sup> Conversely, patients with heart failure with the lowest serum SFPR5 levels have worse ventricular diastolic filling dynamics and a higher risk of adverse heart failure outcomes.<sup>170-172</sup>

Overexpression of SFPR5 or treatment with recombinant SFPR5 preserves systolic function and reduces cardiac inflammatory responses and adverse remodeling in experimental heart failure.<sup>160,165</sup> The effect of GLP-1 receptor agonism to mitigate experimental diabetic nephropathy is accompanied by elevated circulating levels of SFPR5.<sup>173</sup> In the clinical setting, weight loss or treatment with GLP-1 receptor agonists is accompanied by increases in circulating SFPR5.<sup>174,175</sup>

**Extracellular nicotinamide phosphoribosyltransferase.** Nicotinamide phosphoribosyltransferase (NAMPT) was initially characterized as a proinflammatory cytokine (referred to as visfatin),<sup>176</sup> but NAMPT is now recognized as the rate-limiting step in the salvage pathway for the systemic biosynthesis of nicotinamide adenine dinucleotide (NAD+), the principal cofactor for SIRT1 activation.<sup>177</sup> SIRT1 signaling plays a critical role in the mitigation of obesity-related microvascular dysfunction and the development of dysmetabolism-related HFP EF.<sup>178,179</sup>

NAMPT typically acts within cells, but an extracellular form of NAMPT (referred to as eNAMPT) is released from adipocytes in response to SIRT1 (often as a component of adipoxosomes<sup>180</sup>) to exert endocrine effects.<sup>181-183</sup> eNAMPT acts both as a systemic NAD+ biosynthetic enzyme<sup>183</sup> and as a natural antagonist of the receptor for C-C-chemokine ligand 5 (RANTES), a proinflammatory Domain III adipokine.<sup>181</sup>

Obesity and visceral adiposity are accompanied by a decrease in eNAMPT expression and intracellular NAD+ levels in adipocytes,<sup>184</sup> and these changes are reversed with weight loss.<sup>185</sup> Experimental adipocyte-specific NAMPT or eNAMPT suppression induces a systemic NAD+-deficiency, leading to multiorgan metabolic dysfunction.<sup>186-188</sup> These studies demonstrate the importance of adipocyte secretion as an endocrine mediator of adipose dysfunction to distant sites.

Extracardiac synthesis of eNAMPT, acting to sustain circulating levels of NAD+, alleviates experimental cardiac pressure overload.<sup>189</sup> Cardiomyocyte NAMPT deficits promote maladaptive hypertrophy,

degrade antioxidant defenses, impair cardiomyocyte viability, and exacerbate cardiomyopathy,<sup>190-192</sup> and NAMPT inhibition is accompanied by cardiotoxicity.<sup>193</sup> The expression of NAMPT is depleted in the myocardium of patients with HFpEF, and low serum levels of eNAMPT are associated with a poor prognosis in HFpEF.<sup>194</sup> In contrast, therapeutic augmentation of circulating levels of NAD<sup>+</sup> improves metabolic and antioxidant profiles in HFpEF.<sup>195,196</sup>

**Zinc  $\alpha$ 2-glycoprotein.** Zinc  $\alpha$ 2-glycoprotein (ZAG) functions as a lipid-mobilizing adipokine, inhibiting lipogenesis and promoting lipolysis.<sup>197,198</sup> In adipocytes, ZAG interacts with  $\beta$ 2- and  $\beta$ 3-adrenergic receptors (and through G protein-coupled receptor signal transduction) stimulates uncoupling protein-1, augmenting mitochondrial function and biogenesis, and adipose tissue browning.<sup>199,200</sup> These actions cause marked shrinkage of subcutaneous and visceral fat depots and organ lipid content.

Cancers that cause cachexia promote the secretion of ZAG into the circulation, where it exerts endocrine effects to promote the catabolism of white adipose tissue.<sup>201</sup> However, in states of obesity, the presence of visceral adiposity and adipose tissue inflammation inhibits the expression of ZAG in adipocytes, promoting further adipogenesis.<sup>197,198,201,202</sup> Clinically, ZAG signaling is deficient in patients with obesity and visceral adiposity. Circulating levels of ZAG are inversely correlated with body mass index and indexes of visceral adiposity, and they track closely with levels of adiponectin.<sup>203-206</sup>

ZAG overexpression or recombinant ZAG induces lipolysis and reduces body weight, decreases blood pressure, and promotes urinary sodium excretion, and mitigates collagen deposition in the heart and kidneys.<sup>207,208</sup> These observations point to adiposity-related ZAG suppression as a potential contributor to the plasma volume expansion, hypertension, and cardiac fibrosis seen in HFpEF. ZAG levels in the circulation are sufficient to exert an antifibrotic effect,<sup>207</sup> further supporting an endocrine action.

Interestingly, serum levels of ZAG are increased in patients with severe HFrEF and may contribute to cardiac cachexia.<sup>209</sup> In marked contrast, serum ZAG levels are decreased in patients with a HFpEF phenotype (ie, those with hypertension who have central obesity or have diabetes with diastolic filling abnormalities).<sup>210,211</sup> Intriguingly, GLP-1 receptor agonism and SGLT2 inhibition up-regulate adipocyte expression of ZAG and increase circulating levels of ZAG in patients with insulin resistance.<sup>207,212-214</sup> These observations suggest that modulation of ZAG may contribute to the therapeutic effects of these drugs in adiposity-related HFpEF.

**Neuregulin-4 (NRG-4).** Neuregulins signal through receptor tyrosine kinases encoded by the ErbB family.<sup>215</sup> Interest in neuregulins was awakened when trastuzumab, an ErbB2 monoclonal antibody used in oncology, produced cardiotoxicity, leading to the disappointing development of neuregulin-1 $\beta$ 3 for the treatment of heart failure.<sup>216</sup> However, ErbB4 (not ErbB2) plays a critical role in inhibiting lipogenesis and promoting adipose tissue browning,<sup>217</sup> and of the neuregulins, only neuregulin-4 (NRG-4) (which selectively binds to ErbB4) is primarily secreted by adipocytes (specifically by those residing in brown adipose tissue<sup>218,219</sup>) and functions in an endocrine manner.<sup>220</sup>

NRG-4 reduces oxidative and proinflammatory stress and improves mitochondrial function in adipocytes,<sup>221-223</sup> thus alleviating obesity and insulin resistance, possibly through an AMPK-dependent mechanism. However, serum levels and adipocyte expression of NRG-4 are decreased in obesity and visceral adiposity, fatty liver disease, and in diabetic chronic kidney disease.<sup>224-229</sup> Adipocyte-mediated bloodstream delivery of NRG-4 appears to be important.<sup>230</sup> Intraperitoneal NRG-4, intravenous NRG-4 gene transfer, adipocyte-specific expression of NRG-4, or transplantation of NRG-4-overexpressing adipose-derived mesenchymal stem cells act to alleviate hepatic steatosis, improve whole body metabolic health, and prevent obesity.<sup>223,231-234</sup>

Therapeutic administration of NRG-4 alleviates experimental cardiomyopathy<sup>235-237</sup> and diabetic nephropathy.<sup>238</sup> Pressure-overload hypertrophy is accompanied by decreased cardiomyocyte expression of NRG-4, but adenoviral delivery of NRG-4 inhibits maladaptive cardiomyocyte proliferation and ameliorates fibrosis,<sup>239</sup> supporting the potential relevance of NRG-4 to the pathogenesis of HFpEF.

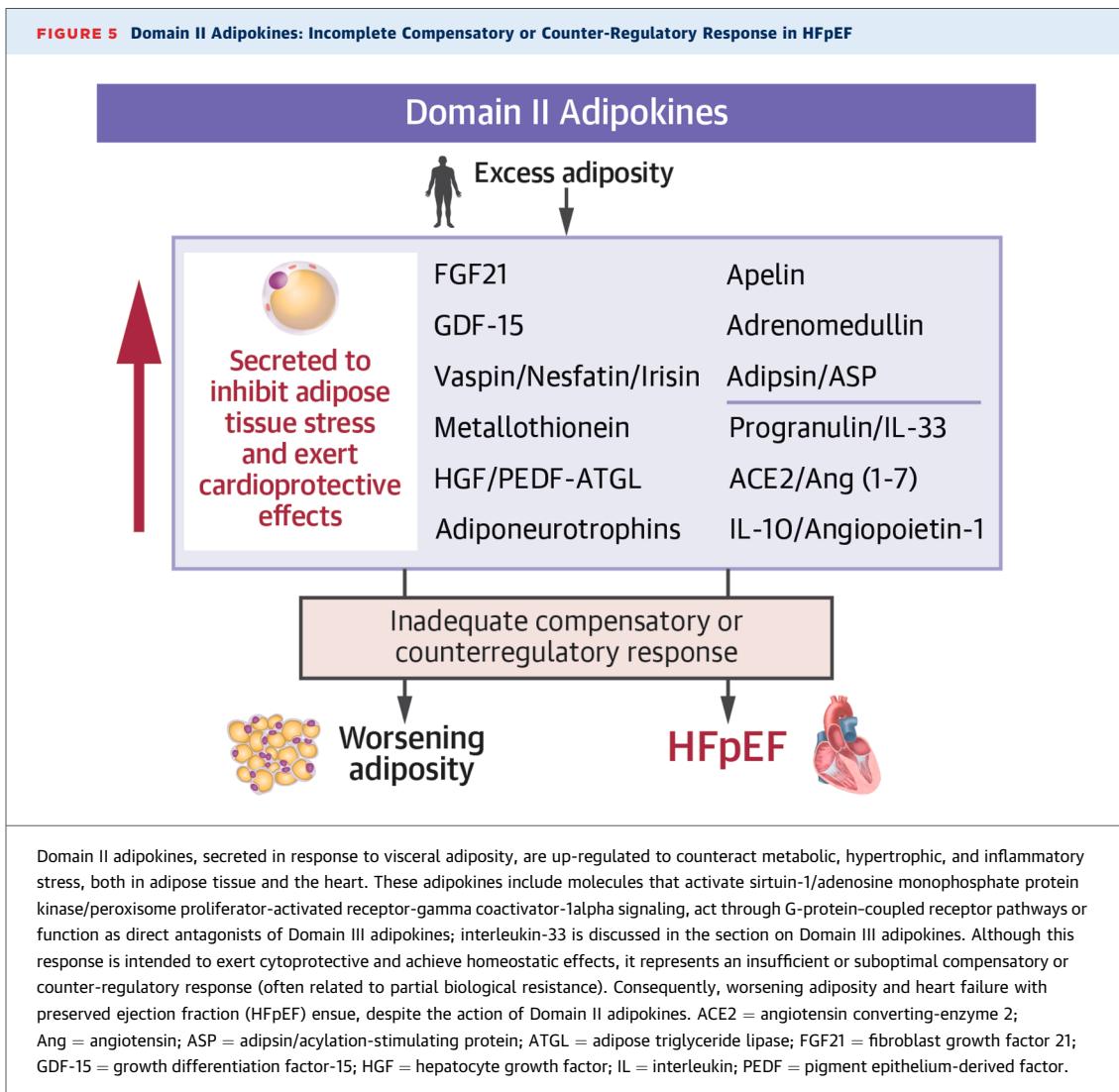
## PART VI: DOMAIN II ADIPOKINES: CARDIOPROTECTIVE MOLECULES WHOSE ENHANCED SECRETION IN OBESITY ACTS AS A COMPENSATORY OR COUNTERREGULATORY MECHANISM

Domain II adipokines inhibit cellular stress, hypertrophy and inflammation in white adipose tissue and the heart (Table 3 and Figure 5). In lean individuals, adipocytes typically secrete only small quantities of Domain II adipokines. Consequently, their characterization has conventionally been linked to their synthesis in the liver, skeletal muscle, and central nervous system, thus explaining their classification as hepatokines, myokines, and neurotrophins.

**TABLE 3 Domain II Adipokines**

Protein or Signaling Axis	Adipocyte Source and Cellular Signaling	Biological Effects Relevant to Adipose Tissue and the Heart	Changes in Obesity, Visceral Adiposity, and Heart Failure
<i>Signaling Through SIRT1/AMPK/PGC-1α and PI3K-Akt-mTOR</i>			
Fibroblast growth factor 21 (FGF21)	Endocrine signaling, also epicardial secretion. FGF21 acts through adiponectin-dependent mechanisms.	FGF21 reduces visceral lipid overload. FGF21 from adipocytes (not cardiomyocytes) inhibits cellular stress and proinflammatory signaling.	Compensatory increases in serum FGF21 in obesity, visceral adiposity, and HFpEF.
Growth differentiation factor (GDF-15)	Secreted by adipocytes (and other cells) to suppress appetite/obesity.	GDF-15 mitigates myocardial apoptosis, inflammation, hypertrophy, and fibrosis.	Compensatory increases in obesity and HFpEF.
Vaspin	Endocrine signaling, vaspin enhances autophagy and suppresses NF-κB.	Vaspin inhibits proinflammatory adipokines and maladaptive hypertrophy, and it mitigates hypertension by promoting vasodilation.	Compensatory increase in obesity. Higher levels in patients with heart failure predict better outcome.
Nesfatin-1	Secreted by adipocytes to suppress food intake, enhance insulin secretion.	Cardioprotective effects in cardiomyocytes and in experimental cardiopathy.	
Irisin	Secreted by brown adipocytes to promote thermogenesis, irisin inhibits adipogenesis in white adipocytes.	Signals through SIRT1/PGC-1α to promote mitochondrial biogenesis, reduce cellular stress, and enhance autophagy. Irisin ameliorates maladaptive hypertrophy and fibrosis.	Irisin resistance leads to compensatory increases in obesity and HFpEF. High levels have better prognosis.
Metallothionein	Metallothionein is secreted by adipocytes (often within adipoxosomes) and exerts antioxidant effect.	Metallothionein prevents obesity-related cardiac hypertrophy and fibrosis in a PGC-1α-dependent manner.	Increased adipocyte expression in obesity. Undergoes endocytosis by failing heart.
Hepatocyte growth factor (HGF)	Secreted by adipose tissue, HGF promotes vascularization and antagonizes obesity.	HGF exerts cardioprotective effects. Elevated serum HGF levels identify patients with obesity-related LV hypertrophy prone to HFpEF.	Compensatory increases in serum HGF in obesity and HFpEF.
Pigment epithelium-derived factor/adipose triglyceride lipase (PEDF/ATGL) signaling	Substantial synthesis of PEDF by adipocytes. PEDF promotes breakdown of fat depots through up-regulation of ATGL.	PEDF exerts broad range of cardioprotective effects and maintains vascular endothelial integrity. Modulation of ATGL influences the course of experimental HFpEF.	Compensatory increases in serum PEDF in obesity and heart failure.
Extraneuronal adiponeurotrophins	Secreted by adipocytes during adipogenesis to cause shrinkage of white adipose tissue.	Non-neuronal sources of adiponeurotrophins mitigate pressure-overload-induced cardiac hypertrophy and ameliorate heart failure.	Circulating levels increased in obesity. Cardiac expression reduced in heart failure.
<i>Signaling Through G-Protein Coupled Receptors or β-Arrestin</i>			
Apelin	Signals through APJ receptor, the effects of apelin are mediated by SIRT1 and AMPK.	Apelin promotes tolerance to pressure overload, ischemic injury, or obesity. It exerts positive inotropic, vasodilator, and diuretic effects.	Increased levels in obesity and HFpEF. Deficient cardiac synthesis in heart failure.
Calcitonin peptide family (adrenomedullin and calcitonin gene-related peptide [CGRP])	Diet-induced obesity leads to adipocyte-specific secretion of adrenomedullin, acting in an endocrine manner.	Adrenomedullin and CGRP attenuate cardiac hypertrophy, inflammation, and fibrosis in experimental HFpEF.	Serum levels of adrenomedullin are increased in obesity and in HFpEF.
Adipsin and acylation-stimulating protein (ASP)	Adipsin and ASP are secreted by adipocytes to regulate energy homeostasis.	Adipocyte-specific overexpression of adipsin exerts favorable effects on experimental HFpEF by alleviating microvascular injury.	Compensatory increase in obesity and heart failure.
<i>Antagonists of Domain III Adipokines</i>			
Progranulin	Progranulin acts a Wnt antagonist (when CTRP is deficient) as a compensatory response.	Heightened expression and release of progranulin in adipose tissue in obesity. Progranulin mitigates injury and age-related adverse ventricular hypertrophy.	Compensatory increase in obesity and heart failure (including HFpEF).
Angiotensin converting-enzyme-2 (ACE2)/angiotensin (1-7) signaling	ACE2 and Ang(1-7) are secreted by adipocytes as natural antagonists of angiotensin II to inhibit adipogenesis and adipose tissue inflammation.	ACE2 and Ang(1-7) attenuate cardiac hypertrophy, inflammation and fibrosis. ACE2 silencing and overexpression aggravates and alleviates HFpEF, respectively.	ACE2 increased in obesity and ACE2/Ang(1-7) increased in HFpEF. High levels have better prognosis.
Interleukin-10 (IL-10) and angiopoietin-1 (Ang-1)	Secreted by adipocytes, Ang-1 and IL-10 antagonize effects of Domain III adipokines.	IL-10 and Ang-1 induce weight loss and ameliorate adipocyte stress, and they exert cardioprotective and vasculoprotective effects.	Compensatory increase in obesity and HFpEF. High Ang-1 has better prognosis.

ACE2 = angiotensin converting-enzyme 2; Ang = angiotensin; ASP = adipsin/acylation-stimulating protein; ATGL = adipose triglyceride lipase; FGF21 = fibroblast growth factor 21; GDF-15 = growth differentiation factor-15; HGF = hepatocyte growth factor; IL = interleukin; PEDF = pigment epithelium-derived factor; other abbreviations as in Tables 1 and 2.



However, in obesity and visceral adiposity, the synthesis of Domain II adipokines is dramatically heightened, and adipocytes emerge as the major site of production, because adipose tissue comprises as much as 50% of body weight in people with obesity. The enhanced secretion of Domain II adipokines functions both as a mechanism to compensate for the loss of signaling of Domain I adipokines and as a means of counterbalancing the actions of Domain III adipokines. Although circulating levels of Domain II adipokines exert favorable effects on the myocardium, HFpEF still ensues, presumably because the compensatory or counter-regulatory responses are insufficient or overwhelmed. Despite their elevated circulating levels, the cellular responses to Domain II adipokines may be muted, because obesity induces

biological resistance to the mechanisms that drive the cytoprotective effects of these adipokines (Box 6 and Box 7).

#### DOMAIN II ADIPOKINES THAT SIGNAL THROUGH NUTRIENT DEPRIVATION AND SURPLUS PATHWAYS.

Many of the Domain II adipokines exert effects by through nutrient deprivation or surplus signaling pathways, acting to enhance SIRT1/AMPK/PGC-1 $\alpha$  signaling or interfere with the PI3K-Akt-mTOR pathway, thus alleviating the cellular stresses that typically accompany states of nutrient excess.<sup>85,93,94</sup>

**Fibroblast growth factor 21.** Typically produced by the liver in lean individuals, fibroblast growth factor 21 (FGF21) is secreted by adipocytes in obesity, particularly within brown adipose tissue, exerting its

**BOX 6. Key Features of Domain II Adipokines (Part 1)**

1. Doman II adipokines include FGF21, GDF-15, vaspin, irisin, PEDF/ATGL, HGF, apelin, adrenomedullin, and adipoin. Several Domain II adipokines—ACE2/Ang(1-7), progranulin, interleukin 10, and angiopoietin-1—are direct antagonists of Domain III adipokines.
2. Domain II adipokines exert protective effects on both adipose tissue and the heart, muting adipose inflammation and cardiac hypertrophy and fibrosis. Many Domain II adipokines stimulate healthy thermogenesis in brown adipose tissue.
3. In lean people, adipocytes secrete only small quantities of Domain II adipokines, and other organs (eg, liver, skeletal muscle, central nervous system and others) represent the primary site of synthesis. However, as fat mass expands and adipocytes in visceral fat heighten their synthesis, adipose tissue emerges as the predominant site of production and of circulating levels.
4. The secretion of Domain II adipokines compensates for the loss of signaling of Domain I adipokines and counterbalances the actions of Domain III adipokines, but these responses appear to be insufficient to prevent HFpEF, often because obesity promotes resistance to their biological actions.

effects via the fibroblast growth factor receptor 1 and its coreceptor,  $\beta$ -Klotho.<sup>240,241</sup> Acting through SIRT1/AMPK and the release of adiponectin, FGF21 enhances insulin sensitivity, facilitates lipolysis and mitochondrial oxidative metabolism, augments energy expenditures, and shrinks visceral and hepatic fat depots. These effects of FGF21 protect against diet-induced obesity and diabetes.<sup>242-246</sup>

Cardiomyocytes are not an important source of FGF21, but intriguingly, cardiac injury is followed by the secretion of FGF21 from adipocytes,<sup>247</sup> which (acting through an endocrine mechanism) exerts a cardioprotective effect. Experimentally, enhanced FGF21 signaling in cardiomyocytes reduces oxidative stress and proinflammatory signaling, up-regulates autophagic flux, mitigates cardiac remodeling, and maladaptive hypertrophy and exerts a broad range of cardioprotective effects.<sup>247-250</sup>

However, obesity and diabetes reduce the expression of  $\beta$ -Klotho and fibroblast growth factor receptor 1, and this action interferes with the metabolic and cardiac response to FGF21, thus leading to FGF21 resistance.<sup>251-253</sup> As a compensatory response, serum FGF21 levels are elevated in adults with visceral adiposity.<sup>254-257</sup> Similarly, serum FGF21 levels are increased in patients with HFrEF and HFpEF in proportion to the severity of diastolic filling

**BOX 7. Key Features of Domain II Adipokines (Part 2)**

1. Serum levels of Domain II adipokines are increased in people with obesity/visceral adiposity and with HFpEF, and they are associated with the severity of clinical symptoms and prognosis in heart failure. Increased circulating levels may be seen years before the onset of heart failure.
2. Consistent with the compensatory and counter-regulatory actions of Domain II adipokines, patients with established heart failure who have elevated levels have a more favorable prognosis.
3. Domain II adipokines suppress the development of cardiac hypertrophy and fibrosis and alleviate the evolution of cardiomyopathy and HFpEF in experimental models. Many Domain II adipokines enhance vasodilation and inhibit vascular smooth muscle proliferation, thus acting to lower blood pressure.
4. Selective up-regulation of Domain II adipokine synthesis only in adipose tissue produces favorable effects on the course of experimental HFpEF. Transplantation of vaspin-expressing adipose tissue produces cardioprotective effects, and adipocyte-specific overexpression of adipoin ameliorates HFpEF.
5. Bariatric surgery and current drugs for HFpEF produce increases in FGF21, GDF-15, and ATGL. Drugs for HFpEF also increase circulating levels of other Domain II adipokines (e.g., irisin, apelin, HGF), whereas these are decreased by bariatric surgery, presumably because marked weight loss reduces the stimulus to secretion.

abnormalities, and these increased levels have adverse prognostic significance.<sup>258,259</sup> However, the expression of FGF21 in cardiomyocytes remains suppressed, thus demonstrating the importance of extracardiac production.<sup>260</sup>

Experimentally, dual GLP-1/glucagon receptor agonism increases adipose tissue expression and circulating levels of FGF21,<sup>261</sup> and SGLT2 inhibition increases myocardial FGF21 expression in experimental obesity.<sup>262</sup> Clinically, the FGF21 analogue pegozafermin has been shown to alleviate hepatic steatosis and fibrosis in patients with nonalcoholic fatty liver disease.<sup>263</sup>

**Growth differentiation factor-15.** Growth differentiation factor-15 (GDF-15), a member of the transforming growth factor- $\beta$  superfamily, is secreted by adipose tissue, liver, and heart under conditions of metabolic stress,<sup>264-266</sup> acting in an endocrine manner to restore tissue and whole-body homeostasis.

GDF-15 suppresses appetite<sup>267</sup> and promotes lipolysis and inhibits inflammatory responses in white adipose tissue.<sup>267-271</sup> It stimulates

thermogenesis in brown adipocytes<sup>272</sup> and enhances energy expenditure in skeletal muscles,<sup>273</sup> often coreleased with FGF21 to mediate an integrated AMPK-dependent mitochondrial stress response.<sup>274,275</sup> Heightened endocrine GDF-15 signaling leads to weight loss, and GDF-15 overexpression alleviates obesity.<sup>265,276</sup> Delivery of recombinant GDF-15 causes a catabolic state,<sup>277</sup> whereas experimental GDF-15 suppression promotes high-fat diet-induced obesity.<sup>278</sup> In the clinical setting, ponsegrumab (a GDF-15 antibody) produces weight gain in patients with cachexia.<sup>279</sup>

However, as in the case of FGF21, obesity and visceral adiposity leads to resistance to the biological action of GDF-15,<sup>280</sup> perhaps related to downregulation of its receptor or as a result of adipocyte-specific mitochondrial abnormalities,<sup>281,282</sup> and as with leptin, this resistance may be tissue-specific. Accordingly, serum GDF-15 levels are increased in patients with obesity and visceral adiposity.<sup>283-286</sup> Adipocyte secretion has been implicated in these heightened circulating levels GDF-15, because experimental obesity induces up-regulation of GDF-15 expression in adipocytes, but not in the liver.<sup>287</sup>

Adipocyte-specific secretion of GDF-15 exerts important systemic actions,<sup>288</sup> indicating that the endocrine actions of GDF-15 can yield cardioprotective effects. Treatment with or overexpression of GDF-15 induces autophagy and mitigates apoptosis and proinflammatory pathways<sup>289,290</sup> and alleviates cardiac hypertrophy, myocardial fibrosis,<sup>290-292</sup> and the diastolic filling abnormalities of HFpEF.<sup>293</sup> These actions may be mediated by an effect of GDF-15 to suppress endothelial inflammation.<sup>294,295</sup> Counter-regulatory upregulation of GDF-15 may explain why circulating levels of GDF-15 are increased in patients who subsequently develop heart failure or cardiac fibrosis<sup>296-298</sup> or already have subclinical cardiac fibrosis or diastolic filling abnormalities.<sup>299-301</sup> Serum GDF-15 levels are increased and predict outcomes in patients with established heart failure, including those with HFpEF and obesity.<sup>302-308</sup> SGLT2 inhibitors further increase serum levels of GDF-15 in patients with heart failure.<sup>309,310</sup>

**Vaspin.** Vaspin (visceral adipose tissue-derived serine protease inhibitor) functions as an insulin-sensitizing adipokine,<sup>311</sup> which is minimally expressed in the visceral and subcutaneous fat of lean people. However, as body mass increases, the expression of vaspin increases strikingly in adipocytes.<sup>311,312</sup> Heightened adipocyte expression and secretion of vaspin (particularly from brown fat<sup>313</sup>) causes elevation of serum vaspin levels in obesity,

visceral adiposity, and other insulin-resistant states.<sup>314-316</sup>

The heightened secretion of vaspin represents a counterbalancing endocrine response. Vaspin overexpression inhibits the development of diet-induced obesity,<sup>317</sup> and serum vaspin levels decline with weight loss.<sup>318</sup> Recombinant vaspin inhibits the expression of leptin, resistin, and proinflammatory cytokines in adipose tissue and enhances the expression of adiponectin.<sup>319</sup> The loss of visceral brown fat in experimental lipodystrophy is accompanied by impaired vaspin signaling, and importantly, transplantation of vaspin-expressing adipose tissue in this model produce cardioprotective effects.<sup>320</sup>

By activating AMPK and suppressing PI3K-Akt-mTOR signaling, vaspin enhances autophagy and reduces organellar stress,<sup>321-326</sup> while inhibiting maladaptive cardiac hypertrophy<sup>321</sup> and proinflammatory signaling<sup>324,327</sup> in the heart. It prevents cell death and preserves cardiac function in experimental cardiomyopathy and heart failure.<sup>321,323,324</sup> Vaspin also attenuates vascular smooth muscle proliferation,<sup>328</sup> and it suppresses the hypertensive responses to obesity by enhancing nitric-oxide-mediated vasodilation.<sup>329,330</sup>

Clinically, failure to trigger a compensatory increase in circulating vaspin levels appears to have adverse prognostic consequences,<sup>331</sup> because patients with low vaspin levels have an increased risk of heart failure hospitalizations.<sup>332</sup> Fenofibrate, which directly increases the expression of vaspin in adipocytes,<sup>333</sup> is accompanied by a decreased risk of heart failure hospitalization in patients with insulin resistance.<sup>334</sup>

**Nesfatin-1.** Originally described as an anorexigenic neuropeptide localized to the hypothalamus, nesfatin-1 is produced by adipocytes during differentiation and acts as a counter-regulatory adipokine.<sup>335</sup> Human obesity and visceral adiposity is accompanied by increased serum levels of nesfatin-1.<sup>335,336</sup> Nesfatin-1 reduces food intake,<sup>337</sup> promotes insulin secretion and insulin sensitivity,<sup>338-340</sup> inhibits adipocyte differentiation,<sup>341</sup> and suppresses adiposity-related inflammation and in oxidative stress.<sup>342,343</sup> Nesfatin-1 promotes expansion of brown fat,<sup>344</sup> mediated by enhanced SIRT1/PGC-1 $\alpha$  signaling and inhibition of mTOR.

Although nesfatin-1 in the central nervous system may lead to sympathetic activation and hypertension,<sup>345-347</sup> blood-borne nesfatin-1 (eg, as from adipocytes<sup>348</sup>) produces cardioprotective effects in isolated cardiomyocytes,<sup>349</sup> in models of ischemic and postinfarction injury and in experimental cardiomyopathy.<sup>350-354</sup> In the clinical setting, failure to

trigger a compensatory increase in circulating nesfatin-1 levels appears to have adverse prognostic consequences, because patients with heart failure who have low nesfatin levels have an increased risk of adverse outcomes.<sup>355</sup>

**Irisin.** Originally described as a myokine released by skeletal muscle during exercise, irisin is a PGC-1 $\alpha$ -dependent adipokine, which is formed by protease cleavage of the transmembrane protein, fibronectin type III domain containing 5.<sup>356</sup> When expressed and secreted by adipocytes,<sup>357,358</sup> irisin acts to ameliorate obesity by promoting thermogenesis in brown fat and by reducing adipogenesis (while enhancing browning) in white adipose tissue.<sup>356,358-361</sup>

Serum levels of irisin are related to its expression in adipocytes<sup>357</sup> and are increased in patients with obesity, especially those with visceral adiposity and systemic inflammation. These heightened levels act as a counter-regulatory response to the development of irisin resistance<sup>357,359,362-366</sup>; reports that patients with obesity have decreased serum irisin levels are related to the confounding influence of diabetes.<sup>366,367</sup> High preoperative levels of irisin predict the weight loss following gastric bypass surgery<sup>368</sup> (consistent with alleviation of irisin resistance), and irisin levels decrease following bariatric procedures.<sup>369</sup>

Acting by up-regulating SIRT1/PGC-1 $\alpha$ ,<sup>356,370</sup> irisin exerts a broad range of cardioprotective effects, promoting fatty acid oxidation and mitochondrial biogenesis,<sup>371</sup> reducing oxidative and endoplasmic reticulum stress<sup>371-377</sup> and proinflammatory signaling,<sup>374</sup> enhancing autophagic flux,<sup>378,379</sup> and preventing cardiomyocyte death.<sup>375,376</sup> Excessive levels may exert deleterious effects,<sup>380,381</sup> a finding that parallels similar observations with SIRT1.<sup>382</sup> Irisin ameliorates maladaptive cardiac hypertrophy and fibrosis,<sup>372,377,378,383</sup> causes systemic vasodilation,<sup>384</sup> and mitigates the development of experimental heart failure.<sup>372,373</sup>

Serum levels of irisin are decreased following cardiac injury and in HFrEF,<sup>385-387</sup> indicating that up-regulation of cardiomyocyte synthesis during stress<sup>388</sup> is not likely to be an important source of circulating irisin. In marked contrast, serum levels of irisin are increased in patients with HFpEF,<sup>389</sup> presumably because the expanded adipose tissue mass emerges as the primary source of irisin production. Patients with HFpEF with higher levels are less likely to have clinical exacerbations and have a more favorable prognosis,<sup>194,390,391</sup> supporting the hypothesis that adipocyte-derived irisin exerts cardioprotective effects. Extracellular irisin can prime bone marrow mesenchymal cells to secrete

cardioprotective exosomes,<sup>392</sup> and circulating irisin increases cardiac homing of adipose tissue-derived mesenchymal stem cells for repair.<sup>393</sup>

**Metallothionein-1.** Metallothioneins are a family of small cysteine-rich polypeptides, which function in energy transfer, act as heavy metal chelators, and exert antioxidant effects.<sup>394</sup> Adipocyte hypertrophy is accompanied by up-regulation of metallothionein synthesis, which (as a counterbalancing response) constrains adipogenesis and prevents diet-induced obesity.<sup>395-397</sup> Metallothioneins secreted by adipocytes contribute importantly to circulating levels,<sup>398</sup> potentially as a component of adipocyte-derived extracellular vesicles.<sup>399</sup> Metallothionein-1 promotes thermogenesis in healthy brown fat,<sup>400</sup> but experimental and clinical obesity induces the expression of metallothionein by adipocytes in white adipose tissue,<sup>401-403</sup> acting to limit adiposity.<sup>397,404</sup>

Silencing of metallothionein not only worsens obesity, but it also exacerbates obesity-related cardiac hypertrophy and fibrosis.<sup>405,406</sup> Metallothionein reduces cardiomyocyte oxidative and organellar stress,<sup>407,408</sup> promotes mitochondrial biogenesis and autophagy, and prevents apoptosis (all acting through PGC-1 $\alpha$ ).<sup>409-412</sup> Metallothionein also exerts cardioprotective effects across diverse cardiac injuries and metabolism-related cardiomyopathy,<sup>406,413-415</sup> and it ameliorates aging-associated ventricular diastolic dysfunction.<sup>407</sup> Patients with end-stage heart failure show the accumulation of metallothionein-containing lipovesicles in the subepicardial myocardium,<sup>416</sup> possibly a result of the endocytosis of epicardial adipexosomes. Presumably triggered by hemodynamic stress, these dissipate following left ventricular assist device support.<sup>416</sup>

**Hepatocyte growth factor.** Originally identified by its actions within the liver, hepatocyte growth factor (HGF) is cleaved into a 2-chain active protein that signals through the c-Met tyrosine kinase receptor. Adipocytes secrete HGF during adipogenesis,<sup>417-420</sup> and as adipose mass expands during obesity, adipocyte-derived HGF mediates the vascularization that is needed to mitigate stress and inflammation in adipose tissue,<sup>421,422</sup> thus lessening the severity of diet-induced obesity.<sup>423</sup>

Acting through AMPK,<sup>424-426</sup> HGF functions as a counterbalancing response to fat mass accumulation, particularly in promoting pancreatic  $\beta$ -cell hyperplasia in response to insulin resistance.<sup>427</sup> However, the effectiveness of this compensatory mechanism is blunted, because obesity-related increases in plasminogen activator inhibitor (PAI) act as a natural antagonist of HGF activation.<sup>428</sup> Circulating levels of

HGF are increased in patients with obesity, visceral adiposity, and organ steatosis<sup>429-432</sup>; are primarily driven by adipose tissue synthesis<sup>433,434</sup>; and decline following bariatric surgery.<sup>434,435</sup>

Elevated serum levels of HGF identify patients likely to have new-onset heart failure (especially HFpEF) in the general community,<sup>436,437</sup> and obesity-related increases in circulating levels of HGF are associated with increases in left ventricular mass and progressive concentric remodeling years before the diagnosis of HFpEF.<sup>438</sup> Serum levels of HGF are also increased in patients with established heart failure, particularly in those with HFpEF, and have prognostic significance.<sup>439-443</sup>

Circulating HGF can signal through c-Met receptors in the heart to exert a broad range of cardioprotective effects, acting to attenuate myocardial injury, apoptosis, fibrosis, hypertrophy, and adverse ventricular remodeling.<sup>444-447</sup> Polymorphisms that up-regulate c-Met are accompanied by a decreased risk of heart failure.<sup>448</sup> Yet, the cardioprotective effects of HGF may depend on the delivery of measured levels from an extracardiac source,<sup>444,449-451</sup> because excessive cardiac-specific c-Met overexpression leads to maladaptive hypertrophy and cardiomyopathy.<sup>452-454</sup> Adenoviral intramyocardial HGF delivery has been evaluated in clinical trials of patients with postinfarction ventricular dysfunction,<sup>455</sup> but not in patients with obesity and HFpEF.

**Pigment epithelium-derived factor and adipose triglyceride lipase.** Originally described in the retina, pigment epithelium-derived factor (PEDF) is one of the most abundant proteins released by adipocytes, and it is secreted (often as a component of adipoexosomes) to reach circulating levels in the micromolar range, comparable to those achieved by adiponectin.<sup>456</sup> PEDF signals through several receptors<sup>457</sup> and primarily activates adipose triglyceride lipase (ATGL), leading to the breakdown of triglycerides and the release of fatty acids.<sup>458</sup> It also inhibits vascular endothelial growth factor receptor 2, leading to suppression of angiogenesis.<sup>459</sup>

ATGL signals through nutrient deprivation pathways, ie, AMPK, SIRT1, PGC-1 $\alpha$ , and PPAR $\alpha$ ,<sup>460-462</sup> and changes in adipose tissue can modulate signaling at distant sites, ie, adipose-selective ATGL silencing abrogates PPAR $\alpha$  activity in the liver.<sup>461,462</sup> In experimental obesity, mineralocorticoid receptor antagonism promotes AMPK-mediated ATGL signaling in brown adipose tissue.<sup>463</sup> PEDF is expressed during adipogenesis,<sup>457</sup> where it mediates triglyceride degradation in white adipose tissue and thermogenesis in brown fat.<sup>464,465</sup> PEDF ameliorates adipose tissue inflammation and oxidative

stress,<sup>466,467</sup> but the ATGL-mediated release of free fatty acids leads to insulin resistance.<sup>468</sup> Adipocyte-specific overexpression of ATGL alleviates obesity.<sup>469</sup>

Serum levels of PEDF are elevated in patients with obesity,<sup>470-475</sup> where its lipolytic effects may act as a counterbalancing mechanism. Circulating levels of PEDF are also increased in patients with heart failure and have prognostic significance.<sup>476</sup> PEDF exerts a broad range of cardioprotective effects, including a reduction in oxidative stress, inflammation, and apoptosis and augmentation of autophagy in cardiomyocytes<sup>477-480</sup> as well as maintenance of the integrity of the vascular endothelium (with a reduction in leakage and cardiomyocyte edema)<sup>481-484</sup> and a decrease in ventricular hypertrophy, fibrosis, and remodeling.<sup>485,486</sup> ATGL produces similar favorable effects on stressed or injured heart.<sup>487</sup> Experimental systemic disruption of ATGL signaling leads to ventricular hypertrophy and HFpEF as well as to triglyceride overload and cardiomyopathy.<sup>462,487,488</sup>

Paradoxically, adipocyte-specific suppression of ATGL improves tolerance of hearts to catecholamine injury, mitigates hypertrophic responses to pressure overload, and prevents experimental HFpEF.<sup>489-493</sup> These effects that may be related to diminution of the proinflammatory actions of heightened serum levels of free fatty acids, triggered by ATGL-induced lipolysis.<sup>490,493,494</sup> Nevertheless, endocrine PEDF signaling appears to be important in obesity-related HFpEF, because myocardial steatosis is a characteristic feature of the disease,<sup>495</sup> and signaling through PEDF and ATGL mitigates lipid overload and improves diastolic filling abnormalities in metabolic HFpEF.<sup>496</sup>

**Extraneuronal adiponeurotrophins.** Originally characterized by their actions within the central nervous system, several neuronal growth factors—nerve growth factor (NGF), neurotrophin-3 (NT-3), brain-derived neurotrophic factor (BDNF), and ciliary neurotrophic factor (CNTF)—suppress appetite and enhance energy expenditure, an action attributed to sympathetic innervation-mediated transmutation of adipose tissue.<sup>497,498</sup> However, independent of these neuronal effects, these adiponeurotrophins are secreted by noninnervated adipocytes during adipogenesis and in response to proinflammatory signaling.<sup>499-502</sup> These extraneuronal forms play an important role in peripheral energy homeostasis,<sup>503</sup> while exerting cytoprotective paracrine and endocrine effects.<sup>504-506</sup>

Circulating levels of NGF, NT-3, and CNTF are increased in patients with obesity,<sup>507-509</sup> and BDNF gene polymorphisms are linked to obesity.<sup>510</sup> The increase in CNTF (along with obesity-related up-

regulation of the adipocyte CNTF receptor<sup>502</sup>) represents a counter-regulatory response. Extraneuronal CNTF induces thermogenesis in brown fat (by promoting PGC-1α),<sup>503,511,512</sup> reduces the mass of white adipose tissue,<sup>513</sup> and mitigates insulin resistance by promoting AMPK signaling in skeletal muscle.<sup>514</sup> Moreover, further augmentation of serum CNTF levels causes weight loss experimentally<sup>515,516</sup> and in patients with obesity in clinical trials.<sup>517,518</sup> NGF, BDNF, and NT-3 are also synthesized by adipocytes and produce extraneuronal effects similar to CNTF.<sup>497,501,519,520</sup>

NGF, BDNF, NT-3, and CNTF exert cardioprotective effects in experimental models. Their systemic overexpression ameliorates hypertrophy and cardiac remodeling, and their suppression leads to worsening cardiomyopathy.<sup>521-530</sup> Experimental and clinical hypertrophy and heart failure are accompanied decreased cardiac expression of NGF and NT-3,<sup>531-533</sup> suggesting that increased circulating levels of adiponeurotrophins and up-regulation of CNTF receptors in obesity<sup>502,534</sup> mediate a compensatory response.<sup>535</sup>

**DOMAIN II ADIPOKINES ACTING THROUGH G PROTEIN-COUPLED RECEPTOR SIGNALING.** Several domain II adipokines signal through G protein-coupled receptors linked to cyclic AMP (apelin, adrenomedullin, and calcitonin gene-related peptide) or through a β-arrestin-mediated inhibition of G-protein coupled receptor signaling (adipsin/acylation-stimulating protein [ASP]).

**Apelin.** Apelin acts as an agonist at the G-coupled APJ receptor.<sup>536</sup> Secreted by adipose tissue, apelin inhibits adipogenesis in white adipose tissue,<sup>537</sup> but enhances brown adipogenesis and browning of white adipocytes.<sup>538</sup> These effects appear to be related to its actions to improve glucose and lipid metabolism, promote mitochondrial oxidation and biogenesis, and mitigate oxidative stress and proinflammatory pathways.<sup>539-542</sup> As a result, overexpression of apelin confers resistance to obesity.<sup>543</sup> In nutrient surplus states, apelin expression within and secretion by adipocytes is enhanced, presumably as a counter-regulatory response.<sup>536</sup> Serum levels of apelin are increased in people with obesity and decline following weight loss.<sup>536,544-546</sup>

Apelin exerts positive inotropic effects in the healthy and failing heart and systemic vasodilator effects in patients with central obesity.<sup>547,548</sup> Apelin mitigates the development of maladaptive cardiac hypertrophy, inflammation, microcirculatory dysfunction, and fibrosis.<sup>549</sup> Experimental knockout of apelin undermines the ability of the heart to tolerate pressure overload, ischemic injury, or

obesity.<sup>550-552</sup> Furthermore, apelin decreases the activity of the epithelial sodium channel and inhibits the actions of vasopressin on the renal medullary collecting tubule; both effects can promote a diuresis.<sup>553,554</sup>

In patients with HFrEF, serum apelin levels are decreased (and have adverse prognostic significance),<sup>555-557</sup> and apelin production in the failing heart is deficient.<sup>558</sup> However, although cardiac levels of apelin are also decreased in experimental obesity-related HFrEF,<sup>559</sup> serum levels of apelin are increased in patients with HFrEF (particularly if they have obesity),<sup>560</sup> consistent with enhanced production by the expanded adipose mass. Orally active apelin agonists have been evaluated for the treatment of patients with HFrEF,<sup>561,562</sup> but not for patients with HFrEF.

**Calcitonin peptide family (adrenomedullin and calcitonin gene-related peptide).** The calcitonin peptide family includes structurally similar polypeptides –adrenomedullin, calcitonin gene-related peptide (CGRP), and amylin—which signal through G protein-coupled receptors linked to cyclic AMP. Differential heterodimerization leads to differential agonism of the calcitonin receptor by adrenomedullin and CGRP.<sup>563,564</sup>

Circulating levels of adrenomedullin are increased in both experimental and clinical obesity (especially in states of visceral adiposity).<sup>565-572</sup> Dietary nutrient excess leads to adipocyte-specific expression of adrenomedullin, with adipocytes being the principal source of systemic adrenomedullin in obesity.<sup>565-568</sup> Adrenomedullin stimulates thermogenesis in brown fat, while inhibiting adipogenesis and inflammation, mitigating insulin resistance in white adipose tissue,<sup>573-575</sup> and suppressing hyperaldosteronemia.<sup>576</sup> Adipocytes also secrete CGRP,<sup>577</sup> and in response, CGRP exerts lipid mobilizing effects.<sup>578</sup> Serum levels of CGRP decline following bariatric surgery.<sup>579</sup>

Both adrenomedullin and CGRP act to attenuate myocardial hypertrophy, inflammation, and fibrosis in experimental models of pressure-overload HFrEF or obesity-related hypertension.<sup>580-587</sup> Achievement of supraphysiological levels of adrenomedullin and CGRP produces positive inotropic, lusitropic, and vasodilator effects in patients with heart failure.<sup>588,589</sup> Circulating levels of adrenomedullin (and its precursors) are related to increased left ventricular mass<sup>590,591</sup>, presage the onset of HFrEF in the general population<sup>592</sup>; and are increased in patients with HFrEF,<sup>593</sup> with higher levels being associated with increased pulmonary artery and left ventricular filling pressures, and worse functional capacity and prognosis.<sup>593-597</sup> Interestingly, both neprilysin inhibition

and mineralocorticoid receptor antagonism are accompanied by further increases in circulating adrenomedullin in HFpEF in the clinical setting.<sup>598,599</sup>

**Adipsin and ASP.** Adipsin (also known as complement factor D) leads to the production of ASP, a polypeptide that promotes the uptake and synthesis of triglycerides (while reducing the release of fatty acids) by adipocytes.<sup>600-602</sup> ASP exerts its metabolic effects by signaling through the C5L2 receptor,<sup>602-604</sup> which is coupled to a β-arrestin pathway that inhibits G protein-coupled receptor signal transduction.<sup>605-607</sup>

Adipsin and ASP are involved in the regulation of energy balance, acting to preserve pancreatic β-cell function and survival.<sup>608,609</sup> They promote lipid storage and adaptive adipogenesis, primarily in subcutaneous adipose tissue,<sup>603,610</sup> while promoting thermogenesis in brown fat.<sup>611</sup> Acting in concert, these effects minimize ectopic visceral fat depots. Silencing of the C5L2 receptor abrogates the benefits of adipsin and ASP, leading to adipose tissue inflammation, insulin resistance, and visceral adiposity.<sup>612-614</sup>

In states of nutrient excess, resistance to the actions of adipsin and ASP develops (caused by C5L2 down-regulation),<sup>615-617</sup> and compensatory augmentation of synthesis leads to heightened circulating levels of both adipsin and ASP in patients with central obesity.<sup>226,618-622</sup> Adipsin and ASP can exert endocrine effects as components of adiposomes.<sup>623,624</sup> Importantly, overexpression of adipsin specifically in adipocytes exerts favorable effects on experimental HFpEF or following myocardial infarction<sup>624-626</sup>—observations that directly support the adipokine hypothesis of HFpEF. This benefit appears to be mediated through an action to alleviate cardiac microvascular injury and improve mitochondrial health and fatty acid oxidation.<sup>624-626</sup> Circulating levels of adipsin and ASP are increased in patients with heart failure in proportion to the severity of systemic inflammation and diastolic filling abnormalities.<sup>627,628</sup>

**DOMAIN II ADIPOKINES THAT DIRECTLY ANTAGONIZE DOMAIN III ADIPOKINES.** Several Domain II adipokines are positioned as natural endogenous antagonists of Domain III adipokines, eg, progranulin, angiotensin converting-enzyme 2, angiotensin (1-7), interleukin (IL)-10, and angiopoietin-1 (Ang-1). IL-33 (discussed in the section on Domain III adipokines) can also be included in this category.

**Progranulin.** Progranulin acts an endogenous antagonist of Wnt-Frizzled signaling,<sup>629</sup> with a function similar to the CTRPs and SFRP5. Whereas CTRP and SFRP5 synthesis is deficient in obesity,

progranulin is secreted by hypertrophied and inflamed adipose tissue, apparently to compensate for the obesity-related suppression of CTRP3 and CTRP9.<sup>630,631</sup> Serum levels of progranulin are increased in people with obesity or the metabolic syndrome, proportional to the magnitude of systemic inflammation.<sup>632</sup> Monocytes residing in adipose tissue are a primary source of progranulin, which antagonizes the effect of inflammation to promote adiposity.<sup>633</sup>

Progranulin prevents pathological hypertrophy and remodeling following experimental myocardial and pressure overload.<sup>634,635</sup> Depletion of progranulin causes mitochondrial dysfunction, thus undermining vascular health<sup>636</sup> and accelerating age-related progression of ventricular hypertrophy.<sup>631</sup> Serum levels of progranulin are elevated in patients with heart failure (including those with HFpEF), and these levels (and changes in these levels) precede the occurrence of worsening heart failure events and parallel the clinical course of heart failure.<sup>637,638</sup>

**Angiotensin converting-enzyme 2/angiotensin (1-7) signaling.** Acting as an endogenous antagonist to the effects of angiotensin II, angiotensin converting-enzyme 2 (ACE2) not only inactivates angiotensin II, but also converts it into angiotensin(1-7) (Ang[1-7]), which signals through the Mas receptor to oppose the biological actions of angiotensin II.<sup>639</sup> Activation of ACE2-Ang(1-7)-Mas signaling promotes thermogenesis in brown fat<sup>640,641</sup> and reduces diet-induced obesity and visceral fat expansion,<sup>641-644</sup> while attenuating lipogenesis and ameliorating inflammation in white adipose tissue.<sup>640,644-649</sup>

Additionally, ACE2 and Ang(1-7) exerts a broad range of cardioprotective effects, including a reduction in oxidative stress and suppression of hypertrophic, proinflammatory, and profibrotic signaling in cardiac tissue, leading to alleviation of experimental hypertension and heart failure,<sup>650-653</sup> including HFpEF.<sup>654,655</sup> ACE2 silencing and overexpression aggravates and alleviates HFpEF, respectively.<sup>652,656,657</sup> Expressed in both adipocytes and endothelial cells, the cardioprotective effects of ACE2-Ang(1-7) may be mediated by a paracrine action of epicardial adipose tissue. Yet, an additional endocrine action seems plausible, because transgenic overexpression of Ang(1-7) in noncardiac tissue—yielding sustained increases in circulating Ang(1-7)—produces anti-inflammatory actions in adipose tissue and direct cardioprotective effects.<sup>649,658</sup>

Obesity is accompanied by increased adipocyte levels of ACE2<sup>659</sup> as well as increased circulating levels of ACE2 but decreased circulating levels of Ang (1-7),<sup>660-662</sup> raising the possibility that states of

adiposity may lead to resistance to the action of ACE2 to generate Ang(1-7). Epicardial adipocytes taken from mice or humans with obesity and HFP EF show increased expression of ACE2,<sup>639,662</sup> consistent with a compensatory response to ACE2 resistance. Yet, cytoprotective ACE2 signaling seems to be (at least partially) preserved in states of nutrient excess, because experimental global knockout of ACE2 in mice fed a high-fat diet results in epicardial adipose tissue inflammation and HFP EF.<sup>662</sup>

Clinically, circulating levels of soluble ACE2 are increased in patients with hypertrophy and diastolic filling abnormalities.<sup>663</sup> Circulating levels of both ACE2 and Ang(1-7) are increased in patients with HFP EF,<sup>664,665</sup> particularly those with a favorable prognosis.<sup>666</sup> Recombinant human ACE2 has been used to treat heart failure in clinical trials.<sup>667</sup>

**IL-10 and Ang-1.** Obesity is characterized by the activation of both inflammation and angiogenesis, and these pathways are constrained by the effect of Domain II counter-regulatory adipokines, which act as inhibitors of intracellular JAK/STAT, Wnt, and NF- $\kappa$ B signaling.<sup>668-670</sup> IL-10 is secreted by adipocytes to mute the deleterious effects of proinflammatory cytokines (TNF- $\alpha$  and IL-1 $\beta$ ).<sup>671</sup> Ang-1 is secreted by adipocytes to interact with the Tie2 receptor, and this interaction is prevented by angiopoietin-2 (ANGPT2), a Domain III adipokine.<sup>672,673</sup>

Both IL-10 and Ang-1 inhibit adipogenesis and adipocyte stress,<sup>674,675</sup> and IL-10 and Ang-1 plasmids induce a reduction in body weight.<sup>673,676</sup> Serum levels of IL-10 and adipose tissue Ang-1 levels are increased in people with obesity and visceral adiposity,<sup>677-679</sup> consistent with a compensatory mechanism.

Both IL-10 and Ang-1 exert cardioprotective effects following myocardial injury, acting to reduce maladaptive hypertrophy, cardiomyocyte inflammation, and apoptosis.<sup>680-684</sup> IL-10 ameliorates obesity-related myocardial inflammation.<sup>685</sup> Up-regulation of Ang-1 maintains the structural integrity and quiescence of blood vessels<sup>672</sup> and ameliorates the evolution of experimental nephropathy in obese mice.<sup>686,687</sup>

Clinically, increases in circulating levels of Ang-1 presage a lower risk of heart failure events following kidney injury.<sup>688</sup> Serum levels of IL-10 are increased in patients with heart failure in proportion to increased levels of proinflammatory adipokines.<sup>689-692</sup> Increases in serum levels of IL-10 (or its receptor) are associated with inflammation-associated diastolic filling abnormalities in hypertrophic cardiomyopathy,<sup>693</sup> coronary artery disease,<sup>694</sup> and HFP EF.<sup>695,696</sup> Therapeutic up-regulation

of IL-10 ameliorates the adverse cardiac remodeling seen in experimental HFP EF.<sup>684</sup>

**COMPLEXITIES IN THE CHARACTERIZATION OF CARDIOPROTECTIVE ADIPOKINES.** The observations summarized in the previous text (and in **Tables 2 and 3** and in **Figures 4 and 5**) suggest that a robust crosstalk exists between adipocytes and cardiomyocytes, which determines the health of the heart and the development of cardiomyopathy, an effect that is modulated through suppression or augmentation of the synthesis and release of adipocyte-secreted cardioprotective molecules. Obesity may cause: 1) suppression of cardioprotective Domain I adipokines, leading to myocardial hypertrophy, inflammation and fibrosis, and thus, HFP EF, caused by unopposed action of Domain III adipokines; or 2) heightened adipocyte secretion of cardioprotective Domain II adipokines that act as an endogenous (yet often inadequate) compensatory response to the loss of Domain I adipokines or as a counterbalancing response to Domain III adipokines. The adipose-cardiac crosstalk may be bidirectional, ie, the predilection of cardiac injury to progress to cardiomyopathy may be mediated through or counteracted by an intermediary mechanism that involves the activation of a biological response within adipose tissue.<sup>142,247</sup> Conversely, relief of hemodynamic stresses in patients with cardiomyopathy may cause muting of inflammatory signaling within adipose tissue.<sup>129</sup>

It is intriguing that most of Domain II adipokines appear to stimulate thermogenesis in brown fat, suggesting that there may exist a special link between brown adipose tissue and the activation of counterbalancing mechanism that mediate cardioprotection (**Figure 5**). The heart is normally bathed in and nurtured by adipose tissue with features of brown fat, and both brown adipocytes and cardiomyocytes possess exceptional quantities of mitochondria. Brown fat thermogenesis requires the uncoupling of oxidative phosphorylation from ATP synthesis in healthy mitochondria, a mechanism that necessitates enhanced signaling through SIRT1 and PGC-1 $\alpha$ ,<sup>697</sup> and these are key mediators of cardioprotective pathways.<sup>95</sup>

However, not all proteins that both heighten brown adipocyte metabolism and alleviate cardiomyocyte stress are necessarily relevant to the development of adiposity-induced HFP EF. As an example, both bone morphometric proteins (BMPs) 7 and 9 stimulate brown fat thermogenesis,<sup>698,699</sup> and both BMP7 and BMP9 can alleviate obesity.<sup>700,701</sup> Serum levels of BMP9 are reduced in people with obesity or visceral adiposity,<sup>702,703</sup> and both BMP7

and BMP9 alleviate myocardial inflammation and fibrosis, thereby mitigating the effects of pathological ventricular remodeling and diabetic cardiomyopathy.<sup>704-706</sup> However, BMP7 levels are not reduced in obesity, and BMP9 is primarily secreted by hepatocytes, not adipocytes. Therefore, neither BMP7 nor BMP9 informs the adipokine hypothesis of HFpEF. Nonetheless, BMP7 and BMP9 mimetics may have therapeutic potential in adiposity-related HFpEF.<sup>700,705,707-709</sup>

Similarly, follistatin-like 1 (FSTL-1), an extracellular glycoprotein, acts as an endogenous antagonist of BMP4.<sup>710</sup> Typically described as a myokine, FSTL-1 is also produced by developing adipocytes and has been reported to participate in brown adipose tissue thermogenesis.<sup>711,712</sup> Serum levels of FSTL-1 are increased both in people with obesity and with heart failure (including HFpEF).<sup>713,714</sup> However, there is no evidence that FSTL-1 represents a counter-regulatory mechanism that inhibits obesity. In fact, FSTL-1 may be required for the development of adiposity<sup>711</sup> and may promote adipose tissue inflammation.<sup>715</sup> Furthermore, independent of a mediating influence of adipocytes, up-regulation of FSTL-1 in the heart suppresses hypertrophy and protects against cardiac injury,<sup>716,717</sup> and conversely, cardiac-specific abrogation of FSTL-1 worsens aldosterone-mediated HFpEF.<sup>714</sup> Taken collectively, it does not appear that adipocyte-secreted FSTL-1 participates in orchestrating crosstalk between adipose tissue and the heart in patients with obesity or heart failure.

#### PART VII: DOMAIN III ADIPOKINES: MOLECULES THAT ARE SECRETED BY DYSFUNCTIONAL HYPERTROPHIED ADIPOCYTES AND EXERT DELETERIOUS EFFECTS ON THE HEART

Obesity and visceral adiposity are accompanied by adipose tissue proliferation and inflammation. As stress within the fat depots escalates, the adipose secretome shifts to proteins that promote systemic inflammation, plasma volume expansion, coronary microvascular rarefaction, and myocardial hypertrophy, inflammation, and fibrosis. Unlike the cardioprotective Domain I and II adipokines, Domain III adipokines drive the pathogenetic mechanisms that lead to HFpEF. They may be synthesized primarily by hypertrophied and proliferating adipocytes, or alternatively, by adipose-resident inflammatory, stromal, or mesenchymal stem cells, which are stimulated by adipocyte-mediated paracrine signaling (triggered by nutrient excess). These proteins act by up-regulation of the PI3K-Akt-mTOR-

PPAR $\gamma$  pathway, by promoting canonical and noncanonical Wnt signaling, and by activation of JAK/STAT and TGF $\beta$ -Smad signaling.

The Domain III adipokines, summarized in **Table 4** and **Figure 6**, are presented as 5 functional clusters: 1) major adipocyte-specific secreted proteins that act as endocrine mediators of adiposity-driven cardiomyopathy; 2) adipose-secreted growth factors and their binding proteins; 3) adipose-derived matrix-lular glycoproteins and other extracellular matrix glycoproteins; 4) adipose-secreted chemokines and angiopoietins; and 5) soluble endogenous antagonists and other proinflammatory proteins (including canonical proinflammatory cytokines).

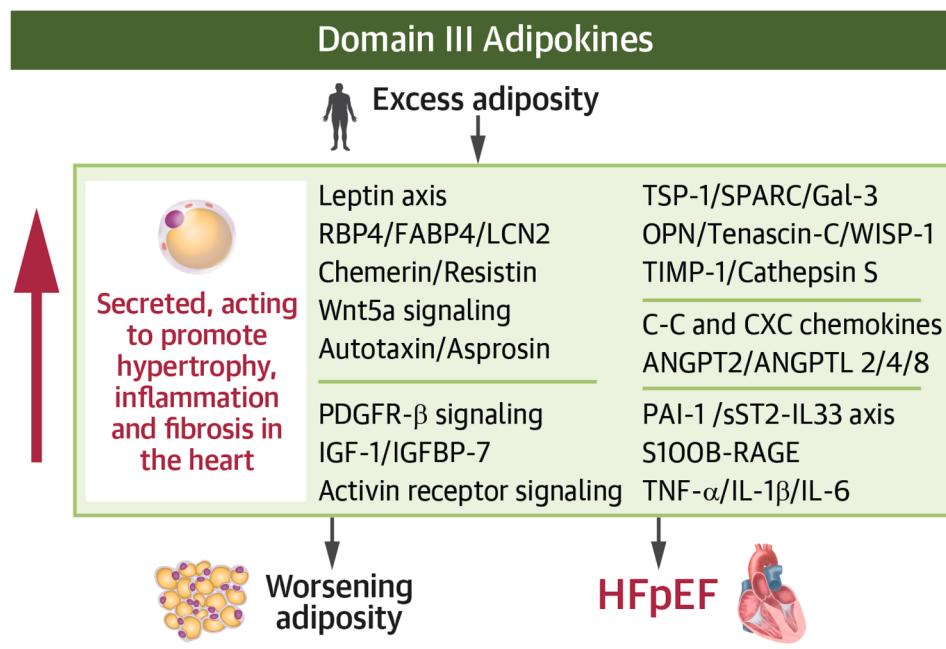
#### MAJOR ADIPOCYTE-SECRETED PROTEINS ACTING AS MEDIATORS OF ADIPOSITY-DRIVEN HFpEF.

These proteins are secreted primarily (if not exclusively) by adipocytes, and such secretion is the principal determinant of their circulating levels, with serum levels often in the high nanomolar or even micromolar range. These adipokines signal through the JAK/STAT pathway (eg, leptin, lipocalins), through G protein-coupled receptors (eg, chemerin, autotaxin, and asprosin), or through the Wnt/JNK pathway (eg, extracellular Wnt5a).

#### Leptin and the leptin-angiotensin II-aldosterone-neprilysin axis.

The most studied Domain III adipokine is leptin, a master regulator of energy balance, which signals primarily through the JAK2/STAT3 pathway.<sup>718</sup> Serum levels of leptin are primarily driven by secretion from adipocytes and are closely correlated with percent body fat and epicardial fat mass.<sup>718,719</sup> The short-term actions of leptin in healthy individuals to promote satiety, lower blood pressure, and shield cardiomyocytes are transformed into maladaptive responses during chronic hyperleptinemia, as occurs in obesity.<sup>20,720,721</sup>

The secretion of leptin by adipocytes is a major driver of neurohormonal activation in obesity. Leptin stimulates adrenergic- and angiotensin-dependent mechanisms (including augmentation of renal sympathetic nerve traffic).<sup>722,723</sup> This adipokine (rather than angiotensin II) may be the major cause of aldosterone overproduction in obesity.<sup>724,725</sup> Experimentally, leptin directly augments sodium retention mediated by an action at multiple renal tubular sites.<sup>20,726</sup> Additionally, leptin triggers and potentiates systemic inflammatory responses<sup>727,728</sup> and contributes to ventricular hypertrophy,<sup>729-731</sup> impaired relaxation,<sup>732</sup> endothelial dysfunction and myocardial fibrosis.<sup>733-735</sup> Changes in left ventricular mass are correlated with changes in leptin after bariatric surgery.<sup>731</sup> The secretion of leptin from

**FIGURE 6** Domain III Adipokines That Drive the Central Mechanisms Underlying the Development of HFpEF

Domain III adipokines represent the key pathological mediators of the adipose-heart axis in heart failure with preserved ejection fraction (HFpEF), acting to promote cardiac hypertrophy, inflammation, and fibrosis, as well as pulmonary and systemic hypertension. They are presented as 5 functional clusters: 1) major adipocyte-specific secreted proteins acting as endocrine mediators of adiposity-driven cardiomyopathy; 2) adipose-secreted growth factors and binding proteins; 3) adipocyte matrix-cellular glycoproteins and other extracellular matrix glycoproteins; 4) adipocyte-secreted chemokines and angiopoietins; and 5) soluble endogenous antagonists and other proinflammatory proteins (including canonical proinflammatory cytokines). Unopposed signaling through Domain III adipokines further exacerbates adiposity and promotes the development of HFpEF. ANGPT2 = angiopoietin-2; ANPTL = angiopoietin-like protein; FABP4 = fatty acid binding protein 4; Gal-3 = galectin 3; IGF-1 = insulin-like growth factor-1; IGFBP-7 = insulin-like growth factor binding protein-7; IL = interleukin; LCN2 = lipocalin 2; OPN = osteopontin; PAI-1 = plasminogen activator inhibitor; PDGFR $\beta$  = platelet-derived growth factor receptor- $\beta$ ; RAGE = receptor for advanced glycation products; RBP4 = retinol binding protein 4; SPARC = secreted protein acidic and rich in cysteine; sST2 = soluble suppression of tumorigenicity 2; TIMP-1 = tissue inhibitor of proteinase-1; TNF- $\alpha$  = tumor necrosis factor- $\alpha$ ; TSP-1 = thrombospondin-1; WISP-1 = Wnt1-induced secreted protein-1.

epicardial adipose tissue may be particularly likely to cause myocardial injury.<sup>736</sup>

Circulating levels of leptin presage the development of heart failure (particularly HFpEF) in elderly individuals in the general community.<sup>737,738</sup> In patients with established heart failure, levels of leptin are particularly identified with HFpEF (rather than HFrEF),<sup>67,739</sup> and they fully account for the influence of obesity to increase the risk of heart failure.<sup>740</sup> The magnitude of hyperleptinemia is correlated with symptom severity, exercise intolerance, clinical instability, and an adverse prognosis.<sup>14,741,742</sup>

Interestingly, many of the deleterious actions of leptin may be mediated (in part) by its effects to promote signaling through angiotensin II, aldosterone, and neprilysin, as components of the leptin-angiotensin II-aldosterone-neprilysin axis (Box 8).<sup>20</sup> The action of leptin to promote sodium retention and myocardial fibrosis may be related to the enhanced action of aldosterone.<sup>38,743-745</sup> Increased renal

sympathetic nerve traffic caused by hyperleptinemia causes the release of neprilysin by the kidneys,<sup>743</sup> which (by degrading natriuretic peptides) can lead to additional cardiac hypertrophy and fibrosis.<sup>744,745</sup>

Independent of leptin, obesity leads to increased synthesis of angiotensin II, aldosterone, and neprilysin by adipocytes,<sup>39,41,746,747</sup> and this heightened activity contributes to further adipogenesis and worsening adiposity<sup>748-750</sup> and the development of HFpEF.<sup>6,64,69,751</sup> Importantly, increased adipocyte synthesis of angiotensin II promotes adipose tissue inflammation and changes in the adipocyte secretome, which can adversely influence adjoining cardiovascular structures.<sup>752-755</sup> Transplantation of perivascular adipose tissue in which angiotensin II signaling has been pharmacologically suppressed prevents vascular injury in recipient animals.<sup>752</sup> Adipocyte-specific angiotensinogen gene silencing is sufficient to mute adipose tissue inflammation,<sup>756</sup> and adipocyte-specific up-regulation of the

**TABLE 4** Domain III Adipokines

Protein or Signaling Axis	Adipocyte Source and Cellular Signaling	Biological Effects Relevant to Adipose Tissue and the Heart	Changes in Obesity, Visceral Adiposity, and Heart Failure
<b>Major Adipocyte-Specific and Adipocyte-Secreted Adipokines Driving Adiposity-Related Cardiomyopathy</b>			
Leptin-angiotensin II-alosterone neprilysin axis	Adipocyte secretion of leptin, angiotensin, aldosterone, and neprilysin. Mutual amplification of synthesis and actions, exerting endocrine effects.	Interplay promotes adipogenesis, systemic inflammation, neurohormonal activation, myocardial hypertrophy, and fibrosis.	Increased serum levels in obesity and heart failure. Interactions mediate obesity- and adiposity-related HFpEF.
<b>Growth Factors and Their Binding Proteins</b>			
Platelet-derived growth factor receptor (PDGFR)-β signaling.	Expansion of white adipose tissue through proliferation of PDGFRβ+ preadipocytes, leading to adipose tissue dysfunction.	Adipocyte-specific overexpression of PDGF-D (signaling through PDGFRβ) leads to PDGF-D-mediated cardiac fibrosis, exacerbated by obesity.	Serum and adipose tissue levels of PDGFRβ ligands are increased in obesity and adiposity. Up-regulated PDGFRβ signaling in HFpEF.
TGF-β superfamily—activin type I and type II signaling (GDF-3/ALK7 and activin A).	Adipocyte expression of GDF-3, ALK7, and activin A is enhanced by nutrient excess and drives obesity.	Activin A mediates epicardial adipose tissue cardiotoxicity. GDF3/ALK7 and activin A promote cardiac fibrosis. Activin type II receptor antagonism alleviates experimental HFpEF.	Serum levels of activin A are increased in obesity and HFpEF. Increased serum levels of GDF-3 in adverse cardiac remodeling.
Insulin-like growth factor-1 (IGF-1) receptor signaling.	Unlike other insulin-like growth factor binding proteins, IGFBP7 stimulates the IGF-1 receptor, with deleterious effects.	Signaling through IGFBP7 or IGF-1R leads to cardiac hypertrophy, fibrosis, and senescence, especially in the setting of aging and obesity.	Obesity increases IGF-1R expression and serum levels of IGFBP7. Serum IGFBP7 levels are linked to HFpEF.
<b>Matricellular Glycoproteins and Extracellular Matrix Modulators</b>			
Thrombospondin-1	Adipocyte secretion, also as part of extracellular vesicles, signaling through Wnt/β-catenin.	Thrombospondin-1 (through CD47) leads to cardiac hypertrophy, fibrosis, pulmonary hypertension, and HFpEF.	Increased serum levels in obesity and heart failure. Circulating marker of cardiac hypertrophy.
Secreted protein acidic and rich in cysteine (SPARC)	Adipocyte secretion, also within extracellular vesicles, signaling through Wnt/β-catenin.	SPARC promotes adipose tissue inflammation and cardiac fibrosis, the latter effect mediated by extracardiac source.	Increased serum levels in obesity and heart failure and related to diastolic filling abnormalities.

*Continued on the next page*

mineralocorticoid receptor leads to vascular dysfunction.<sup>757</sup> The suppression of natriuretic peptides signaling in patients with obesity and HFpEF<sup>42,758,759</sup> can further promote aldosterone synthesis, impair renal sodium excretion and trigger myocardial inflammation and fibrosis, thus potentiating the actions of leptin.<sup>20,760</sup>

Sustained hyperleptinemia or hyperaldosteronemia is sufficient to recapitulate HFpEF experimentally.<sup>751,761</sup> The coordinated activation of

leptin, angiotensin II, aldosterone, and neprilysin in obesity—together with their interplay to cause mutual amplification of their synthesis and actions—plays a seminal role in mediating the effect of obesity to cause HFpEF. Current drugs for HFpEF suppress the secretion or counter the actions of leptin and interfere with the actions of angiotensin II, aldosterone, and neprilysin.<sup>762</sup>

**Lipocalins (retinol binding protein 4, fatty acid binding protein 4, lipocalin 2, and chitinase-3**

**TABLE 4** Continued

Protein or Signaling Axis	Adipocyte Source and Cellular Signaling	Biological Effects Relevant to Adipose Tissue and the Heart	Changes in Obesity, Visceral Adiposity, and Heart Failure
Matricellular lectins—extracellular galectin 3	Adipocytes secrete galectin-3 and are a primary source of circulating levels, thus enabling fibrosis at distant sites.	Mediates obesity-related cardiac lipotoxicity, fibrosis, and microvascular dysfunction. Adipose tissue activation leads to galectin-3 mediated stimulation of cardiac fibroblasts.	Increased serum levels in obesity, adiposity, and heart failure, especially HFpEF, with prognostic significance.
Osteopontin, tenascin-C, and Wnt1-induced secreted protein-1 (WISP1/CCN4)	Obesity leads to adipocyte secretion into extracellular matrix, signaling through Wnt/β-catenin.	Act to promote adipose tissue inflammation and cardiac hypertrophy and fibrosis, and cardiomyopathy.	Increased serum levels in obesity, adiposity, and heart failure, particularly HFpEF.
Tissue inhibitor of metalloproteinase 1 (TIMP1)	Obesity is accompanied by heightened adipocyte expression of TIMP1.	TIMP1 promotes maladaptive cardiac fibrosis. Adipocyte exosomes can stimulate TIMP1 in distant fibroblasts.	Increased serum levels in obesity, adiposity, and HFpEF, with prognostic significance.
Cathepsin S–protease-activated receptor 2 (PAR2) signaling	Cysteine protease, secreted by adipocytes and adipose tissue stromal cells, acting in paracrine and endocrine manner.	Signaling through PAR2, cathepsin S promotes adipogenesis, cardiac hypertrophy, and cardiomyopathy.	Increased serum levels in obesity and in heart failure, particularly HFpEF and in cardiac hypertrophy.
<i>Chemokines and Angiogenesis Proteins</i>			
C-C chemokine ligand 2 (CCL2) and C-C chemokine ligand 5 (CCL5, also known as RANTES)	Adipocytes secrete CCL2 and CCL5, which can (through paracrine or endocrine effects) promote inflammation in the heart.	CCR2 and CCR5 antagonists alleviate adipose inflammation and obesity. CCL2 antibodies prevent cardiac fibrosis and diastolic filling abnormalities. Extracardiac CCR2 suppression mitigates experimental cardiomyopathy.	Increased serum levels of both CCL2 and CCL5 in obesity, visceral adiposity, and heart failure. Decreased cardiac expression of CCL2 in the failing human heart.
CXC chemokine ligand 8 (CXCL8) and CXC chemokine 12 (CXCL12)	Adipocytes secrete CXCL8 and CXCL12, which (by signaling through CXCR2 and CXCR4, respectively) promote local and systemic inflammatory responses.	Signaling through CXCL8/CXCR2 and CXCL12/CXCR4 is implicated in adverse remodeling and fibrosis in models of HFpEF, effects muted by CXCR2 and CXCR4 antagonism.	Increased serum levels of both CXCL8 and CXCL12 in obesity, adiposity and heart failure, especially HFpEF.
Angiopoietin-2 (ANGPT2)	Normally secreted by endothelial cells and adipocytes to promote vascular stability and metabolic homeostasis.	Inflammation causes ANGPT2 to act as Tie2 receptor antagonist, thereby promoting vascular fragility, endothelial apoptosis, and microvascular rarefaction.	Serum levels are increased in obesity and heart failure, especially in HFpEF.
Angiopoietin-like protein-2, -4, and -8 (ANGPTL2, ANGPTL4 and ANGPTL8)	Sustained heightened secretion of ANGPTL2, ANGPTL4 and ANGPTL8 by adipocytes promotes local and systemic inflammation.	Adipocyte-specific genetic ablation of ANGPTL4 prevents vascular injury. ANGPTL2 has deleterious effects on cardiomyocytes and activates fibroblasts in diet-induced HFpEF.	Serum levels of ANGPTL2, ANGPTL4 and ANGPTL8 are increased in obesity. Serum ANGPTL2 and ANGPTL4 are increased in HFpEF.
<i>Soluble Endogenous Antagonists and Other Proinflammatory Proteins</i>			
Plasminogen activator inhibitor (PAI-1)	Obesity causes marked increase in PAI-1 secretion from adipocytes, promoting further obesity.	Increased circulating PAI-1 leads to cardiac fibrosis. Transplantation of adipose tissue lacking PAI-1 attenuates cardiac metabolic abnormalities in recipient mice fed a high-fat diet.	Increased serum levels in obesity, adiposity, and HFpEF, especially with their coexistence, with prognostic significance.
Soluble suppression of tumorigenicity 2 (sST2) and the interleukin-33/ST2 axis	Adipose tissue secretes sST2. sST2 acts as a decoy to prevent IL-33 from exerting cardioprotective and anti-inflammatory effects.	Inflamed adipose tissue is the source of circulating sST2. sST2 promotes fat inflammation and augments vascular hyperplasia and myocardial fibrosis.	Increased serum levels of sST2 in obesity, adiposity, and HFpEF, with prognostic significance, driven by extracardiac source.
Calgranulin (S100B)-RAGE (receptor for advanced glycation endproduct) signaling	Adipocytes secrete S100B in proportion to fat mass. Obesity up-regulates RAGE cell-surface expression on cardiomyocytes.	S100B-RAGE signaling promotes cardiomyocyte apoptosis, myocardial hypertrophy and fibrosis, and cardiomyopathy, alleviated by RAGE silencing.	Increased in S100B and RAGE obesity and heart failure. The decoy function of soluble RAGE decreased in obesity. RAGE may mediate cardiomyopathy.
Canonical proinflammatory cytokines (tumor necrosis factor-α [TNF-α], interleukin-1β [IL-1β], interleukin 6 [IL-6])	Adipose tissue production of TNF-α, IL-1β, and IL-6 in obesity is likely related to production by infiltrating inflammatory cells.	Studies of the effect of inhibition of TNF-α, IL-1β, and IL-6 on the evolution of experimental HFpEF have produced inconsistent results.	Increased serum levels in obesity and HFpEF, but also increases in levels of receptor decoys and endogenous antagonists.

HFpEF = heart failure with preserved ejection fraction.

**BOX 8. Domain III: Leptin-Angiotensin II-Aldosterone-Neprilysin Axis**

1. In obesity, adipose tissue secretes heightened quantities of leptin, angiotensin II, aldosterone, and neprilysin, with the magnitude of hyperleptinemia being directly proportional to the increase in fat mass. The secretion of leptin by adipocytes is as a major driver of renal sympathetic nerve traffic angiotensin II and aldosterone production, and it causes sodium retention in patients with obesity or visceral adiposity.
2. The mutually reinforcing interplay of leptin, angiotensin II, aldosterone, and neprilysin promotes systemic inflammatory responses, plasma volume expansion and redistribution, and ventricular hypertrophy and myocardial fibrosis. Sustained hyperleptinemia or hyperaldosteronemia is sufficient to recapitulate HFpEF experimentally.
3. Circulating levels of leptin precede and predict the development of heart failure (particularly HFpEF, but not HFrEF) in elderly individuals, and they fully account for the influence of obesity to increase the risk of heart failure. The magnitude of hyperleptinemia is correlated with symptom severity and exercise intolerance and is associated with an adverse prognosis.
4. Adipocyte-specific up-regulation of the mineralocorticoid receptor leads to vascular dysfunction. Transplantation of perivascular adipose tissue in which angiotensin II signaling has been suppressed prevents vascular injury in recipient animals.
5. Bariatric surgery and GLP-1 receptor agonism reduce circulating levels of leptin, angiotensin II, aldosterone, and/or neprilysin. Current drugs for HFpEF suppress the secretion or counter the actions of leptin and interfere with the actions of angiotensin II, aldosterone, and neprilysin.

**like-1).** Lipocalins are glycoproteins with an anti-parallel beta-barrel structure, of which 3 act as transporters of lipophilic molecules—retinol binding protein 4 (RBP4), fatty acid binding protein 4 (FABP4), and lipocalin 2 (LCN2) (also known as neutrophil gelatinase-associated lipocalin [NGAL]). These adipokines comprise a substantial proportion of the total production of proteins by adipocytes<sup>763-765</sup> (with RBP4 circulating in the micromolar range), exerting an important influence on lipid metabolism, insulin sensitivity, and cardiac and vascular health (Box 9).

During nutrient excess, adipocytes secrete RBP4, FABP4, and LCN2 into the bloodstream,<sup>765-770</sup> and LCN2 further facilitates the release of RBP4 and enhances the action of retinoic acid to promote thermogenesis in brown fat.<sup>771,772</sup> Through an endocrine

**BOX 9. Domain III: Major Non-Leptin Adipocyte-Secretory Mediators of HFpEF**

1. In obesity and visceral adiposity, adipocytes drive the secretion of a suite of prohypertrophic, proinflammatory, and profibrotic adipokines, including the lipocalins (RBP4, FABP4, and LCN2), chemerin, resistin, Wnt5a, autotaxin, and asprosin.
2. These Domain III adipokines promote maladaptive cardiac remodeling and fibrosis, and they also impair vascular function, augment arterial stiffness, and enhance the evolution of systemic and pulmonary hypertension. Their experimental suppression ameliorates HFpEF.
3. Circulating levels of these Domain III adipokines are increased in people with obesity and visceral adiposity, and they are associated with left ventricular hypertrophy and diastolic filling abnormalities in the general population and predict the subsequent development of HFpEF. Serum levels are increased in patients with HFpEF, identifying patients with more severe disease and a poor prognosis.
4. Adipocyte secretion plays the central role in mediating the cardiac and vascular injury produced by these adipokines. Adipocyte-specific secretion of chemerin promotes vascular injury. Adipocyte-specific silencing of autotaxin blocks the deleterious effects of obesity on the heart, preventing the development of cardiac hypertrophy, cardiomyopathy and heart. Genetic silencing of resistin—specifically in adipose tissue—reduces circulating levels of resistin and acts to preserve cardiac function during experimental pressure overload, despite having no influence on the cardiac expression of resistin. Mice with selective deletion of LCN2 in adipose tissue—but not those with selective deletion of LCN2 in the kidney—are protected from aldosterone-induced renal injury.
5. Bariatric surgery, GLP-1 receptor agonists, and SGLT2 inhibitors reduce circulating levels of RBP4, FABP4, LCN2, chemerin, resistin, Wnt5a, autotaxin, and/or asprosin.

action (often within extracellular microvesicles<sup>773</sup>), the secretion of RBP4, FABP4, and LCN2 by adipocytes promotes lipolysis,<sup>767,768,774</sup> insulin resistance,<sup>766,767,770,775</sup> macrophage activation and adipose tissue inflammation,<sup>776-778</sup> and end-organ steatosis.<sup>779-781</sup> Lipocalins signal through the JAK/STAT pathway, and RBP4 primes the NLRP3 inflammasome, allowing its activation by proinflammatory interleukins.<sup>782</sup> FABP4, RBP4, and LCN2 are also linked to PPAR $\gamma$  signaling.<sup>766,783,784</sup> Obesity (particularly visceral adiposity) is accompanied by increased circulating levels of RBP4, FABP4, and

LCN2,<sup>785-791</sup> which drive end-organ steatosis, inflammation, and fibrosis.<sup>779-781,792,793</sup>

Acting in concert, RBP4, FABP4, and LCN2 exert deleterious effects on the heart by impairing cardiac contractility and enhancing myocardial injury, maladaptive remodeling and fibrosis.<sup>794-800</sup> The lipocalins also increase blood pressure, promote vascular smooth muscle cell proliferation, impair endothelial function, and enhance arterial stiffness.<sup>801-807</sup> Increased circulating levels of RBP4, FABP4, and LCN2 are associated with left ventricular hypertrophy and diastolic filling abnormalities in the general population or in people with obesity,<sup>795,808-811</sup> and their serum levels are increased in patients with heart failure (including HFpEF), where they presage a poor prognosis.<sup>795,812-816</sup> Mendelian randomization studies have linked RBP4 to an increased risk of heart failure.<sup>817</sup>

Importantly, mice with selective deletion of LCN2 in adipose tissue—but not those with selective deletion of LCN2 in the kidney—are protected from aldosterone-induced renal injury.<sup>818</sup> This finding is consistent with evidence that this adipocyte-secreted molecule with deleterious endocrine effects is an important mineralocorticoid receptor target.<sup>818-820</sup> Conversely, pressure overload-induced cardiac hypertrophy leads to increased expression of RBP4 in adipocytes (but not in cardiomyocytes),<sup>796</sup> and serum levels of RBP4 in patients with advanced heart failure decline following left ventricular assist device implantation.<sup>821</sup> These observations indicate mutual lipocalin-mediated endocrine crosstalk between adipocytes and cardiomyocytes in the pathogenesis of cardiac stress.

Chitinase-3 like-1 (known as YKL-40) also has an antiparallel beta-barrel structure (but without transporter activity), but it is characterized as a proinflammatory glycoprotein that modulates the remodeling of the extracellular matrix.<sup>822</sup> Secreted from adipocytes in visceral fat during states of inflammation,<sup>823</sup> YKL-40 acts to inhibit collagen degradation,<sup>824</sup> thus promoting fibrosis within adipose tissue and at adjacent and distant sites.<sup>825</sup> Obesity is accompanied by increased expression of YKL-40 in adipocytes, leading to an increase in serum levels,<sup>823</sup> which decline following bariatric surgery.<sup>823,826</sup> The expansion of epicardial adipose tissue in states of excess adiposity leads to the secretion of YKL-40 and to fibrosis in the underlying myocardium.<sup>825</sup>

YKL-40 suppression mitigates myocardial inflammation and remodeling following experimental myocardial infarction<sup>827</sup>; but unloading of the failing heart does not lower the expression of YKL-40.<sup>828</sup>

Clinically, heightened circulating levels of YKL-40 are associated with an elevated risk of incident heart failure,<sup>829</sup> and they are indicative of myocardial involvement in systemic inflammatory states.<sup>830</sup> Serum levels of YKL-40 are increased in patients with heart failure and have prognostic significance,<sup>831-833</sup> and elevated levels are also associated with clinical pressure-overload states and HFpEF, especially in those with cardiac hypertrophy, diastolic filling abnormalities, and poor outcomes.<sup>834-837</sup> Treatment with sacubitril/valsartan and tirzepatide lowers serum levels of YKL-40 in patients with heart failure and diabetes, respectively.<sup>838,839</sup>

**Chemerin.** Originally described as the product of a retinoid-responsive gene known as retinoic acid receptor responder 2 (Rarres2),<sup>840,841</sup> chemerin is secreted during adipocyte differentiation.<sup>841,842</sup> Activated by PPAR $\gamma$  and signaling through G protein-coupled receptors, chemerin directs bone marrow mesenchymal stem cells towards adipogenesis.<sup>843</sup> Experimental sustained increases in chemerin promote visceral adiposity and glucose intolerance,<sup>844-847</sup> and diet-induced obesity is accompanied by increased circulating levels of chemerin.<sup>840,846</sup> Chemerin enhances the recruitment of macrophages to adipose tissue to promote inflammation.<sup>848,849</sup>

Clinically, Rarres2 mRNA expression in visceral adipose tissue is increased in obese individuals,<sup>850</sup> and chemerin expression in visceral (not subcutaneous) fat contributes to the elevated systemic levels of chemerin.<sup>851</sup> Enhanced adipose tissue processing of chemerin in obesity results in heightened circulating levels of bioactive chemerin.<sup>852</sup>

Adipocyte secretion of chemerin exerts important cardiovascular effects. Chemerin promotes hypertension by mediating vasoconstriction and enhancing vascular smooth muscle cell proliferation.<sup>853,854</sup> These effects can be mediated by the secretion of chemerin from perivascular fat.<sup>855</sup> Additionally, chemerin triggers endothelial and myocardial inflammation,<sup>852,856</sup> cardiomyocyte apoptosis,<sup>856,857</sup> and the migration of cardiac fibroblasts,<sup>858</sup> potentially related to the secretion of chemerin by epicardial adipocytes.<sup>859</sup> Chemerin may mediate the adverse cardiac effects of mineralocorticoid receptor signaling<sup>860</sup> and contribute to pulmonary hypertension.<sup>861</sup> Importantly, adipocyte-specific secretion of chemerin adversely affects vascular function.<sup>862</sup>

Increased serum levels of chemerin presage the development of heart failure<sup>863,864</sup> and are correlated with both left ventricular hypertrophy and diastolic filling abnormalities.<sup>864,865</sup> Serum chemerin levels are also increased in patients with established heart

failure (including HFpEF), where elevated levels identify those with impaired functional capacity and a poor prognosis.<sup>815,866-869</sup> Metabolic reprogramming by SGLT2 inhibition can attenuate adipocyte chemerin signaling and organ steatosis, despite minimal weight loss.<sup>870,871</sup> Chemerin receptor antagonism ameliorates the adverse end-organ consequences of metabolic disorders.<sup>872,873</sup>

**Resistin.** Resistin is a cysteine-rich polypeptide that is released by adipocytes and by adipose tissue resident mesenchymal stem cells and inflammatory cells.<sup>874-876</sup> Adipogenesis is accompanied by increased synthesis of resistin by human adipocytes, and the secretion of resistin by adipose tissue attenuates its responsiveness to insulin and promotes regional inflammation.<sup>877-879</sup>

Obesity (especially central adiposity) is accompanied by increased serum levels of resistin and augmented resistin expression in abdominal adipose tissue.<sup>880-882</sup> Heightened circulating resistin levels presage the development of heart failure,<sup>592,883-886</sup> are associated with left ventricular hypertrophy and diastolic filling abnormalities,<sup>887-889</sup> and identify patients with HFpEF.<sup>890</sup> Patients with heart failure have elevated levels of resistin, especially if they have impaired exercise tolerance, limited functional capacity, and an unfavorable prognosis.<sup>14,741,891,892</sup>

Systemic administration or cardiac-specific up-regulation of resistin causes deleterious cardiovascular effects, including proliferation of vascular smooth muscle and enhanced endothelial cell inflammation and oxidative stress,<sup>893-895</sup> impaired function of cardiomyocytes,<sup>896,897</sup> and adverse remodeling and fibrosis.<sup>897-900</sup> Conversely and importantly, genetic silencing of resistin—specifically in adipose tissue—reduces circulating levels of resistin and acts to preserve cardiac function during experimental pressure overload, despite having no influence on the cardiac expression of resistin<sup>901</sup>—exemplifying adipokine-mediated dissemination of adipose tissue biology to the heart.

**Wnt5a-Frizzled-5 receptor signaling.** The wingless-type integration site (Wnt) protein family typically signals through  $\beta$ -catenin, but unlike other Wnt proteins, Wnt5a utilizes a noncanonical mechanism to activate JNK and other downstream pathways.<sup>902</sup> Wnt5a plays an essential role in embryonic cardiac morphogenesis, and its expression subsides postnatally.<sup>902-904</sup> However, in patients with obesity, the synthesis and secretion of Wnt5a by adipocytes (particularly within visceral fat) is heightened.<sup>905,906</sup> Extracellular Wnt5a enhances adipocyte differentiation and augments lipid accumulation,<sup>674,907-909</sup> and it promotes adipose tissue inflammation

independent of fat mass expansion.<sup>10</sup> SFRP5 acts as a decoy receptor for extracellular Wnt5a, thus preventing its interactions with the Wnt5a receptor (Frizzled-5).<sup>164,905,910</sup>

Adipocytes are the primary source for circulating Wnt5a,<sup>911</sup> and thus, serum Wnt5a levels are increased in patients with obesity, especially those with visceral adiposity and systemic inflammation.<sup>906,911-913</sup> Circulating levels of WNT5a exert important endocrine effects, especially in patients with obesity, in whom levels of the SFRP5 decoy are simultaneously suppressed.<sup>910</sup> An increase in the ratio of Wnt5a to SFRP5 in the bloodstream or adipose tissue in patients with obesity is accompanied by increased oxidative stress within the arterial wall and enhanced vascular calcification,<sup>914</sup> and the secretion of Wnt5a from epicardial adipocytes is associated with the presence of coronary artery disease.<sup>915</sup> Furthermore, adipocyte-derived extracellular vesicles can direct mesenchymal stem cells toward adipogenic differentiation (through Wnt5a) and can promote the expression of Wnt5a in cardiac fibroblasts.<sup>916,917</sup>

Extracellular Wnt5a signals through fibroblast Frizzled-5 receptors to promote myocardial fibrosis during pressure overload,<sup>918</sup> and following hemodynamic stress, extracellular Wnt5a enhances cardiomyocyte Wnt5a expression, pathological hypertrophy and heart failure.<sup>919-921</sup> Interference with extracellular Wnt5a suppresses the myocardial expression of Wnt5a in the failing heart,<sup>922</sup> and pharmacological Wnt5a inhibition mitigates the cardiac hypertrophy and fibrosis and alleviates experimental HFpEF.<sup>923</sup>

Serum and cardiac levels of Wnt5a are increased in experimental and clinical heart failure,<sup>922,924,925</sup> being associated with pulmonary hypertension and an adverse prognosis.<sup>926,927</sup> Therapeutic abrogation of Wnt5a signaling—by inhibition of Wnt5a secretion or by Frizzled-5 antagonism—prevents the development of experimental postinfarction heart failure and HFpEF.<sup>922,928,929</sup>

**Autotaxin.** Autotaxin (known as ectonucleotide pyrophosphatase/phosphodiesterase 2) is a secreted lysophospholipase D, which acts extracellularly to catalyze the formation of lysophosphatidic acid,<sup>930</sup> a bioactive lipid that (via endocrine signaling) exerts effects on diverse organs, particularly the heart (Box 9).

Autotaxin is synthesized during adipogenesis and activates the proliferation of white adipose tissue.<sup>930,931</sup> Adipocytes are the principal source of circulating autotaxin,<sup>932</sup> and diet-induced obesity induces the expression of autotaxin by adipocytes.<sup>933,934</sup> Accordingly, serum levels of autotaxin

and lysophosphatidic acid are increased in experimental and clinical obesity<sup>934-939</sup> and lead to further obesity.<sup>940,941</sup>

Once in the bloodstream, lysophosphatidic acid signals through G protein-coupled receptors in the heart (which are up-regulated in obesity) to promote maladaptive myocardial hypertrophy, cardiac fibrosis, and cardiomyopathy through up-regulation of Akt-mTOR and PPAR $\gamma$  signaling and suppression of autophagy.<sup>931,942,943</sup> Inhibition of autotaxin mitigates postinfarction ventricular remodeling.<sup>944</sup> Serum levels of autotaxin are increased in patients with cardiac hypertrophy, left ventricular dysfunction, or with heart failure and have prognostic significance.<sup>938,945,946</sup>

Importantly, adipocyte-specific silencing of autotaxin blocks the deleterious effects of obesity on the heart, preventing the development of cardiac hypertrophy, cardiomyopathy, and heart failure, thus exemplifying the central premise of adipokine hypothesis.<sup>943</sup> Adipocyte-derived autotaxin has been proposed as one of the key mediators of obesity-driven cardiomyopathy.<sup>938,943</sup> Inhibition of the interaction of lysophosphatidic acid and its receptors in the heart alleviates cardiac hypertrophy and heart failure.<sup>946,947</sup> Ziritaxestat, an autotoxin inhibitor, has been developed for the treatment of pulmonary fibrosis.<sup>948</sup>

**Asprosin.** Directly transcribed from the fibrillin gene, asprosin typically acts as a fasting-induced glucogenic polypeptide.<sup>949-951</sup> During nutrient deprivation, asprosin is released by adipocytes to maintain blood glucose, acting in an endocrine manner to increase appetite, promote the hepatic release of glucose, and impair glucose uptake in skeletal muscle.<sup>950-952</sup> However, during nutrient excess, sustained synthesis of asprosin by white adipose tissue promotes lipid deposition and contributes to adipose tissue and skeletal muscle inflammation.<sup>952-954</sup> Adipocyte expression and serum levels of asprosin are increased in patients with obesity,<sup>955-957</sup> particularly those with marked visceral adiposity,<sup>956-959</sup> and these levels decline with weight loss produced by incretin-based drugs and gastric bypass surgery.<sup>960,961</sup> Experimental asprosin gene silencing and the administration of asprosin antibodies alleviate obesity and the metabolic syndrome.<sup>962,963</sup>

Asprosin has been proposed as a key mediator of obesity-related cardiovascular disease<sup>964</sup> by its actions to promote the development of the vascular endothelial dysfunction that characterizes obesity and HFpEF. Asprosin enhances vascular smooth muscle oxidative stress, inflammation, and

**BOX 10. Domain III: Adipose Tissue Secretion of Growth Factors, Matricellular Proteins and Extracellular Matrix Glycoproteins**

1. In states of excess adiposity, adipose tissue secretes heightened quantities of several growth factors—platelet-derived growth factors (especially PDGF-D), transforming growth factor superfamily members (especially activin A), and insulin-like growth factors and their binding proteins (especially IGFBP7)—as well as matricellular proteins (eg, thrombospondin-1, SPARC, and galectin-3) and canonical extracellular matrix glycoproteins (eg, TIMP1 and cathepsin S).
2. These Domain III adipokines play a major role in vascular dysfunction and cardiac fibrosis, often leading to pulmonary hypertension. Both IGF-1 and IGF-1 receptors are up-regulated in the aging heart and predispose to cardiac injury. IGFBP7 (which prolongs the action of IGF-1) and activin A promote cardiac senescence. Thrombospondin-1 enhances vasoconstrictor responses and leads to hypertrophy, fibrosis, and microvascular rarefaction in experimental HFpEF.
3. Adipocyte-specific overexpression of PDGF-D leads to PDGF-D-mediated cardiac fibrosis through an endocrine mechanism. Activin A appears to mediate the adverse paracrine effects of expanded and inflamed epicardial adipose tissue on the adjoining myocardium. Galectin-3 acts as an intermediary in obesity-related cardiac lipotoxicity, myocardial fibrosis, and microvascular endothelial dysfunction, the hallmarks of HFpEF.
4. Serum levels of these Domain III adipokines are increased in patients with obesity and visceral adiposity and are reduced following bariatric surgery. Increased serum levels presage the development of heart failure, and circulating levels are elevated in patients with established HFpEF, where they identify a poor prognosis.
5. Sotatercept, a fusion protein that traps and sequesters ligands of activin type II receptors (particularly activin A) is approved for use in patients with pulmonary arterial hypertension, and it ameliorates the development of experimental HFpEF.

proliferation, and it induces the endothelial-to-mesenchymal transition that leads to cardiac fibrosis.<sup>965-969</sup> Serum levels of asprosin are increased and have prognostic significance in patients with heart failure and dilated cardiomyopathy,<sup>970,971</sup> and they are also increased in elderly diabetic patients who have central obesity and abnormal diastolic filling dynamics.<sup>972</sup>

**ADIPOSE-SECRETED GROWTH FACTORS AND THEIR BINDING PROTEINS RELEVANT TO HEART FAILURE.** Certain growth factors (not exclusively secreted by adipose tissue) play a major role in obesity-driven

adipose biology and its cardiovascular consequences, because their adipose synthesis is heightened by an expanding adipocyte mass (**Box 10**).

**Platelet-Derived Growth Factor Receptor- $\beta$  Signaling.** Platelet-derived growth factors (PDGFs) and their receptors, PDGFR $\alpha$  and PDGFR $\beta$ , play a central role in the response of adipose tissue to the development of obesity,<sup>973,974</sup> while simultaneously activating cardiac fibroblasts that lead myocardial fibrosis.<sup>975</sup>

PDGFR $\alpha$ ++ and PDGFR $\beta$ +-preadipocytes represent different progenitor lineages.<sup>976</sup> In obesity, the pool of PDGFR $\beta$ +-preadipocytes expands greatly, leading to growth of white adipose tissue, PDGF-mediated insulin resistance, and PDGFR $\beta$ +-mediated angiogenesis, while PDGFR $\alpha$ +-preadipocytes are directed toward the formation of adipose tissue fibroblasts.<sup>976-982</sup> The imbalance in PDGFR $\beta$ +/PDGFR $\alpha$ + adipocytes is seminal to the development of adipose tissue dysfunction in obesity.<sup>976,980</sup> Genetic knockout of PDGFR $\beta$  restores healthy adipocyte biology<sup>983</sup> and ameliorates obesity.<sup>981</sup>

Importantly, the biological consequences of PDGFR $\beta$ + preadipocyte dominance can be disseminated from adipocytes to the heart. Adipocyte-specific overexpression of PDGF-D (an endogenous agonist of PDGFR $\beta$  receptors) promotes PDGF-D-mediated maladaptive cardiac remodeling, whereas adipocyte-specific silencing of PDGF-D decreases circulating PDGF-D levels and attenuates deleterious cardiac hypertrophic and fibrotic responses in experimental obesity.<sup>984</sup> The consequences of these effects may be further enhanced by up-regulation of PDGFR $\beta$  in the injured heart.<sup>985</sup> The failing heart exhibits proliferation of PDGFR $\beta$ -mesenchymal stem cells, along with augmented expression of the PDGFR $\beta$  ligands, PDGF-BB and PDGF-D.<sup>986</sup> Genetic overexpression of PDGF-D leads to cardiac fibrosis, cardiomyopathy, and heart failure,<sup>987,988</sup> and PDGFR $\beta$  signaling promotes myocardial hypertrophy.<sup>975,989</sup> Experimental obesity-related augmented expression of PDGF-BB and PDGFR $\beta$  mediates pulmonary hypertension,<sup>990</sup> and is linked to increases in left atrial volume<sup>991</sup> and the end-organ fibrosis seen in HFpEF.<sup>992</sup>

Clinically, circulating and adipose tissue levels of PDGF-BB and PDGF-D (agonists of PDGFR $\beta$  receptors) are increased in people with obesity or insulin resistance,<sup>993-996</sup> and elevated serum levels of PDGFs are seen in patients with HFpEF.<sup>997</sup> Interestingly, adiponectin appears to bind directly to and inhibit PDGF-BB.<sup>998</sup> Anticancer tyrosine kinase inhibitors (eg, imatinib), acting as PDGFR $\beta$  antagonists, ameliorate cardiac fibrosis, and pulmonary hypertension.<sup>986,999,1000</sup> The cardiotoxicity of imatinib and

other tyrosine kinase inhibitors in the clinical setting is not related to their effect to inhibit PDGFR $\beta$ , but to off-target effects.

**TGF- $\beta$  superfamily and activin type I and II receptor signaling.** The TGF- $\beta$  superfamily includes families of mutually reinforcing and antagonistic polypeptides (including bone morphogenetic proteins and growth differentiation factors), which signal through activin type I and II receptors. Stimulation of activin type I and II receptors and downstream Smad 2/3 transcription factors leads to both adipose expansion and cardiac fibrosis.<sup>1001,1002</sup> Although TGF- $\beta$ 1 represents the canonical link between obesity and the Smad2/3-mediated activation of cardiac fibroblasts,<sup>1003,1004</sup> 2 key activin ligands are of particular interest in understanding the link between obesity and heart failure: 1) growth differentiation factor 3 (GDF-3), which signals through activin-like receptor 7 (ALK7), a type I receptor<sup>1005</sup>; and 2) activin A (which signals through the type II receptor).

ALK7 is predominantly expressed in adipocytes,<sup>1006,1007</sup> and ALK7 is up-regulated during adipogenesis.<sup>1008</sup> Obesity and nutrient excess enhances the expression of activin A and GDF-3 in adipocytes.<sup>1002,1007,1009</sup> Genetic overexpression of GDF-3 leads to a profound expansion of fat mass,<sup>1009</sup> and adipocyte-specific up-regulation of activin signaling enhances adipogenesis.<sup>1010</sup> Conversely, pharmacological inhibition or genetic disruption of GDF-3, ALK7, or type II receptor signaling ameliorates experimental obesity.<sup>1011-1014</sup> Obesity-driven up-regulation of GDF-3 mediates adipose tissue inflammation,<sup>1015,1016</sup> whereas experimental or clinical ALK7 loss-of-function polymorphisms are accompanied by reduced adiposity.<sup>1017,1018</sup> Serum levels of activin A are increased in patients with obesity and visceral adiposity<sup>1019,1020</sup> and are reduced by bariatric surgery.<sup>1021,1022</sup>

Activin A has been identified as a key intermediary of the adverse effects of epicardial adipose tissue dysfunction on the adjoining myocardium.<sup>1023</sup> GDF-3/ALK7 and activin A/type II receptor signaling can promote cardiac fibrosis and apoptosis,<sup>1024-1027</sup> and ALK7 silencing alleviates myocardial fibrosis and ventricular dysfunction.<sup>1028</sup> ALK7 promotes vascular smooth muscle proliferation,<sup>1029,1030</sup> and activin A mediates deleterious pulmonary vascular changes.<sup>1031</sup> Heightened serum levels of GDF-3 and activin A are associated with postinfarction ventricular remodeling.<sup>1024,1032</sup>

Clinically, elevated serum levels of activin A identify patients with diabetes who have left ventricular hypertrophy.<sup>1033</sup> Circulating levels of activin

A are increased and have prognostic significance in patients with pulmonary arterial hypertension.<sup>1034</sup> A clinical gain-of-function ALK7 polymorphism is associated with both central obesity and left ventricular hypertrophy.<sup>1035</sup> Circulating levels of activin A are also increased in patients with HFpEF, particularly those with obesity,<sup>1036</sup> in proportion to the severity of diastolic filling abnormalities, and have prognostic significance,<sup>1037</sup> and activin type II receptor antagonism alleviates experimental HFpEF.<sup>1026</sup> Sotatercept, a fusion protein that traps and sequesters ligands of activin type II receptors (particularly activin A) also ameliorates experimental HFpEF,<sup>1026,1031</sup> and it is a U.S. Food and Drug Administration (FDA)-approved treatment for patients with pulmonary arterial hypertension.<sup>1038</sup> Bimagrumab, an activin type II inhibitor, is being developed for the treatment of patients with obesity.<sup>1039</sup>

**Insulin-like growth factor-1 receptor signaling.** Insulin-like growth factor-1 (IGF-1), the key mediator of the effects of growth hormone, signals through its cognate receptor, insulin growth factor-1 receptor (IGF-1R). The interactions of IGF-1 and IGF-1R are attenuated by a family of insulin-like growth factor binding proteins (IGFBPs), which typically act to limit IGF-1R activation.

Adipocytes secrete IGF-1 into the circulation.<sup>1040</sup> IGF-1 promotes adipogenesis and adipose hypertrophy,<sup>1041,1042</sup> and the expression of IGF-1R in adipocytes is up-regulated in diet-induced obesity.<sup>1043</sup> Pharmacological antagonism of the IGF-1R with cixutumumab mitigates against the development of diet-induced obesity,<sup>1044</sup> and suppression of endothelial IGF-1R ameliorates adjoining adipose tissue dysfunction.<sup>1045</sup> Serum levels of IGFBP1 (an endogenous antagonist of IGF-1R in adipocytes<sup>1046</sup>) are decreased by obesity.<sup>1047-1049</sup> The resulting unrestrained IGF-1R signaling contributes to obesity-related cardiac hypertrophy<sup>1050</sup> and to angiotensin II-mediated cardiac fibrosis.<sup>1051</sup> IGF-1R expression is up-regulated in the aging and the failing human heart,<sup>1052,1053</sup> and experimental suppression of IGF-1R signaling prolongs cardiac survival.<sup>1052,1054</sup>

Interestingly, in contrast to other IGFBPs, IGFBP7 has a low affinity for IGF-1, and it acts to accentuate (rather than inhibit) IGF-1R signaling.<sup>1055-1057</sup> Adipose tissue is a significant source of IGFBP7,<sup>1058</sup> and serum levels of IGFBP7 are increased in patients with central obesity and organ steatosis.<sup>1059,1060</sup>

Importantly, IGFBP7 signals through IGF-1R to promote cardiomyocyte senescence, leading to adverse ventricular remodeling and cardiac fibrosis; these derangements can be ameliorated by IGFBP7 silencing.<sup>1061-1063</sup> The effect of IGFBP7 to induce

senescence is intertwined with a similar action of activin A.<sup>1064</sup> IGFBP7 and activin A appear to inhibit each other, suggesting an interplay that prevents excessive senescence.<sup>1064</sup>

Clinically, serum levels of IGFBP7 are associated with left ventricular hypertrophy in the general population,<sup>301</sup> and they are consistently elevated in patients with HFpEF, in proportion to the severity of diastolic filling abnormalities and left atrial enlargement, and have prognostic significance.<sup>1065-1070</sup> Interestingly, the failing heart is not a source of either circulating IGF-1 or IGFBP7 in HFpEF, since it extracts both proteins from the circulation.<sup>1071,1072</sup> The role of IGFBP7-mediated IGF-1R signaling in linking adiposity and HFpEF warrants further investigation.

**ADIPOSE TISSUE MATRICELLULAR GLYCOPROTEINS AND OTHER EXTRACELLULAR MATRIX GLYCOPROTEINS.** Obesity can drive adipocytes to secrete certain adipokines into the extracellular matrix, where they can promote adipogenesis and adipose tissue inflammation, while signaling to the myocardium to promote cardiac inflammation and fibrosis. These adipokines can be grouped into 2 broad categories: 1) matricellular proteins; and 2) canonical extracellular matrix glycoproteins (Box 10).

Despite their localization in the extracellular matrix, matricellular proteins do not have scaffolding functions, and they are grouped together<sup>1073</sup> because 1) they are expressed during embryonic development and in response to injury; 2) they play a key role in the extracellular matrix to promote cell counter-adhesion, in contrast to most matrix proteins (which promote adhesion); and 3) following their secretion into the extracellular matrix, they can exert effects on adjoining tissues or be released into the circulation, often as components of adipoexosomes.<sup>1074</sup> This mechanism allows matricellular proteins to function as signaling molecules, generally acting through the Wnt/β-catenin pathway.

Canonical extracellular matrix glycoproteins (eg, tissue inhibitor of proteinase-1 and cathepsin S) directly modulate the degradation of scaffolding proteins (collagen and elastin), but additionally, they drive crosstalk between adipocytes and fibroblasts, thus being positioned to exert adverse effects on both adipose and cardiac tissue biology. YKL-40 (discussed earlier) can also be classified into this group.

**Wnt/β-catenin signaling matricellular glycoproteins.** These include thrombospondin-1, secreted protein acidic rich in cysteine (SPARC) (osteonectin), galectin-3, Wnt1-induced secreted protein-1/cellular

communication network factor 4 (WISP1/CCN4), osteopontin, and tenascin-C.

**Thrombospondin-1.** Acting through its receptor CD47, thrombospondin-1 promotes remodeling of the extracellular matrix to stimulate adipocyte proliferation and amplify adipose tissue inflammation.<sup>1075-1079</sup> Thrombospondin-1 is preferentially expressed in visceral adipocytes (rather than subcutaneous fat) in obese subjects,<sup>1080,1081</sup> and it is shed from human white adipose tissue as a key component of extracellular vesicles.<sup>1082</sup> Experimentally, the release of thrombospondin-1 into the circulation mediates high fat diet-induced insulin resistance and skeletal muscle fibrosis,<sup>1083</sup> and signaling through CD47 promotes further obesity.<sup>1084</sup> Circulating levels of thrombospondin-1 are increased in patients with obesity.<sup>1085,1086</sup>

Signaling through CD47 receptors on cardiomyocytes, thrombospondin-1 promotes hypertrophy and heart failure.<sup>1087</sup> Silencing of CD47 signaling promotes autophagic cellular housekeeping and prevents hypertrophy and apoptosis in cardiomyocytes following injury.<sup>1088-1091</sup> Thrombospondin-1 is a key mediator of cardiac fibrosis,<sup>1092-1094</sup> acting to modulate extracellular matrix remodeling in heart failure.<sup>1095</sup> Additionally, thrombospondin-1 enhances vasoconstrictor responses<sup>1096</sup> and has been implicated in experimental systemic and pulmonary hypertension.<sup>1096,1097</sup> It mediates the development of hypertrophy, fibrosis, and microvascular rarefaction in experimental HFpEF, an effect that is blocked by thrombospondin-1 antagonists.<sup>1098-1100</sup>

In the clinical setting, circulating thrombospondin-1 is a marker for the identification of cardiac hypertrophic states.<sup>1101</sup> Thrombospondin-1/CD47 signaling is up-regulated and mediates vasoconstrictor responses in the pulmonary arteries of patients with pulmonary arterial hypertension.<sup>1102</sup> Endocrine activation of CD47 may be particularly important, because patients with heart failure have increased circulating levels (but low cardiac expression) of thrombospondin-1.<sup>1103-1105</sup>

**Secreted protein acidic rich in cysteine.** Acting on collagen and metalloproteinases, SPARC regulates the assembly and organization of the extracellular matrix, thereby playing a key role in cellular growth.<sup>1106</sup> In response to dietary excess, SPARC is secreted during adipocyte differentiation and proliferation,<sup>1107,1108</sup> leading to its up-regulation in human adipocytes in obesity.<sup>1109</sup> Serum levels of SPARC are correlated with adipocyte expression, body mass index, and visceral fat mass,<sup>1107,1109,1110</sup> and they decline following bariatric surgery.<sup>1111</sup> SPARC modulates adipose tissue remodeling by

enhancing the postsynthetic maturation of collagen<sup>1112</sup> and proinflammatory signaling,<sup>1113,1114</sup> leading to adipose and visceral organ inflammation and fibrosis.<sup>1115,1116</sup>

As a result of its effects in the extracellular matrix, SPARC contributes to the development of cardiac inflammation, myocardial fibrosis, and diastolic filling abnormalities during aging and hemodynamic stress.<sup>1117-1121</sup> SPARC impairs vascular endothelial function, predisposing to systemic and pulmonary hypertension.<sup>1122-1124</sup> SPARC is packaged in circulating extracellular vesicles, whose numbers are increased in patients with hypertension.<sup>1125</sup> Serum levels of SPARC are elevated and have adverse prognostic significance in patients with heart failure.<sup>1126,1127</sup>

Importantly, extracardiac sources of SPARC mediate cardiac fibrosis. Transplantation of SPARC-expressing bone marrow mesenchymal stem cells taken from mice with pressure overload recapitulates the cardiac fibrosis and myocardial stiffness phenotype in recipient mice that are not under hemodynamic stress.<sup>1128</sup> These observations support cross-talk between extracardiac sources and the heart, akin to other adipokines.<sup>129,134,143,821</sup>

**Matricellular lectins (galectin-3).** Extracellular galectin-3 is a pentameric ligand for the  $\beta$ -galactoside residues of numerous glycoproteins, driving their crosslinking and the formation of higher order lattices that bind to integrins, thus playing a critical role in signaling between fibroblasts and the extracellular matrix.<sup>1129,1130</sup>

Galectin-3 is up-regulated and secreted during adipogenesis<sup>1131-1133</sup> and promotes adverse adipose tissue remodeling and organ steatosis, effects that are prevented by galectin-3 inhibition.<sup>1134,1135</sup> Adipocytes represent an important source of circulating galectin-3, explaining the strong parallelism between visceral adipose tissue expression and serum levels of galectin-3 during the evolution of obesity-related heart disease.<sup>1136</sup> Circulating levels of galectin-3 are increased in patients with obesity, particularly those with visceral adiposity and systemic inflammation.<sup>1137-1143</sup>

Experimental studies have implicated galectin-3 in the pathogenesis of obesity-related cardiac lipotoxicity, microvascular dysfunction, and myocardial fibrosis<sup>1137,1144-1147</sup>—the hallmarks of HFpEF. Enhanced expression of galectin-3 in the failing heart is localized to cardiac fibroblasts and macrophages.<sup>1148</sup> Infusions of galectin-3 stimulate fibroblast proliferation and collagen deposition,<sup>1149</sup> and knockout or suppression of galectin-3 alleviates cardiac fibrosis.<sup>1137,1149</sup> Importantly, neurohormonal stimulation of white adipose tissue leads to galectin-

3-mediated activation of cardiac fibroblasts,<sup>491</sup> demonstrating a role for adipose tissue-cardiac signaling in the pathogenesis of HFP EF.

Clinically, galectin-3 is an indicator of the presence of latent heart failure or the future risk of heart failure in the general community,<sup>1143,1150</sup> and particularly, of diastolic filling abnormalities, left atrial enlargement or HFP EF in patients with obesity or diabetes.<sup>1137,1150-1152</sup> Circulating levels of galectin-3 are increased in patients with heart failure, are related to the severity of ventricular remodeling, and have prognostic significance.<sup>1153-1155</sup> Serum levels of galectin-3 are particularly increased in those with HFP EF,<sup>1156-1158</sup> in whom circulating levels are correlated with obesity,<sup>1159</sup> diastolic filling abnormalities,<sup>1160</sup> and fibrosis.<sup>1146,1161</sup> Cardiac stress is not the source of circulating galectin-3, since it is not reduced by mechanical cardiac support or heart transplantation,<sup>1162,1163</sup> thus reinforcing the importance of extracardiac production.

*Osteopontin, tenascin-C, and Wnt1-induced secreted protein-1.* Three additional matricellular proteins—osteopontin, tenascin-C, and WISP1/CCN4—have been implicated as mediators of obesity-related heart failure.

The adipocyte expression of all 3 glycoproteins is up-regulated in obesity.<sup>1164-1167</sup> All 3 play a role in promoting adipogenesis and adipose tissue inflammation<sup>1165-1170</sup> and are secreted into the extracellular matrix and released at heightened levels into the circulation, particularly in patients with obesity and organ steatosis.<sup>1171-1175</sup> As with other matricellular proteins, these adipokines are involved in the deposition of collagen, the postsynthetic collagen processing and remodeling of the extracellular matrix.<sup>1167,1176</sup>

Experimentally, all 3 matricellular proteins promote myocardial hypertrophy and fibrosis.<sup>1177-1181</sup> Overexpression of osteopontin in cardiomyocytes leads to cardiomyopathy,<sup>1182</sup> and silencing of tenascin C alleviates experimental HFP EF.<sup>1181</sup> Clinically, epicardial adipocytes may be an important source of osteopontin,<sup>1183</sup> and serum levels of tenascin-C and osteopontin are increased and have prognostic significance in patients with heart failure,<sup>1184,1185</sup> including those with HFP EF.<sup>1186</sup> Elevated serum levels of tenascin-C are associated with cardiac hypertrophy and ventricular remodeling<sup>1187,1188</sup> and with diffuse cardiac fibrosis in patients with HFP EF.<sup>1189</sup>

**Canonical extracellular matrix glycoproteins.** Exemplified by tissue inhibitor of metalloproteinase 1 (TIMP1) and cathepsin S, these are secreted by adipocytes and act as regulators of the extracellular matrix, thereby acting to modulate

adipose biology and mediate the development of cardiac fibrosis.

*TIMP1 and CD63 signaling.* There exists a delicate balance between a family of metalloproteinases (MMPs) (which act to degrade components of the extracellular matrix) and a family of tissue inhibitors of metalloproteinases (TIMPs), which oppose the effects of MMPs.<sup>1190</sup> Unlike matricellular proteins, these proteins do not counter cellular adhesion or modulate cellular morphology. Nevertheless, MMPs and TIMPs influence the biology of both adipocytes and cardiac fibroblasts.<sup>1190,1191</sup>

TIMP1 is particularly noteworthy, because it not only inactivates most MMPs, but it also exerts MMP-independent effects by interacting with the CD63 receptor and signaling through integrin  $\beta 1$ .<sup>1192</sup> Obesity augments the expression of TIMP1 in adipocytes,<sup>1193,1194</sup> and in turn, TIMP1 up-regulation promotes the expansion of fat mass in high fat diet-induced obesity by promoting adipocyte hypertrophy, leading to organ steatosis.<sup>1195-1197</sup>

In parallel, TIMP1 expression is increased in the hypertrophied and fibrotic myocardium of experimental and clinical pressure overload.<sup>1198,1199</sup> Persistence of fibrosis following alleviation of the hemodynamic stress is related to continued myocardial TIMP1 expression,<sup>1200</sup> and TIMP1 silencing ameliorates cardiac fibrosis.<sup>1201</sup> In replacement fibrosis following major cardiac tissue loss, up-regulation of TIMP1 causes adaptive collagen deposition to stabilize ventricular structure, and such an action is antagonized by MMPs.<sup>1202-1204</sup> In contrast, in states of pressure overload or HFP EF, TIMP1 causes maladaptive fibroblast activation that is mediated through CD63, is exacerbated by aldosterone, and is not reversed by MMPs.<sup>1200,1205</sup>

In the clinical setting, serum levels of TIMP1 are increased in people with obesity, particularly those with central adiposity or organ steatosis.<sup>1206-1208</sup> Heightened serum levels presage those with obesity who are likely to develop heart failure during follow-up.<sup>1209</sup> Increased serum levels (often with increased cardiac expression) of TIMP1 are seen in patients with hypertension,<sup>1210</sup> left ventricular hypertrophy,<sup>1211</sup> and chronic pressure overload and are related to the severity of interstitial fibrosis and diastolic filling abnormalities.<sup>1198,1212,1213</sup> Serum levels of TIMP1 levels are increased in HFP EF and have prognostic significance.<sup>80,1214,1215</sup>

Intriguingly, circulating levels may represent important biological mediators of TIMP1 signaling, since adipose tissue can release TIMP1 and CD63 as components of secreted extracellular microvesicles.<sup>1216</sup> Endocytosis of these TIMP1-carrier

adipoexosomes by recipient fibroblasts induces their own production of TIMP1,<sup>1217</sup> explaining why adipocyte-secreted exosomes can induce TIMP1 at distant sites.<sup>1218</sup>

**Cathepsin S/protease-activated receptor 2 signaling.** Cathepsins are cysteine proteases that typically function under acidic conditions in the lysosome, but cathepsin S is adapted to a neutral pH, allowing it to be biologically active when secreted. Cathepsin S has elastase activity, but more importantly, cathepsin S cleaves and activates protease-activated receptor 2 (PAR2), which has potent proinflammatory effects.

Cathepsin S is expressed by adipocytes and promotes adipogenesis,<sup>1219,1220</sup> explaining why adipose-tissue expression and serum levels of cathepsin S are increased in parallel in patients with obesity (and visceral adiposity) and are reduced by weight loss.<sup>1221-1224</sup> In diet-induced obesity, cathepsin S inhibition alleviates adipogenesis, inflammatory infiltration, and organ lipid accumulation.<sup>1219</sup> Simultaneously, PAR2 is up-regulated in adipose tissue stromal cells in experimental obesity<sup>1225,1226</sup> and promotes adipogenesis and adipose tissue inflammation, effects that are muted by PAR2 antagonism.<sup>1227,1228</sup>

Experimentally, the elastase activity of cathepsin S may undermine the ability of the heart to tolerate hemodynamic and metabolic stresses.<sup>1229,1230</sup> Additionally, cathepsin S signaling through PAR2 promotes the development of cardiomyopathy by enhancing oxidative stress and proinflammatory signaling in cardiomyocytes and endothelial cells.<sup>1231,1232</sup> Suppression or antagonism of PAR2 alleviates cardiac hypertrophy, myocardial inflammation, fibrosis, and apoptosis.<sup>1233-1236</sup>

Clinically, serum levels of cathepsin S are increased in patients with cardiac hypertrophy and are correlated with left ventricular mass and diastolic filling abnormalities.<sup>1237</sup> Circulating levels of cathepsin S are also increased and have prognostic value in patients with heart failure, particularly with HFpEF.<sup>1238,1239</sup> Yet, paradoxically, cardiac PAR2 expression may be suppressed in patients with HFpEF,<sup>1240</sup> being regarded a maladaptive response that may induce further cardiac fibrosis and diastolic dysfunction.<sup>1240</sup>

**ADIPOSE TISSUE-SECRETED CHEMOKINES AND ANGIOPOIETINS.** Obesity can drive adipocyte synthesis and secretion of chemokines and angiopoietins, which not only promote cell migration to induce inflammation and vasculogenesis, but also have important effects on lipid metabolism and cardiac remodeling (Box 11).

**BOX 11. Domain III: Adipose Tissue-Secreted Chemokines and Angiopoietins**

1. Obesity is accompanied by enhanced adipose tissue secretion of several chemokines—CCL2, CCL5, CXCL8, CXCL12—and several angiopoietins or angiopoietin-like proteins—ANGPT2, ANGPTL2, ANGPTL4, and ANGPTL8.
2. Chemokines are chemoattractants for inflammatory cells that promote adverse ventricular remodeling. Angiopoietins and angiopoietin-like proteins target the vascular endothelium to cause inflammation, which is transmitted to the adjacent myocardial tissue. Chemokines, angiopoietins, or angiopoietin-like proteins are important mediators of cardiac fibrosis and microvascular rarefaction, thereby playing a role in experimental diet-induced HFpEF.
3. Serum levels of these Domain III adipokines are increased in patients with obesity. Increases in serum levels precede and presage the development of HFpEF, and they are increased in patients with established HFpEF in proportion to its severity. Adiposity-related enhanced secretion by epicardial adipocytes exerts adverse effects on the underlying myocardium.
4. Adipocyte-specific ablation of ANGPTL4 abrogates its effects to inhibit lipoprotein lipase, thereby promoting vascular injury. Suppression of CCR2 in bone marrow inflammatory cells ameliorates experimental cardiomyopathy. CCL5/CCR5 signaling may mediate aldosterone-induced end-organ injury.
5. Weight loss produced by bariatric surgery and incretin receptor agonists reduces circulating levels of adipose tissue-secreted chemokines, angiopoietins, and angiopoietin-like proteins.

**Adipocyte-secreted C-C and CXC chemokines.**

Chemokines are chemoattractant polypeptides that promote cell migration and enhance proinflammatory responses. Chemokines are grouped based on the spacing of the first 2 of 4 conserved N-terminal cysteine residues, ie, those with 2 adjacent cysteines are named C-C chemokines, and those where the 2 cysteines separated by 1 amino acid are named CXC chemokines. Chemokines are further identified as ligands or receptors and designated with an L or R; hence, CCL refers to a C-C chemokine ligand (ie, agonist) and CXCR refers to a CXC receptor.

**Chemokine (C-C) motif ligands (CCL2 and CCL5).** The 2 most well-characterized C-C chemokines are CCL2 (also known as monocyte chemoattractant protein-1) and CCL5 (RANTES). CCL2 and CCL5 signal through their respective receptors, CCR2 and CCR5, to mobilize inflammatory cells from the bone marrow into the bloodstream.

Obesity causes increased expression of both CCL2 and CCL5 in adipocytes,<sup>1241,1242</sup> thereby evoking adipose tissue inflammation, suppression of lipolysis and adaptive thermogenesis, and further obesity.<sup>1243-1245</sup> Enhanced adipocyte-specific expression of CCL2 leads to insulin resistance and visceral adiposity,<sup>1246</sup> and serum CCL2 levels are increased in patients with visceral adiposity and decreased by weight loss.<sup>1247-1249</sup> CCR2 antagonism mitigates against the development of obesity and organ steatosis produced by a high-fat diet.<sup>1250</sup> Endogenous NAMPT is a natural antagonist of CCR5,<sup>181</sup> and dual CCR2/CCR5 antagonists alleviate adipose tissue inflammation and insulin resistance.<sup>1251,1252</sup> In obesity, epicardial adipocytes heighten their secretion CCL2 and CCL5 onto the adjoining myocardium in proportion to the expansion of fat mass.<sup>1253-1255</sup>

Cardiac-specific overexpression of CCL2 promotes adverse ventricular remodeling and myocardial fibrosis,<sup>1256,1257</sup> but the relevance of this observation is uncertain since (in contrast to experimental models) the failing human heart shows down-regulation of the ligand CCL2, but up-regulation of the receptor CCR2,<sup>1258-1260</sup> pointing to enhanced sensitivity to an extracardiac source. It is therefore noteworthy that serum CCL2 levels are elevated in patients with hypertension who are at increased risk of diastolic filling abnormalities.<sup>1261</sup> Serum levels of both CCL2 and CCL5 are increased in heart failure in proportion to the severity of disease and prognosis.<sup>1262-1265</sup>

Importantly, adipose tissue-specific suppression of CCL2 has favorable effects at distant sites,<sup>1266</sup> and suppression of CCR2 in inflammatory cells residing in the bone marrow acts to ameliorate experimental cardiomyopathy.<sup>1267</sup> Knockout of CCR2 alleviates obesity-related end-organ injury;<sup>1245</sup> and antibodies to CCL2 prevent cardiac fibrosis and diastolic filling abnormalities following experimental pressure overload.<sup>1268</sup> CCL5/CCR5 signaling mediates aldosterone-induced end-organ injury,<sup>1269</sup> and systemic CCR2 or CCR5 antagonism alleviates pressure-overload hypertrophy,<sup>1258</sup> pulmonary and systemic vascular hypertrophy and proliferation,<sup>1270,1271</sup> and postinfarction heart failure.<sup>1272,1273</sup>

**Chemokine (CXC) motif ligands (CXCL8 and CXCL12).** Although many CXC chemokines are linked to obesity and heart failure, the 2 most studied are 1) CXCL8 (also known as IL-8, signaling through the CXCR2 receptor); and 2) CXCL12 (also known as stromal cell-derived factor-1, signaling through the CXCR4 receptor). CXCL8 and CXCL12 interact synergistically to regulate inflammatory responses.<sup>1274,1275</sup>

Obesity leads to heightened adipocyte secretion of both CXCL8 and CXCL12, which act to promote

insulin resistance and recruit inflammatory and bone marrow mesenchymal stem cells to adipose tissue, especially visceral fat,<sup>1276-1282</sup> effects that are blocked by CXCR2 antagonism.<sup>1283,1284</sup> Obesity (especially central adiposity) is accompanied by increased serum levels of both CXCL8 and CXCL12,<sup>1278,1285-1288</sup> with adipocytes in white adipose tissue being a primary source of circulating levels.<sup>1289</sup> Obesity enhances the number of circulating CXCR4-positive bone marrow mesenchymal stem cells and their recruitment to visceral fat.<sup>1277</sup>

CXCL8 and CXCL12 signaling has also been implicated in the pathogenesis of adverse ventricular remodeling and myocardial fibrosis seen in angiotensin II or aldosterone-excess models of HFP EF,<sup>1290,1291</sup> effects that are blocked by CXCR2 and CXCR4 antagonism.<sup>1292-1295</sup> Serum levels of both CXC chemokines are increased in patients at risk of and with established heart failure, especially with HFP EF.<sup>1296-1301</sup>

Experimentally, enhanced signaling through CXCL12/CXCR4 has been linked to cardiac repair if it takes place immediately following cardiac injury.<sup>1302-1305</sup> These observations have led some investigators to propose that CXCL12 overexpression could cause circulating mesenchymal stem cells to target the myocardium and mature into cardiomyocytes.<sup>1306</sup> However, trials have not confirmed this hypothesis,<sup>1307,1308</sup> and instead, sustained CXCL12 signaling (continuing beyond the early phase of injury) promotes cardiac fibrosis rather than regeneration.<sup>1309</sup> Because CXCL12 is degraded by dipeptidyl peptidase 4,<sup>1310</sup> dipeptidyl peptidase 4 inhibitors potentiate CXCL12 signaling and promote cardiac fibrosis,<sup>1311</sup> possibly explaining why their use has been accompanied by an increased risk of heart failure in certain large-scale clinical trials in type 2 diabetes.<sup>1312,1313</sup>

**Angiopoietins and angiopoietin-like proteins.** Originally recognized for their action to modulate angiogenesis, angiopoietins and angiopoietin-like proteins are structurally similar families have important effects on lipid metabolism and systemic inflammation. The 2 families are distinguished by the fact that angiopoietins are ligands for the Tie-2 receptor tyrosine kinase, whereas angiopoietin-like proteins are not. Both angiopoietins and angiopoietin-like proteins also signal through cell adhesion molecules.

**Angiopoietin-2.** Ang-1 is secreted by adipocytes to interact with the Tie2 receptor, and this action is opposed by angiopoietin-2 (ANGPT2), which is expressed primarily in vascular endothelial cells.<sup>672,673</sup> ANGPT2 is also expressed in adipocytes to promote thermogenesis in brown fat and to enhance

fatty acid storage in subcutaneous adipose tissue.<sup>1314,1315</sup> The expansion of adipose tissue requires an adequate blood supply,<sup>1316</sup> and physiological levels of adipocyte- or endothelium-derived ANGPT2 promote healthy vascular proliferation and metabolic homeostasis, signaling through  $\alpha 5\beta 1$  integrin (rather than Tie2) as its primary receptor.<sup>1314,1317-1319</sup>

However, following inflammatory stress or collagen deposition,<sup>1320-1323</sup> the actions of ANGPT2 (or a spliced variant<sup>1324</sup>) are directed away from  $\alpha 5\beta 1$  integrin and toward Tie2 as its primary receptor.<sup>1322,1325</sup> This redirection coerces ANGPT2 to act as an antagonist of Ang-1.<sup>1320</sup> Because Ang-1/Tie2 signaling promotes vascular stability, the effects of heightened ANGPT2 signaling are transformed from an action that facilitates the healthy growth of blood vessels to an effect that enhances endothelial cell apoptosis, vascular fragility and leakiness, and angiotoxicity.<sup>1322,1326-1328</sup>

These pathophysiological relationships may explain why obesity and visceral adiposity are accompanied by increased adipose tissue and serum levels of ANGPT2 and soluble Tie2.<sup>1325,1329</sup> Levels of ANGPT2 parallel those of other Domain III adipokines (leptin, thrombospondin-1, and CCL2).<sup>1103,1327,1328</sup> Epicardial adipose tissue secretes ANGPT2, leading to inflammation in the adjoining myocardium.<sup>1023</sup> Heightened serum levels of ANGPT2 are linked to the genesis of myocardial and vascular inflammation,<sup>1320,1329,1330</sup> particularly in patients with metabolic disorders.<sup>1331,1332</sup> The vasculotoxic effects of ANGPT2 may underlie the pathogenesis of microvascular rarefaction<sup>1328,1333</sup>—a hallmark of HFpEF—often accompanied by end-organ fibrosis.<sup>1326,1334</sup>

Clinically, serum levels of ANGPT2 are increased in patients with hypertensive vascular disease<sup>1335</sup> and are associated with visceral adiposity and obesity.<sup>1336,1337</sup> Heightened levels presage the development of heart failure in the general community.<sup>1338</sup> Serum ANGPT2 levels are elevated in patients with established heart failure in parallel with the severity of disease and prognosis,<sup>1339-1342</sup> particularly in HFpEF.<sup>836,1343</sup>

**Angiopoietin-like proteins 2, 4, and 8.** Angiopoietin-like proteins comprise a family of 8 polypeptides, with ANGPTL2, angiopoietin-like 4 (ANGPTL4), and angiopoietin-like 8 (ANGPTL8) being the most relevant to obesity and heart failure.

Although typically linked to endothelial cells, ANGPTL2, ANGPTL4, and ANGPTL8 are robustly synthesized in adipocytes and promote adipogenesis and lipid accumulation, signaling through cell adhesion molecules.<sup>1344-1350</sup> Additionally, ANGPTL4 and ANGPTL8 modulate the activity of lipoprotein lipase

to promote triglyceride storage into adipose tissue.<sup>1351,1352</sup> Whereas physiological levels of ANGPTL2 and ANGPTL8 maintain healthy adipose homeostasis,<sup>1353</sup> obesity is accompanied by sustained up-regulation of ANGPTL2, ANGPTL4, and ANGPTL8,<sup>1354-1356</sup> which acts to promote adipose tissue inflammation.<sup>1347,1354</sup> Conversely, ANGPTL2, ANGPTL4, and ANGPTL8 silencing alleviates obesity, ectopic fat deposition, and adipose tissue dysfunction.<sup>1345,1356-1358</sup>

Serum levels of ANGPTL2, ANGPTL4, and ANGPTL8 are increased in patients with obesity and visceral adiposity.<sup>1359-1362</sup> In addition, ANGPTL2, ANGPTL4, and ANGPTL8 are released by epicardial adipose tissue to exert paracrine effects,<sup>1363-1365</sup> and ANGPTL2 can be up-regulated within injured cardiac tissue and lead to autocrine effects.<sup>1366</sup> Obesity-driven elevation of ANGPTL2 expression in human adipose tissue is associated with systemic insulin resistance.<sup>1344</sup> Importantly, adipocyte-specific genetic ablation of ANGPTL4 promotes the action of lipoprotein lipase, thereby minimizing the development of organ steatosis and atherosclerotic vascular injury,<sup>1358,1367</sup> another example of signaling between adipose tissue and the cardiovascular system.

ANGPTL4 induces angiogenesis,<sup>1368</sup> and ANGPTL2 enhances vascular inflammation<sup>1369,1370</sup> and high-fat-diet-induced endothelial dysfunction,<sup>1371</sup> and impairs cardiac tolerance to injury.<sup>26,1372</sup> ANGPTL2 augments adverse ventricular remodeling in experimental HFpEF,<sup>1373</sup> and ANGPTL4-mediated fibroblast activation has been implicated in HFpEF induced by nutrient excess.<sup>1374</sup> Circulating ANGPTL2 levels are increased in experimental HFpEF, and serum ANGPTL2 and ANGPTL4 levels are elevated in patients with HFpEF, especially in those with obesity, systemic inflammation and worse exercise performance.<sup>1375-1378</sup> Elevated urinary levels of ANGPTL2 in patients with HFpEF presage an increased risk of adverse heart failure events.<sup>1379</sup>

**SOLUBLE ENDOGENOUS ANTAGONISTS AND OTHER PROINFLAMMATORY ADIPOKINES.** Obesity can trigger the adipose tissue synthesis of certain adipokines that 1) act as natural endogenous antagonists of cytoprotective proteins; or 2) can accentuate adipose tissue inflammation and myocardial injury (Box 12).

**Plasminogen activator inhibitor.** Urokinase plasminogen activator exerts adipoprotective effects because it generates plasmin (promoting proteolysis of the extracellular matrix), and it activates certain adipokines (eg, hepatocyte growth factor) that maintain healthy adipocyte biology in a plasmin-

**BOX 12. Domain III: Soluble Endogenous Antagonists and Other Proinflammatory Proteins**

1. This grouping of Domain III adipokines includes plasminogen activator inhibitor-1 (PAI-1), endogenous inhibitors of the ST2/interleukin-33 axis, calgranulin-RAGE signaling, and canonical proinflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , IL-6).
2. PAI-1 is a major adipocyte-derived proinflammatory adipokine and acts as an endogenous antagonist of HGF (a Domain II adipokine). It exerts profibrotic effects in the heart and is a marker of cardiac aging. A soluble form of ST2 (sST2) acts a decoy molecule to prevent IL-33 from interacting with ST2 and exerting its cardioprotective effects. Canonical proinflammatory cytokines signal through the NF- $\kappa$ B inflammasome.
3. With the expansion of fat mass, adipose tissue is transformed into a major organ for the production of PAI-1, sST2, RAGE ligands, and canonical cytokines, whose circulating levels are increased in obesity. Increased circulating levels precede the development of heart failure, and they are increased in established HFP EF and presage an adverse prognosis.
4. Transplantation of adipose tissue lacking PAI-1 attenuates cardiac metabolic abnormalities in recipient mice fed a high-fat diet, demonstrating adipose-cardiac adipokine signaling.
5. Circulating levels of PAI, sST2 and canonical cytokines are reduced by bariatric surgery, incretin receptor agonists and current drugs for HFP EF. However, inhibition of canonical cytokines has not been demonstrated to have favorable effects in experimental HFP EF.

independent manner.<sup>428,1380,1381</sup> PAI-1 is the endogenous suppressor of urokinase plasminogen activator, thus promoting adipose tissue dysfunction and fibrosis.<sup>1382</sup>

Obesity is accompanied by heightened expression of PAI, particularly in white adipose tissue residing in visceral fat.<sup>1383,1384</sup> With obesity, adipose tissue is transformed into a major PAI-1 producing organ, because adipocytes acquire the ability to respond to inducers of PAI-1 transcription.<sup>1385</sup> The secretion of PAI-1 by adipocytes parallels the degree of adipocyte hypertrophy and represents the principal driver of circulating PAI-1.<sup>1385,1386</sup> PAI-1 silencing alleviates adipose tissue inflammation and diet-induced obesity.<sup>1383,1387,1388</sup>

Clinically, serum PAI-1 levels are elevated in patients with central obesity,<sup>1389,1390</sup> are correlated with visceral mass fat, and decline following bariatric surgery.<sup>1391-1393</sup> Increased circulating levels of PAI-1 presage the development of the metabolic syndrome in the general population<sup>1394</sup> and are

correlated with the degree of clinically measured cardiac fibrosis.<sup>1395</sup> They are a marker of aging-related heart failure,<sup>1396</sup> and predict the subsequent development of HFP EF.<sup>1397</sup> Serum levels of PAI are increased in patients with established heart failure, particularly those with obesity or HFP EF,<sup>1398</sup> and have prognostic significance.<sup>1399</sup> PAI-1 levels are lowered by SGLT2 inhibition, GLP-1 receptor agonists, angiotensin receptor blockers, and mineralocorticoid antagonism.<sup>1400-1403</sup>

Interestingly, in the heart, low physiologic levels of PAI-1 are cardioprotective,<sup>1404-1407</sup> but sustained elevated levels are profibrotic.<sup>1408-1411</sup> Fibrosis in experimental HFP EF is paralleled by increased PAI-1 expression in the myocardium.<sup>1404</sup> Obesity itself has only a modest effect on expression of PAI-1 in the myocardium.<sup>1412</sup> Yet, importantly, transplantation of adipose tissue lacking PAI-1 attenuates cardiac metabolic abnormalities in recipient mice fed a high-fat diet<sup>105</sup>—demonstrating that PAI-1 secreted from adipocytes is capable of influencing the function of the heart.<sup>105,1413</sup>

**Soluble suppression of tumorigenicity (sST2) and the ST2/IL-33 axis.** Tissue injury leads to the extracellular release of IL-33, which exerts compensatory cytoprotective effects (typically in an autocrine or paracrine manner) by interacting with the cell-surface ST2 (suppression of tumorigenicity 2) receptor. In inflammatory states, a soluble form of ST2 (referred to sST2) lacking its cell-penetrating domains is secreted into the extracellular space and acts as a decoy receptor, binding to IL-33 and preventing its homeostatic effects.<sup>1414</sup>

In obesity and visceral adiposity, adipose tissue is the primary secretory site for sST2, which acts to disrupt the functionality of the IL-33/ST2 axis at distant sites.<sup>1414-1418</sup> During nutrient excess, enhanced IL-33/ST2 signaling<sup>1419</sup> initially serves to attenuate adipose tissue inflammation and aldosterone-induced adipogenesis,<sup>1420</sup> thus positioning IL-33/ST2 as a Domain II adipokine. Silencing of ST2 exacerbates diet-induced adiposity.<sup>1421</sup>

However, as obesity advances and is sustained, the expanded and inflamed adipose tissue mass expresses and drives heightened circulating levels of sST2.<sup>1418,1422</sup> By diverting IL-33 away from ST2, enhanced sST2 signaling promotes fat accumulation, insulin resistance, and inflammatory responses.<sup>1418</sup> Serum sST2 levels are reduced by bariatric surgery<sup>1423</sup> and GLP-1 receptor agonism.<sup>1424</sup> sST2 can also be released by epicardial adipocytes and act in a paracrine manner to suppress the activity of IL-33 and cause fibrosis in the adjoining myocardium.<sup>1417,1425,1426</sup>

Signaling through the IL-33/ST2 axis attenuates adverse ventricular remodeling, prevents heart failure and improves survival after myocardial injury or mechanical stress.<sup>1427-1431</sup> Conversely, disruption of IL-33/ST2 signaling by sST2 promotes adverse cardiac remodeling, vascular hyperplasia, and myocardial fibrosis.<sup>1430-1433</sup> sST2 may enhance collagen deposition by an effect that is independent of its actions as a IL-33 decoy.<sup>1434</sup>

Clinically, circulating levels of sST2 presage the onset of heart failure<sup>1435</sup> and are increased in patients with established heart failure,<sup>1436</sup> including those with HFpEF. They reflect the severity of ventricular hypertrophy, diastolic filling abnormalities, and prognosis,<sup>303,1157,1436,1437</sup> and they decline following treatment with sacubitril/valsartan or liraglutide.<sup>80,1424</sup> Of note, the heart is not a source of circulating sST2. Heightened circulating sST2 levels are driven by extracardiac synthesis and are linked to systemic inflammation,<sup>1438-1442</sup> presumably triggered by visceral adiposity.<sup>1417,1422</sup> As further evidence of adipose-cardiac mutual crosstalk, changes in the IL-33/ST2 axis triggered by cardiac diastolic stress can produce a peripheral inflammatory response.<sup>1440,1443</sup>

**Calgranulin-receptor for advanced glycation products signaling.** S100B is the best studied member of a family of 20 calcium-binding proteins (known as calgranulins) that are released from injured tissues and signal through the membrane-bound receptor for advanced glycation products (RAGE).<sup>1444</sup>

Low physiological levels of S100B promote intracellular homeostasis,<sup>1445</sup> but with heightened extracellular levels, S100B acts as a damage-associated molecular pattern molecule,<sup>1446</sup> signaling through RAGE to promote deleterious inflammatory reactions.<sup>1447</sup> Originally described as being restricted to astrocytes and a marker of neuronal stress, S100B is synthesized during adipogenesis,<sup>1448</sup> and the secretion of S100B from adipocytes is the primary source of the blood-borne protein.<sup>1449-1451</sup> Enhanced expression of S100B or RAGE by hypertrophied adipocytes in visceral white adipose tissue<sup>1452-1454</sup> leads to adipose tissue expansion and inflammation.<sup>1451,1455-1459</sup> As a result, serum levels of S100B are increased in patients with obesity and visceral adiposity<sup>1452-1454,1460,1461</sup> and decrease following prolonged starvation.<sup>1462</sup> RAGE antagonism alleviates diet-induced obesity.<sup>1463</sup>

Circulating S100B can interact with cardiac membrane-bound RAGE, whose expression in cardiomyocytes is up-regulated by diet-induced obesity<sup>1464</sup> and by aging and cardiac hypertrophy.<sup>1465,1466</sup> Enhanced S100B-RAGE signaling can

promote derangements in calcium handling, cellular stress, mitochondrial abnormalities and apoptosis,<sup>1467-1470</sup> as well as cardiac hypertrophy and fibrosis and cardiomyopathy.<sup>1466,1471,1472</sup> Genetic or pharmacological suppression of RAGE ameliorates adverse ventricular remodeling in pressure-overload HFpEF.<sup>1473,1474</sup> Serum levels of S100B and RAGE are increased in patients with heart failure in parallel with its severity and prognosis, especially those with diastolic filling abnormalities.<sup>1475-1478</sup>

Interestingly, the circulating form of RAGE (ie, soluble RAGE) is a decoy molecule that is cardioprotective, because it binds to RAGE ligands (eg, S100B) and prevents the deleterious effects of RAGE in the heart.<sup>1479,1480</sup> However, serum levels of soluble RAGE are decreased in patients with obesity,<sup>1481</sup> thus attenuating its ability to interfere with RAGE signaling. Of note, advanced glycation end products (prominent in patients with type 2 diabetes) and beta-amyloid (prominent in cardiac amyloidosis) also act as extracellular ligands for deleterious RAGE signaling.<sup>1482,1483</sup>

**Canonical NF-κB-linked proinflammatory cytokines.** The canonical proinflammatory cytokines—TNF- $\alpha$ , IL-1 $\beta$ , and IL-6—play a prototypical role in mediating inflammatory responses. Although they are secreted by hypertrophied adipocytes,<sup>1484,1485</sup> the recruitment of inflammatory cells to adipose tissue is the primary driver of the increased expression of canonical cytokines in visceral fat in diet-induced obesity.<sup>1486</sup>

Early studies suggested that TNF- $\alpha$  might worsen obesity,<sup>1487</sup> but subsequent work has shown that TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 signaling does not increase body weight or impair insulin resistance.<sup>1488-1491</sup> Serum levels of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 are increased in patients with obesity in proportion to visceral fat, but these changes are also accompanied by a parallel increase in their decoy receptors and antagonists.<sup>1485,1492-1497</sup>

Experimentally, TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 are capable of exerting both favorable and adverse cardiac effects, and suppression of these cytokines have yielded inconsistent effects on the evolution of experimental HFpEF.<sup>1498-1505</sup> Serum levels of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 are increased in patients with heart failure,<sup>1506,1507</sup> especially with HFpEF and obesity.<sup>1378,1508</sup> However, these patients also show increased levels of soluble TNF- $\alpha$  receptors and IL-1 $\beta$  receptor antagonists,<sup>836,1509,1510</sup> and the net effect of potential agonist-antagonist interactions in states of excess adiposity is not known. TNF- $\alpha$  antagonists increase the risk of worsening heart failure in patients with HFrEF,<sup>1511,1512</sup> but in these studies, reverse TNF- $\alpha$  signaling may have led to unintended

agonist effects.<sup>1510,1513</sup> Therefore, in contrast to the other adipokines discussed in this paper, the role of canonical proinflammatory cytokines in the genesis of adiposity-related HFP EF remains unclear.

#### PART VIII. TESTING THE ADIPOKINE HYPOTHESIS OF HFP EF: UNDERSTANDING THE EFFECT OF CURRENT AND FUTURE TREATMENTS ON VISCERAL ADIPOSITY AND THE SECRETION OF ADIPOKINES

A sound and useful conceptual framework should not only reflect the findings of pathophysiological studies, but it should also align with and contribute to an explanation of the available evidence for current treatments. Additionally, a worthwhile paradigm should define a roadmap for the potential repurposing of available drugs and for the development of novel molecules to be tested in clinical trials in HFP EF (Central Illustration 2).

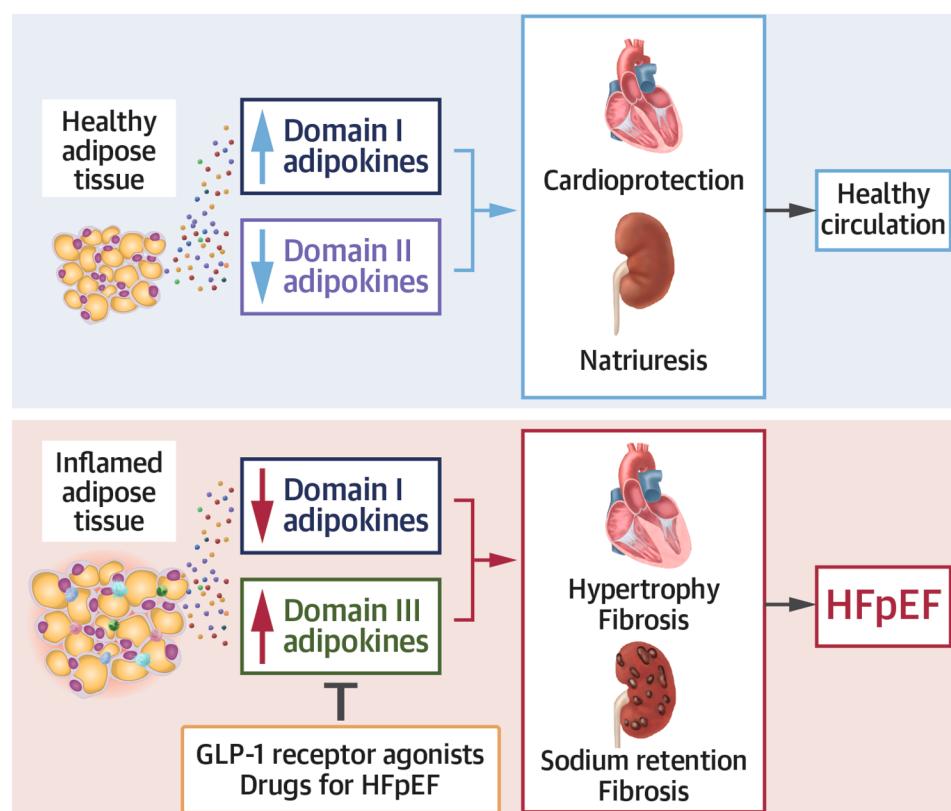
The adipokine hypothesis proposes that an expansion and dysfunctional transformation of

visceral adipose tissue drives the pathogenesis of HFP EF through the altered secretion of bioactive molecules that influence the health of the heart, vasculature, and kidneys. Therefore, it is important to understand whether current interventions for HFP EF act to ameliorate visceral adiposity and restore a healthy adipokine balance. The findings of studies that address these issues are summarized in Box 13.

**BARIATRIC SURGERY AS AN EXEMPLAR OF THE ADIPOKINE HYPOTHESIS OF HFP EF.** The most persuasive evidence that dietary caloric excess and visceral adiposity drive the adipokine derangements seen in HFP EF is provided by the distinctive pattern of physiological and clinical responses seen following bariatric surgery.

Gastric bypass surgery results in dietary nutrient deprivation and profound weight loss, which is accompanied by a disproportionately larger reduction in visceral fat mass and alleviation of adipose tissue inflammation.<sup>1514-1517</sup> Bariatric surgery does

**CENTRAL ILLUSTRATION 2** Shifts in the Balance of Adipokines in the Healthy Circulation and in HFP EF



**BOX 13. Biological and Clinical Effects of Bariatric Surgery and Current HFpEF Treatments Are Aligned With the Adipokine Hypothesis**

1. Bariatric surgery, incretin receptor agonists, MRAs, SGLT2 inhibitors, and angiotensin receptor neprilysin inhibitors act to shrink visceral adipose tissue depots. The magnitude of this reduction is disproportionately larger than the decrease in body weight.
2. The suppression of systemic inflammation following bariatric surgery in people with obesity is not related to an effect on circulating inflammatory cells (eg, monocytes), but instead, it is related to suppression of inflammation-related genes in adipose tissue.
3. Bariatric surgery, incretin receptor agonists, MRAs, SGLT2 inhibitors, and angiotensin receptor neprilysin inhibitors act to increase Domain I adipokines, while decreasing Domain III adipokines, thus ameliorating the adipokine derangement seen in patients with visceral adiposity.
4. The responses to bariatric surgery indicate that dietary nutrient deprivation is sufficient to produce a decisive shift in the balance of circulating adipokines to a new set point that would be expected to produce strikingly favorable biological effects in the heart.
5. In people with obesity, adipocytes represent the major source of circulating aldosterone, angiotensin II, and neprilysin. The central role of adiposity in driving neurohormonal activation explains 1) why bariatric surgery leads to decreases in circulating aldosterone, angiotensin II, and neprilysin; and 2) why patients with HFpEF who have obesity and visceral adiposity show particularly favorable responses to treatment with current drugs for HFpEF.
6. Metformin and fenofibrate have favorable effects on adipokine biology, reduce visceral fat mass, and improve the balance of circulating adipokines in obesity. Experimental and clinical observations support the potential for a benefit of these drugs in HFpEF.

not merely reduce the number and size of adipocytes, but it radically alters the biology of adipose tissue so as to fundamentally change the profile of its secretory state.<sup>1515,1518</sup> Most importantly, the suppression of systemic inflammation following surgery in people with obesity is not related to an effect on circulating inflammatory cells (eg, monocytes), but instead, it is linked to the suppression of inflammation-related genes in adipose tissue.<sup>1519</sup>

Surgical weight loss is accompanied by increases in serum levels or adipose tissue expression of Domain I adipokines (ie, adiponectin)<sup>1111,1520</sup> and nearly

universal decreases in serum levels or adipose tissue expression of Domain III adipokines (leptin,<sup>546,622,731</sup> aldosterone,<sup>1521</sup> angiotensin,<sup>1522</sup> neprilysin,<sup>1522</sup> FABP4,<sup>1523</sup> RBP4,<sup>1524</sup> YKL-40,<sup>826</sup> chemerin,<sup>848</sup> resistin,<sup>1525,1526</sup> Wnt5a,<sup>905</sup> asprosin,<sup>961</sup> activin A,<sup>1021,1022</sup> thrombospondin-1,<sup>1527</sup> SPARC,<sup>1111</sup> TIMP1,<sup>1528</sup> cathepsin S,<sup>1224</sup> CCL2,<sup>826,1249</sup> ANGPTL2,<sup>435</sup> PAI,<sup>1393,1525</sup> sST2,<sup>1423</sup> TNF- $\alpha$ ,<sup>1525</sup> IL-1 $\beta$ ,<sup>1519</sup> and IL-6),<sup>1520</sup> although serum levels of IGF-1 increase.<sup>1529,1530</sup> Additionally, obesity surgery generally results in a decline in serum levels of Domain II adipokines (ie, vaspin,<sup>318,1531</sup> irisin,<sup>368,369</sup> HGF,<sup>435</sup> apelin,<sup>546</sup> acyl-stimulating protein,<sup>622</sup> and IL-10<sup>1519</sup>), presumably because the need for their compensatory and counterbalancing actions diminishes. Soluble RAGE (a counter-regulatory decoy molecule that is deficient in obesity<sup>1481</sup>) declines further.<sup>1532</sup> However, when obesity underlies the development of biological adipokine resistance (as appears to be the case of FGF21, GDF-15, ATGL, and progranulin), levels of these adipokines increase following gastric bypass surgery,<sup>1533-1536</sup> and this increase may help to drive postoperative weight loss and metabolic improvements.<sup>1533</sup>

These responses to bariatric surgery demonstrate that *dietary nutrient deprivation is sufficient* to produce a decisive shift in the balance of circulating adipokines to a new set point that would be expected to produce strikingly favorable biological effects in the heart. As a result of the selective suppression of inflammation-related genes in adipose tissue,<sup>1519</sup> the amelioration of systemic inflammation following bariatric surgery is likely related to heightened signaling of anti-inflammatory Domain I adipokines, coupled with suppression of proinflammatory Domain III adipokines.

Accordingly, bariatric surgery ameliorates left ventricular hypertrophy (in patients with and without HFpEF),<sup>1512,1537</sup> while improving coronary microvascular function and diastolic filling abnormalities.<sup>1538</sup> These beneficial effects are correlated with changes in the adipokine profile and visceral fat mass<sup>731,1514,1539</sup> and may be independent of weight loss.<sup>1540</sup> As a result of these favorable mechanistic actions, gastric bypass surgery is accompanied by a profound decrease in the risk of new-onset heart failure, and in particular, a reduction in hospitalizations for HFpEF.<sup>1541,1542</sup>

**APPLICABILITY OF THE ADIPOKINE HYPOTHESIS TO CURRENT TREATMENTS FOR HFpEF.** To date, studies of the actions of MRAs, GLP1-receptor agonists, SGLT2 inhibitors, sacubitril/valsartan have focused on the effects of these drugs on the heart and

kidney, but these drugs also have well-characterized favorable effects on adipocyte biology.

Therefore, key questions include:

1. Does the obesity-driven transformation of adipose tissue contribute meaningfully to the activation of angiotensin II, aldosterone, and neprilysin in HFpEF?
2. Do MRAs, GLP1-receptor agonists, SGLT2 inhibitors, and sacubitril/valsartan shrink visceral fat mass and ameliorate adipose tissue dysfunction?
3. Do these drugs act to normalize the adiposity-driven imbalance of Domain I and III adipokines?
4. Is the magnitude of the clinical benefit of these drugs in HFpEF influenced by the pretreatment severity of obesity and visceral adiposity?

**Mineralocorticoid receptor antagonists.** Aldosterone is a Domain III adipokine, and adipocytes are a major source of aldosterone in patients with obesity, both because adipocytes secrete aldosterone directly and because adipokines (eg, leptin) act to stimulate the secretion of aldosterone from the adrenal gland.<sup>38-41</sup>

There is a mutual reinforcing link between excess visceral adiposity and circulating levels of aldosterone.<sup>1543</sup> Adipocyte-specific up-regulation of the mineralocorticoid receptor leads to the metabolic syndrome and underlies aldosterone's adverse effects on the cardiovascular system.<sup>757</sup> Conversely, the marked reduction in visceral fat mass produced by bariatric surgery reduces circulating levels of aldosterone.<sup>1521</sup> Mineralocorticoid receptor antagonism inhibits adipocyte expansion and alleviates proinflammatory signaling in adipose tissue.<sup>463,1544</sup>

Spirostanolactone and eplerenone act to reduce visceral fat mass in patients with elevated circulating levels of aldosterone.<sup>1545</sup> As a result, eplerenone reduces waist circumference (ie, central obesity) in patients with hypertension and diabetes<sup>1546</sup> (disproportionately more than the effect on body weight), and spirostanolactone prevents weight gain in patients with HFpEF.<sup>1547</sup> Subantihypertensive doses of mineralocorticoid receptor antagonists ameliorate the abnormalities of ventricular diastolic filling in obesity.<sup>1548</sup>

In experimental studies and in clinical trials of patients with metabolic abnormalities or HFpEF, MRAs have been observed to increase serum levels or adipose tissue expression of Domain I adipokines (ie, adiponectin and eNAMPT<sup>1549,1550</sup>) and Domain II adipokines (ie, GDF-15, adrenomedullin, apelin, HGF, and ATGL<sup>463,599,1543,1551,1552</sup>), while reducing serum levels of Domain III adipokines (ie, leptin, chemerin,

and PAI<sup>1550,1553-1556</sup>), with LCN2 and chemerin representing specific aldosterone targets that are mitigated by MRAs.<sup>818-820,863</sup> These changes represent a major shift in adipokine balance to a state of reduced adipose tissue and myocardial stress.

Consistent with these mechanistic observations, eplerenone appears to be particularly effective in patients with HFrEF who have central obesity.<sup>1557</sup> Furthermore, in patients with HFpEF, there exists a linear relationship between body mass index and the magnitude of the reduction in cardiovascular death or worsening heart failure events with finerenone, with a benefit of the drug being apparent only in patients with obesity.<sup>1558</sup> Similar findings with respect to the influence of obesity have been observed in patients with HFpEF treated with spirostanolactone.<sup>1559</sup>

**GLP1- and dual GLP1/GIP receptor agonists.** Agonism of GLP-1 and GIP receptors on adipocytes contributes to the weight loss produced by incretin-based drugs.<sup>1560,1561</sup> Signaling through these receptors reduces adipocyte hypertrophy, organellar stress, and inflammation, while promoting mitochondrial energetics and brown fat thermogenesis (through up-regulation of SIRT1).<sup>1562-1566</sup> GIP agonism provides an additional lipolytic effect<sup>1567</sup> and drives futile calcium cycling in white adipose tissue.<sup>1568</sup> Sustained stimulation of the GIP receptor in adipocytes contributes importantly to the incremental effect of dual agonists on weight loss.<sup>1560</sup>

In clinical trials, incretin receptor signaling produces a profound reduction in visceral fat,<sup>1569,1570</sup> including the shrinkage of epicardial adipose tissue (which expresses both GLP-1 and GIP receptors<sup>1571</sup>) and of the fat depots surrounding the heart.<sup>27,1572</sup> The reduction in visceral fat following incretin receptor agonism is disproportionately larger than its effect on body weight.<sup>27</sup> GLP-1 receptor agonists alleviate experimental dysmetabolism-related HFpEF, potentially by reducing the accumulation of lipid droplets and adjacent fibrosis within the heart.<sup>1573-1575</sup>

In experimental studies and in clinical trials of patients with diabetes or obesity, incretin-based agonists increase serum levels of adipocyte/adipose tissue expression of Domain I adipokines (ie, adiponectin, CTRP3, omentin-1, SFPR5, eNAMPT, and ZAG),<sup>146,159,174,214,839,1576-1583</sup> while they simultaneously act to reduce levels of most Domain III adipokines (ie, leptin, aldosterone, RBP4, FABP4, resistin, asprosin, galectin-3, PAI, sST2, YKL-40, CCL2, RAGE, and canonical proinflammatory cytokines),<sup>463,838,1401,1424,1563,1565,1577-1579,1584-1590</sup> although serum Wnt5a and ANGPTL-8 levels

increase.<sup>1591,1592</sup> With respect to Domain II adipokines, experimental GLP-1 receptor agonism induces FGF21,<sup>1593</sup> and FGF21 up-regulation may be required for its effect to produce weight loss.<sup>1594</sup> Additionally, GLP-1 receptor agonism increases adipose expression of irisin,<sup>1595</sup> metallothionein,<sup>1596</sup> and ATGL<sup>1597</sup>; however, GDF-15 is unchanged by liraglutide<sup>1598</sup> and is reportedly decreased by trizepatide.<sup>839</sup>

Taken collectively, the pattern of these changes reflects a major reduction in visceral adipose tissue mass, which is accompanied by a consistent shift in the balance of adipokines to a new state of reduced adipose tissue and myocardial stress. The amelioration of systemic inflammation following incretin receptor agonism<sup>26,1599</sup> is likely related to heightened signaling of anti-inflammatory Domain I adipokines, coupled with suppression of proinflammatory Domain III adipokines.

Incretin-based agonists improve the clinical status and outcomes of patients with HFpEF and obesity,<sup>26,1599</sup> and the effects of tirzepatide on health status and exercise tolerance are most marked in those with the highest pretreatment body mass index.<sup>1600</sup> Additionally, the clinical benefits of semaglutide and tirzepatide in HFpEF are related to the magnitude of weight loss.<sup>1601</sup> Importantly, the reduction in visceral fat (particularly, epicardial and paracardiac adipose tissue) is paralleled by amelioration of left ventricular hypertrophy and left atrial enlargement.<sup>27,1602</sup> These observations suggest that changes in the mass and biology of visceral adipose tissue may act as mediators of the cardioprotective effect of incretin-based drugs.

**SGLT2 inhibitors.** SGLT2 inhibitors induce a system-wide state of starvation mimicry,<sup>1603,1604</sup> as evidenced by the induction of ketogenesis, the augmentation of autophagic flux, and the up-regulation of AMPK/SIRT1/PGC-1 $\alpha$  signaling in diverse tissues.<sup>93,95,1605</sup> The expression of SGLT2 in the proximal renal tubule is increased in patients with obesity and diabetes,<sup>1606</sup> but the action of SGLT2 inhibitors to up-regulate nutrient deprivation signaling and inhibit adipogenesis does not depend on the induction of renal glycosuria,<sup>2</sup> because these effects are seen in isolated cultured adipocytes.<sup>1607-1611</sup> Human epicardial adipose tissue exhibits abundant expression of SGLT2, especially in developing adipocytes.<sup>1612,1613</sup>

In experimental obesity, SGLT2 inhibitors reduce adipocyte hypertrophy, inflammation and cellular stress in white adipose tissue, while acting to decrease visceral fat mass. They also promote brown fat thermogenesis through enhanced AMPK/SIRT1/PGC-1 $\alpha$  signaling.<sup>1606-1616</sup> In clinical trials, SGLT2

inhibitors decrease visceral adiposity and waist circumference and alleviate organ steatosis,<sup>1617-1620</sup> acting to reduce epicardial adipose tissue mass.<sup>1620-1623</sup> Yet, in clinical studies, these benefits on visceral adiposity are accompanied by only modest changes in body weight, perhaps caused by compensatory hyperphagia.<sup>1624,1625</sup> The incremental dietary calories do not appear to be stored in visceral fat, which is disproportionately reduced by SGLT2 inhibition. (Long-term changes in weight are not influenced by a diuretic effect because SGLT2 inhibitor-induced natriuresis is truncated by renal tubular counterregulatory mechanisms.<sup>1626</sup> The decline in body weight with SGLT2 inhibitors is related to a decrease in fat mass, not water.<sup>1627</sup>)

With the induction of starvation mimicry, in a manner similar to that seen with incretin receptor agonists, SGLT2 inhibitors have been observed to increase serum levels or adipose tissue expression of Domain I adipokines (ie, adiponectin and ZAG<sup>213,1628,1629</sup>) and Domain II adipokine (ie, FGF21, GDF-15 and apelin<sup>310,1614,1630-1632</sup>), while they simultaneously act to reduce serum levels of a broad range of Domain III adipokines (ie, leptin, RBP4, chemerin, asprosin, PAI, CCL2, CXCL8, RAGE, TNF- $\alpha$  and IL-6),<sup>870,1400,1613,1614,1628,1633-1637</sup> with minimal changes in IGF-1, IGFBP7, sST2, and galectin-3.<sup>1638-1640</sup> Serum FABP4 levels do not change consistently,<sup>1635,1641</sup> but SGLT2 inhibition decreases the expression of FABP4 in epicardial adipocytes.<sup>1613</sup> These changes, considered together, represent a meaningful shift in adipokine balance to a set point of reduced adipose tissue and myocardial stress.

As further evidence of the relevance of this shift, epicardial adipocytes pretreated with empagliflozin exert cytoprotective effects when cocultured with cardiomyocytes in vitro.<sup>1613</sup> Similarly, transplantation of fat tissue that is pretreated with an SGLT2 inhibitor acts to ameliorate the vascular abnormalities in recipient mice with experimental diet-induced obesity.<sup>1642</sup>

SGLT2 inhibition alleviates experimental obesity-related HFpEF,<sup>1643</sup> and in patients with HFpEF, the reduction in body weight is paralleled by decreases in left ventricular filling pressures at rest and exercise.<sup>1644</sup> Accordingly, the pretreatment body mass index influences the magnitude of the effect of SGLT2 inhibitors on weight loss and on health status,<sup>1645-1647</sup> with weight reduction and symptomatic benefits being seen primarily in patients with morbid obesity. The magnitude of SGLT2 inhibitor-related decreases in the risk of hospitalizations for heart failure is greater in patients with type 2 diabetes who have obesity.<sup>1647</sup> These observations, taken

collectively, support an important role of pretreatment (and treatment-related changes in) the mass and biology of visceral adipose tissue in influencing the benefits of SGLT2 inhibitors.

#### **Angiotensin receptor neprilysin inhibition.**

Both angiotensin II and neprilysin are considered Domain III adipokines, and in patients with obesity, the expansion of visceral adipocyte mass represent an important causal mechanism for activation of the renin-angiotensin system and for heightened circulating levels of neprilysin, both because adipocytes secrete angiotensin II and neprilysin directly and because the effect of Domain III adipokines (eg, leptin) to activate renal sympathetic nerves stimulates both angiotensin II and neprilysin.<sup>20,41,746,747,752</sup> The marked reduction in fat mass produced by bariatric surgery reduces circulating levels of angiotensin II and neprilysin.<sup>1521,1522</sup>

Both angiotensin II and atrial natriuretic peptide play opposing roles in adipogenesis and modulating adipocyte biology. Experimentally, interference with angiotensin II receptor signaling reduces adipocyte size, suppresses proliferation, oxidative stress and inflammation, and promotes thermogenesis in white adipose tissue.<sup>1648-1654</sup> In clinical trials, angiotensin receptor blockade shrinks visceral fat mass<sup>1655</sup> and ameliorates adipocyte hypertrophy,<sup>754</sup> with a treatment effect that is disproportionately larger than the effect on body weight. In experimental models or the clinical setting, angiotensin receptor blockers increase serum levels or adipocyte synthesis of Domain I adipokines (eg, adiponectin<sup>1656,1657</sup>) and Domain II adipokines (eg, apelin)<sup>1658,1659</sup> while simultaneously diminishing serum levels or the adipose expression of Domain III adipokines (CCL2, cathepsin S, FABP4, YKL-40, PAI, CCL2, TNF- $\alpha$ , and IL-6).<sup>754,838,1652,1654,1660-1663</sup>

Neprilysin inhibition potentiates these adipokine shifts. Its augmentation of atrial natriuretic peptide signaling inhibits adipogenesis and adipocyte proliferation,<sup>1618</sup> and enhances white adipose lipolysis (an effect attenuated in obesity),<sup>1664-1666</sup> while heightening brown fat thermogenesis<sup>1666-1669</sup> and promoting weight loss.<sup>1670</sup> Of note, augmented natriuretic peptide signaling alleviates obesity only if it takes place in adipocytes (and not in skeletal muscle)<sup>1671</sup>—perhaps because atrial natriuretic peptide directly enhances the release of adiponectin and suppresses the secretion of leptin from adipocytes.<sup>1672-1675</sup> Essentially, natriuretic peptide receptor signaling acts as an adipokine switch, which is biased toward adiposity by the suppressed circulating levels of natriuretic peptides that are characteristic of patients with obesity or HFpEF.<sup>42,759</sup> Sacubitril/valsartan

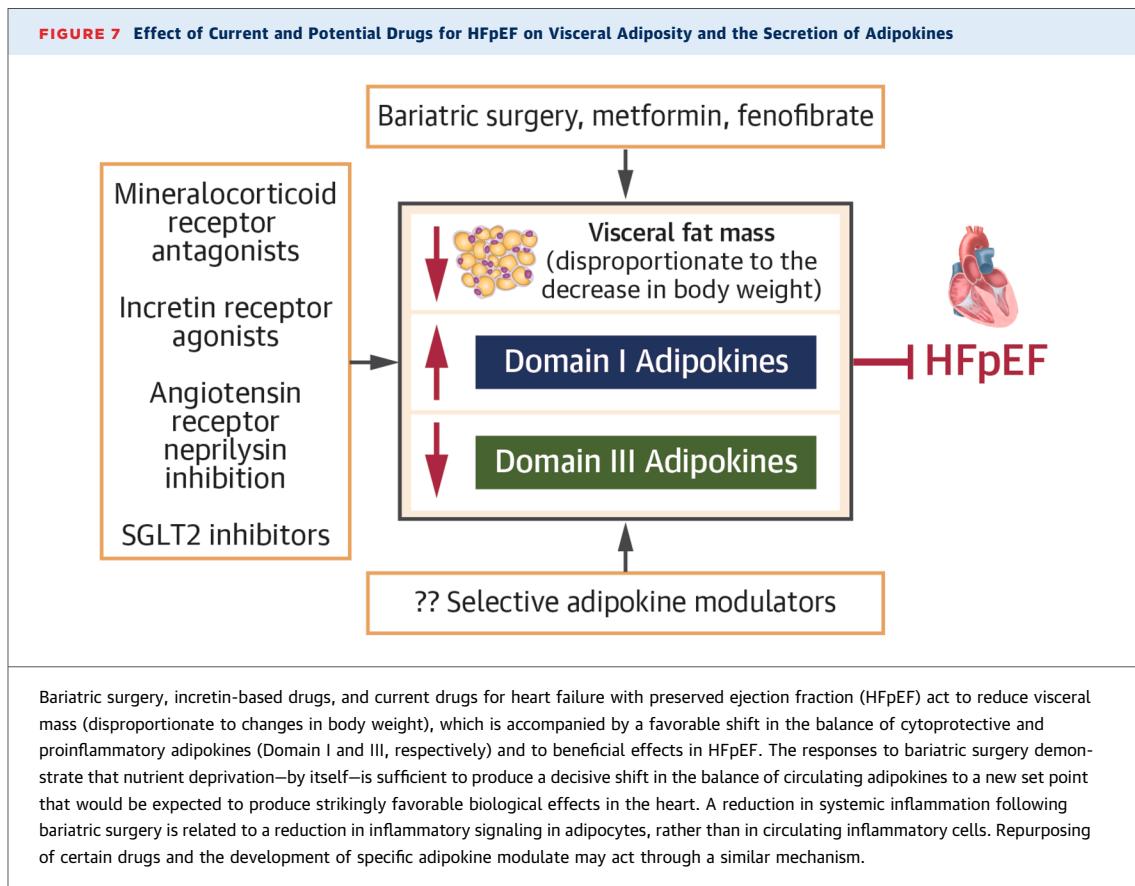
reduces visceral fat mass in experimental obesity-related HFpEF.<sup>1676</sup>

Clinically, atrial natriuretic peptide delivery increases serum levels of adiponectin in patients with or without heart failure,<sup>1672,1677</sup> while reducing serum levels or adipose tissue expression of leptin, RBP4, CCL2, TNF- $\alpha$ , and IL-6.<sup>1673,1676</sup> Neprilysin not only degrades atrial natriuretic peptide, but it also promotes the breakdown of several Domain II adipokines (ie, adrenomedullin, apelin, and ang[1-7]), and thus, neprilysin inhibition increases their serum levels.<sup>1677-1683</sup> Sacubitril/valsartan reduces serum levels of sST2, TIMP1, and YKL-40 in patients with HFpEF.<sup>80,1682</sup>

Consistent with these observations, the benefits of angiotensin receptor blockade in patients with HFpEF seem to be limited to patients with the lowest pretreatment levels of natriuretic peptides (indicative of obesity).<sup>1684</sup> At the same time, neprilysin inhibition appears to produce greater clinical improvement and effects on heart failure outcomes in patients with HFpEF who have obesity or central adiposity.<sup>12,1685</sup> Phosphodiesterase 9 (PDE9) inhibition can potentiate natriuretic peptides beyond that produced by neprilysin inhibition.<sup>1686</sup> PDE9 inhibition alleviates experimental obesity,<sup>1687</sup> and it may lead to additional favorable adipokine shifts that are relevant to patients with HFpEF.<sup>1688</sup>

**Perspective and synthesis.** These findings, taken collectively, indicate that MRAs, incretin-based agonists, SGLT2 inhibitors and angiotensin receptor neprilysin inhibitors exert favorable effects on adipocyte biology, which is manifest experimentally and clinically, by a reduction in visceral adipose tissue mass that is disproportionate to any change in body weight. The shrinkage of visceral fat is accompanied by up-regulation of Domain I adipokines and suppression of Domain III adipokines, experimentally and clinically (Figure 7). These drugs also cause up-regulation of many Domain II adipokines, which may allow for their cardioprotective effects, because the opposing action of Domain III adipokines has been simultaneously minimized.

It is understood that patients with HFrEF respond favorably to treatment with angiotensin receptor neprilysin inhibitors, MRAs, and SGLT2 inhibitors, presumably because the failing heart triggers the activation of neurohormonal systems related to ventricular distension or renal hypoperfusion. However, these conventional hemodynamic triggers are muted in patients with HFpEF, raising questions about the identity of the mechanisms that cause up-regulation of aldosterone, neprilysin, and angiotensin II in this disorder. The near-universal



prevalence of central obesity in HFpEF points to the expansion of visceral adipose tissue as the candidate driving force. When fat mass comprises 50% of body weight in people with obesity, adipocytes emerge as the major source of circulating aldosterone, angiotensin II, and neprilysin,<sup>39,41</sup> which decline following bariatric surgery.<sup>1521,1522</sup> The central role of adiposity in driving neurohormonal activation may explain why patients with HFpEF who have greater obesity and visceral adiposity show particularly favorable responses to neurohormonal antagonists.

**POTENTIAL FOR REPURPOSING OF DRUGS APPROVED FOR NON-HFpEF INDICATIONS.** Several currently available drugs have actions that improve the biology and secretory profile of adipose tissue and produce cardioprotective effects in experimental models, and thus, present an opportunity for being repurposed for the treatment of HFpEF.

**Metformin.** Although often regarded as an anti-hyperglycemic agent that reduces glucose production in the liver, metformin is an AMPK activator that has direct effects on adipocytes to modulate energy

homeostasis. In states of dietary excess, metformin inhibits adipogenesis and lipid droplet accumulation and fusion,<sup>1689</sup> suppresses adipose tissue inflammation and fibrosis,<sup>1690,1691</sup> and minimizes the obesity-related secretion of extracellular vesicles,<sup>1692</sup> while restoring healthy brown fat function.<sup>1690,1693</sup>

As a result of these actions, metformin inhibits the development of experimental diet-induced obesity,<sup>1693</sup> and shrinks visceral fat depots and produces weight loss in patients with obesity.<sup>1694,1695</sup> Many of the Domain I adipokines (eg, adiponectin, CRTP3/9, and omentin-1) and Domain II adipokines (eg, FGF21, GDF-15, and vaspin) signal through AMPK, and thus, metformin mimics the downstream effects of these adipokines and normalizes the adipocyte AMPK deficit that is seen in diet-induced obesity.<sup>1696</sup>

Additionally, metformin acts directly on adipocytes to up-regulate Domain I adipokine signaling (ie, enhanced adiponectin gene expression, protein secretion, and receptors<sup>1697,1698</sup>; increased serum omentin-1 and NRG-4 levels<sup>1699,1700</sup>; and augmented adipocyte expression of CRTP3 and eNAMPT<sup>1696,1701</sup>),

while suppressing adipocyte secretion and serum levels of Domain III adipokines (ie, leptin, FABP4, RBP4, resistin, CCL2, thrombospondin-1, and PAI).<sup>1078,1694,1702-1710</sup> With respect to Domain II adipokines, metformin up-regulates FGF21 and GDF-15,<sup>1693,1711</sup> but it decreases serum levels of vaspin, irisin, and PEDF.<sup>1712-1714</sup>—a pattern similar to that seen with bariatric surgery.

Interestingly, the only clinical trial evidence that metformin has reduced the risk of diabetic complications is derived from a subgroup analysis of the UKPDS (UK Prospective Diabetes Study), and the patients who showed beneficial effects of metformin in that study were specifically those who were overweight.<sup>1715</sup> Metformin reduces epicardial adipose tissue mass in people with obesity,<sup>1715,1716</sup> and it alleviates left ventricular stiffness, diastolic filling abnormalities, and pulmonary hypertension and mitigates against the development of experimental HFrEF, including that produced by obesity.<sup>1717,1718</sup> Its use in hypertensive patients with diabetes is accompanied by a reduced risk of new-onset symptomatic HFrEF,<sup>1719</sup> and in patients with established HFrEF, its use is associated with a lower risk of death.<sup>1720</sup>

**Fenofibrate and pioglitazone.** PGC-1 $\alpha$  is a convergence point for nutrient surplus and deprivation signaling, and the interactions of PGC-1 $\alpha$  with PPAR $\alpha$  and PPAR $\gamma$  lead to opposing effects on adipose and cardiac biology, which are both context- and duration-dependent.<sup>1721</sup> Enhanced PPAR $\alpha$  signaling (as with fenofibrate) reduces adipocyte hypertrophy and adipose tissue inflammation,<sup>1722-1724</sup> promotes brown fat thermogenesis,<sup>1725</sup> shrinks visceral fat mass and organ adiposity,<sup>1724,1726</sup> and ameliorates diet-induced obesity.<sup>1724-1726</sup> In contrast, augmented PPAR $\gamma$  signaling (as with pioglitazone) promotes lipogenesis, adipocyte hypertrophy, and stress<sup>1727-1730</sup>; inhibits fat mobilization and brown fat thermogenesis<sup>1731,1732</sup>; causes weight gain and tissue fat accumulation<sup>1733,1734</sup>; and worsens central obesity.<sup>1734</sup>

Importantly, several Domain I and II adipokines (eg, adiponectin, CTRP3, ZAG, FGF21, irisin, ATGL) enhance PPAR $\alpha$  or diminish PPAR $\gamma$  signaling in adipose and nonadipose tissues.<sup>462,1735-1744</sup> Specifically, the secretion of ATGL from adipocytes can activate PPAR $\alpha$  signaling in the liver and heart.<sup>460-462</sup> Furthermore, the cardiomyopathy seen in ATGL-deficient mice is rescued by PPAR $\alpha$  (but not PPAR $\gamma$ ) agonism.<sup>1745</sup> Therefore, although the favorable changes in serum levels of adipokines produced by

fenofibrate are notable, they may be inconsequential,<sup>1746-1749</sup> because the drug acts directly on their downstream targets.

The opposing effects of PPAR $\alpha$  and PPAR $\gamma$  signaling in adipose tissue are paralleled by their mutually antagonistic actions in the heart. The expression of PPAR $\alpha$  in the heart is suppressed in experimental pressure overload,<sup>1750</sup> and PPAR $\alpha$  silencing promotes and PPAR $\alpha$  agonism with fenofibrate ameliorates maladaptive hypertrophy and experimental cardiomyopathy.<sup>1751-1754</sup> In contrast, prolonged up-regulation of PPAR $\gamma$  leads to mitochondrial oxidative dysfunction, lipid accumulation, maladaptive hypertrophy, and cardiomyopathy.<sup>1755,1756</sup> Experimental cardiomyopathy produced by high-fat diet-induced obesity is alleviated by PPAR $\gamma$  silencing.<sup>1733</sup>

The parallelism between PPAR $\alpha$ /PPAR $\gamma$  signaling in adipose and cardiac tissues appears to be causal, rather than coincidental. For example, the effect of PPAR $\gamma$  agonism with rosiglitazone to induce cardiac hypertrophy is mediated by the drug's effect on *adipose tissue*, because the prohypertrophic action is attenuated by adipocyte-specific (but not by cardiomyocyte-specific) silencing of PPAR $\gamma$ .<sup>1756,1757</sup> The rosiglitazone-mediated cardiac hypertrophic signal appears to be driven by the secretion of microRNA200a from adipocytes. PPAR $\alpha$  and PPAR $\gamma$  also exert mutually opposing effects on renal tubular sodium reabsorption, with PPAR $\alpha$  agonism favoring sodium excretion and PPAR $\gamma$  agonism causing sodium retention.<sup>1758,1759</sup>

In clinical trials of patients with dyslipidemia or diabetes, PPAR- $\alpha$  agonism with fenofibrate reduces the risk of hospitalizations for heart failure,<sup>334</sup> whereas both selective PPAR $\gamma$  and dual PPAR $\alpha$ /PPAR $\gamma$  agonists increase the risk of adverse heart failure outcomes.<sup>1760-1764</sup>

**TNF- $\alpha$  inhibitors, IL-1/IL-1 $\beta$  antagonists and colchicine.** Drugs that directly antagonize canonical proinflammatory cytokine signaling—TNF- $\alpha$  antagonists (eg, etanercept and infliximab), IL-1/IL-1 $\beta$  inhibitors (eg, anakinra and canakinumab), and NLRP3 inflammasome antagonists (eg, colchicine)—mitigate systemic inflammatory responses and might seem appealing for the treatment of adiposity-related HFrEF.

Although etanercept exerted favorable effects on adipose tissue in experimental dietary excess<sup>1765</sup> and colchicine inhibited cardiac fibrosis in experimental obesity,<sup>1766</sup> studies in the clinical setting have not supported these observations. TNF- $\alpha$  antagonism in

patients with or without the metabolic syndrome does not improve their adipokine profiles. Treatment with etanercept and infliximab is accompanied by weight gain, increases in muscle fat mass, and worsening of visceral adiposity.<sup>1767-1771</sup> Furthermore, pretreatment obesity or visceral adiposity attenuates (rather than accentuates) the clinical responses to the anti-inflammatory effects of these drugs.<sup>1772-1775</sup>

Similarly, interference with IL-1 signaling in obesity may not produce favorable effects,<sup>1776</sup> perhaps because excess adiposity leads to enhanced synthesis of an endogenous soluble IL-1 receptor antagonist,<sup>1493</sup> thus predisposing to weight gain<sup>1493,1777</sup> and potentially minimizing the benefits of anakinra and canakinumab. Furthermore, colchicine inhibits (rather enhances) lipolysis,<sup>1778</sup> and does not appear to have benefits on adipose tissue inflammatory cell infiltration or insulin sensitivity.<sup>1779,1780</sup> Similarly, IL-1 antagonism does not exert favorable effects on leptin or adiponectin in patients with visceral adiposity or diabetes.<sup>1776,1781</sup>

Taken together, these observations do not suggest that antagonism of canonical proinflammatory cytokines is likely to be beneficial in the treatment of adiposity-related HFpEF. TNF- $\alpha$  receptor antagonists cause worsening of heart failure in patients with an HFrEF,<sup>1511,1512</sup> but their effects in HFpEF have not been explored. Long-term IL-1 $\beta$  antagonism with canakinumab is accompanied by a decrease in heart failure events in patients with atherosclerotic heart disease,<sup>1782</sup> but the effect of the drug in patients with established heart failure (and particularly HFpEF) is not known. Anakinra does not improve functional capacity in patients with HFpEF and obesity,<sup>1783</sup> and colchicine does not produce symptomatic benefits or prevent worsening heart failure events in patients with established heart failure, despite reduced systemic inflammation.<sup>1784-1786</sup>

These findings suggest that canonical proinflammatory cytokines may not play an important role in adiposity-related HFpEF. Nevertheless, because it decreases systemic inflammation in patients with obesity and chronic kidney disease,<sup>1787</sup> ziltivekimab (an IL-6 antagonist) is being evaluated in a large-scale trial of patients with HFpEF.<sup>1788</sup>

**SELECTIVE ADIPOKINE TARGETING: A ROADMAP FOR NOVEL THERAPEUTIC APPROACHES.** The proposed adipokine hypothesis identifies imbalances in Domain I, II, and III adipokine signaling that might be ameliorated by specifically targeted interventions. Interestingly, many of these adipokines have already been earmarked in the development of new drugs,

although such development has largely focused on disorders other than HFpEF. Examples of novel therapeutic approaches are noted below.

- Adiponectin receptor agonists, AdipoRON and ADP355, have been developed for the treatment of a broad range of conditions, including diabetic nephropathy, neurodegenerative diseases, and nonalcoholic fatty liver disease.<sup>127,1789,1790</sup>
- Several long-acting FGF21 analogues—pegozifermin, efruxifermin, and zalfemfermin—have been shown to alleviate organ steatosis and are being developed for nonalcoholic fatty liver disease.<sup>263,1791,1792</sup>
- A long-acting recombinant GDF-15 dimer (MBL949) and a GDF-15/GFRAL receptor agonist (LY346325) are being developed for the treatment of obesity.<sup>1793,1794</sup>
- AMG 986, an orally active apelin agonist that stimulates the APJ receptor,<sup>561,562</sup> has been evaluated in patients with HFrEF. No studies have been performed in patients with HFpEF.
- Phosphodiesterase 9 inhibitors—CRD-733, osorenesnontrine, tovinontrine, and PF-04447943—can potentiate the natriuretic peptide augmentation produced by neprilysin inhibition. CRD-733 is being developed for HFpEF,<sup>1688</sup> but the others have been developed for schizophrenia and sickle cell disease.
- HGF has been developed for intramyocardial adenoviral delivery, and an engineered bioactive HGF fragment can be delivered in an extracellular matrix-derived hydrogel.<sup>1795</sup> Both have been directed towards the treatment of myocardial infarction.
- LPrA-2, Allo-acA, LDFI, and 9F8 are leptin antagonists—formulated as peptides or antibodies—which are being developed for the treatment of neovascularization-related eye diseases, obesity, and chronic kidney disease.<sup>1796-1798</sup>
- BMS309403, a small molecule inhibitor of FABP4, is being developed for the treatment of cancer.<sup>1799</sup>
- Rosazumab, a humanized monoclonal antibody inhibitor of YKL-40, is currently approved for the treatment of osteoporosis.<sup>1800</sup>
- Antagonists of the chemerin receptor (CCX832 and  $\alpha$ -NETA) have been primarily developed for the treatment of diabetic nephropathy.<sup>872,1801</sup>
- Drugs that inhibit Wnt5a secretion or act as Frizzled-5 antagonists can prevent the development of experimental postinfarction heart failure and HFpEF.<sup>922,928,929</sup> Clinically, Wnt5a antagonists—such as Box5, Wnt5a/FZD2 siRNA, and RNF43—have been developed for the treatment of melanoma and other cancers.<sup>1802</sup>

- Ziritaxestat—an orally active inhibitor of auto-taxin—is being developed for the treatment of idiopathic pulmonary fibrosis.<sup>948</sup>
- Asprosin-neutralizing antibodies are being developed for the treatment of the metabolic syndrome.<sup>963</sup>
- Sotatercept, a trap for activin type II receptor ligands (targeting activin A), is effective (and FDA-approved) for the treatment of pulmonary arterial hypertension,<sup>1038</sup> and it has yielded promising results in experimental HFP EF.<sup>1038</sup> Bimagrumab, an activin type II inhibitor, is being developed for the treatment of obesity.<sup>1039</sup>
- Cixutumumab, an antagonist of the IGF-1 receptor,<sup>1044</sup> has been developed for the treatment of solid tumors.
- LY3000328, a selective cathepsin S inhibitor, has cardioprotective effects and is being investigated for the treatment of abdominal aortic aneurysm.<sup>1803,1804</sup>
- LSKL peptide—a selective thrombospondin-1 antagonist—has been developed and tested for hypertrophic scar formation,<sup>1805</sup> and potentially, for the treatment of cancer.
- Selvigaltin, a small-molecule galectin-3 inhibitor, is being developed for the treatment of hepatic cirrhosis and idiopathic pulmonary fibrosis.
- Azeliragon (TTP488)—a small molecule RAGE inhibitor—is being evaluated for the treatment of cancer.<sup>1806</sup> Another RAGE inhibitor, FPS-ZM1, is being investigated for the treatment of pain.<sup>1807</sup> Small-molecule disruptors of advanced glycation product crosslinks have been evaluated in clinical HFP EF.<sup>1483</sup>
- Ziltivekimab, a humanized monoclonal antibody against the IL-6 ligand, reduces a systemic inflammation in patients with obesity and chronic kidney disease<sup>1787</sup> and is being evaluated in a large-scale trial of patients with HFP EF.<sup>1788</sup>
- Pirfenidone is an orally active antifibrotic agent that is FDA-approved for the treatment of idiopathic pulmonary fibrosis. It has been regarded as a TGF-β1 suppressor,<sup>1808</sup> but it may act as a PPARα agonist, similar to fenofibrate.<sup>1809</sup> Pirfenidone alleviates experimental obesity (while up-regulating adiponectin and down-regulating resistin),<sup>1806</sup> while mitigating obesity-related cardiac steatosis and fibrosis.<sup>1810</sup> Pirfenidone has produced a reduction in extracellular volume by cardiac magnetic resonance imaging in a small short-term trial in patients with HFP EF (largely with obesity).<sup>1811</sup>
- Amycretin and CagliSema act as dual agonists of the GLP-1 and amylin receptors, producing substantial weight loss.<sup>1812</sup> However, even though

amylin is a member of the calcitonin peptide family, amylin is not meaningfully produced by adipocytes. Furthermore, experimental hyperamylinemia causes proteotoxic effects, pathological cardiomyocyte remodeling, and diastolic dysfunction.<sup>1813</sup> The possibility that amylin agonism may simultaneously produce both weight loss and cardiotoxic effects underscores the lessons learned from large-scale trials that some weight loss interventions can have serious off-target adverse effects.<sup>1814,1815</sup>

Whenever newly developed drugs have the capacity to interfere with a mechanism that underlies a broad range of inflammation-driven disorders, the direction of their development often reflects the acceptability of surrogate endpoints in short-term trials to support regulatory approval and/or with the ability to achieve premium pricing in the marketplace. In contrast with cancer, neurodegenerative disease, and rare disorders, the return on investment for a drug that is directed to the treatment of HFP EF may be viewed unfavorably by corporate sponsors.

Nevertheless, new ways of understanding the pathogenesis of HFP EF should logically motivate a change in the direction of drug development toward HFP EF. This opportunity may be particularly relevant for the long list of adipokine-targeting agents (enumerated above) that are currently being advanced for the treatment of obesity or nonalcoholic fatty liver diseases—disorders of visceral adiposity that are closely intertwined with the pathogenesis of HFP EF.

#### PART IX. THE ADIPOKINE HYPOTHESIS OF HFP EF: SYNTHESIS OF THE EVIDENCE

Adipose tissue, often comprising ≈ 50% of body weight in people with obesity, is the body's largest secretory organ, and the adipocyte secretome represents the transducer that translates dietary nutritional signals into the release of messenger molecules from adipose tissue—adipokines—that are transmitted to and influence biological responses in other organs. Excess visceral adiposity triggers a state of heightened adipose tissue stress, characterized by cellular growth and inflammation, which is paralleled by a dramatic shift in the biological secretory profile of adipose tissue. As the mass of visceral fat expands, adipose tissue abandons the nurturing cytoprotective profile that is dominant in lean people, and it produces an altered suite of secreted molecules that act to promote hypertrophy and inflammation in neighboring cells (via a

paracrine effect) and at distant sites following release into the bloodstream (via an endocrine effect).

**ADIPOSE TISSUE IS THE MAJOR SYNTHESIS SITE FOR CIRCULATING ADIPOKINES, AND THESE ADIPOKINES (ACTING BY AN ENDOCRINE OR PARACRINE MECHANISM) TARGET THE HEART.** Many of the key adipokines are principally synthesized by adipocytes, but others are normally produced in the liver, skeletal, or cardiac muscle and other organs in healthy lean people, and therefore, have been commonly regarded as hepatokines, myokines, or cardiokines. Yet, given the enormity of the expanded fat mass in people with obesity, if the biology of the secretome is transformed, adipose tissue emerges as a principal source of synthesis of these adipokines and is the primary determinant of circulating blood levels. Furthermore, adipose tissue (including adipocytes in the bone marrow or lipid accumulation in organs) not only synthesizes numerous proteins, but it is also a source of eicosanoids, metabokines, lipokines, microRNAs, and reprogrammed progenitor and inflammatory cells that migrate to and are taken up by the other tissues, allowing adipose tissue dysfunction to be transmitted beyond the confines of the fat mass, thus igniting the emergence of a systemic disorder that promotes widespread tissue inflammation and growth.

Inflamed and hypertrophied adipose tissue transmits its deranged biology to all organs in the body, explaining why obesity is a major exacerbating factor for cancer, nonalcoholic fatty liver disease, inflammatory arthritic disorders, and chronic kidney disease. Yet, the heart represents a particularly vulnerable target for the dissemination of deranged adipokine signals from the expanded visceral fat mass. The myocardium is not only exposed to the changes in the circulating adipokine profile, but it is bathed in epicardial adipose tissue, which—as the most biologically active visceral fat depot—secretes adipokines directly onto the heart, both in lean adults and in people with obesity. The secretions from healthy epicardial adipocytes exert nurturing and cardioprotective functions, but with visceral adiposity, epicardial fat transmits prohypertrophic, proinflammatory, and profibrotic signals (as part of an altered secretome) onto the adjoining myocardium. Furthermore, the adipokine-mediated expansion of plasma volume places hemodynamic stresses on the heart, which may enhance its susceptibility to the paracrine and endocrine effects of prohypertrophic, proinflammatory, and profibrotic adipokines.

**AN EXPANSION OF VISCELAR FAT MASS DRIVES A SYNCHRONIZED TRANSFORMATION OF ADIPOSE TISSUE SECRETION OF DOMAIN I, II, AND III ADIPOKINES THAT INFLUENCES THE EVOLUTION OF HFpEF.** Although visceral adiposity can adversely influence coronary atherogenesis, the primary cardiovascular consequence of deranged adipokine signaling is HFpEF, a state of myocardial inflammation, coronary microvascular dysfunction, and fibrosis that limits chamber distensibility, and thus, the ability of the ventricles to tolerate adipokine-related hypervolemia. In fact, the clinical, physiological and molecular features of obesity/visceral adiposity and HFpEF are strikingly parallel and substantially superimposable (**Table 1**).

Accordingly, the exercise intolerance of patients with obesity can often be explained by elevated left ventricular filling pressures at rest or exercise. At the same time, central obesity and visceral adiposity consistently precedes and predicts the development of HFpEF, and they are characteristic features of nearly every patient with HFpEF, being closely associated the hemodynamic and clinical severity of the disease and its prognosis in individual patients. Among the visceral fat depots of interest, patients with HFpEF are particularly likely to have an expanded or proinflammatory epicardial adipose tissue mass. The altered balance in the circulating adipokines that characterizes patients with obesity also characterizes patients with HFpEF. The mechanistic and clinical overlap between visceral adiposity and HFpEF is so substantial that it is logical to conclude that one disorder causes the other.

This paper proposes that an expansion of visceral fat mass precedes and is the primary cause of HFpEF, ie, HFpEF results from an adiposity-driven derangement of adipose secretion that yields an altered suite of signaling adipokines, allowing for the heightened adipocyte stress to be disseminated to the heart. This paper presents a novel organization for key adipokine proteins: 1) Domain I adipokines are cardioprotective proteins whose secretion is suppressed and whose adaptive functions are lost in obesity; 2) Domain II adipokines are cardioprotective proteins that are up-regulated by adiposity as a suboptimal compensatory or counter-regulatory response; and 3) Domain III adipokines (whose secretion is heightened in obesity) promote systemic inflammation, sodium retention, and cardiac hypertrophy and fibrosis. Adipokines that belong to the same domain change with a striking degree of parallelism, whereas Domain I and III adipokines demonstrate a consistent inverse relationship, both in healthy individuals and

across a broad range of chronic metabolic and inflammatory disorders.

**KEY LINES OF EVIDENCE THAT VISCERAL ADIPOSITY AND THE RESULTING CHANGE IN THE ADIPOKINE SECRETORY PROFILE REPRESENT THE PRINCIPAL CAUSE OF HFpEF.** The evidence to support the adipokine hypothesis of HFpEF is based on the following 12 well-supported and mutually reinforcing lines of evidence:

1. Epidemiological parallelism between obesity and HFpEF

The surge of HFpEF in clinical practice has closely followed the global epidemic of obesity in the clinical community.

2. Role of dietary nutrient excess in experimental and clinical HFpEF

In both experimental models and in the clinical setting, dietary nutrient excess represents the key originating and causal event in the evolution of HFpEF.

3. Adiposity and adipokine derangements precede and presage HFpEF

In epidemiological studies, changes in adiposity and in circulating adipokines are observed years before the diagnosis of HFpEF and predict its development.

4. Near-universal prevalence and relevance of central obesity in HFpEF

Central obesity and visceral adiposity are present in nearly every patient with HFpEF and are closely related to the hemodynamic and clinical severity of the disease. Among the visceral fat depots of interest, patients with HFpEF are particularly likely to have an expanded or proinflammatory epicardial adipose tissue mass.

5. Biological and clinical parallelism and overlap in obesity and HFpEF

Obesity and HFpEF exhibit striking similarities and parallelism and substantial overlap in their clinical, pathophysiological, and molecular features.

6. Adipocytes are the primary site of adipokine synthesis in obesity

Adipocytes (not cardiomyocytes) typically synthesize and secrete cardioactive adipokines. In people with visceral adiposity or obesity (where fat mass

comprises as much as 50% of body weight), adipose tissue is the dominant source of proinflammatory adipokines.

7. Parallelism of adipokines in obesity and heart failure and with disease severity

Serum levels or adipose tissue expression of adipokines change in parallel in obesity and heart failure. The magnitude of the increase and decrease of circulating adipokines is accompanied by parallel changes in the clinical and hemodynamic severity and prognosis of heart failure.

8. Adipokines have established biological effects on the heart

Adipokines have well-characterized effects on cardiac structure and function that are relevant to HFpEF, and they have been directly implicated in the pathogenesis of HFpEF in experimental studies.

9. Dietary nutrient deprivation ameliorates adiposity, adipokines, and HFpEF

Bariatric surgery cause shrinkage of visceral fat depots (disproportionate to the change in body weight), while simultaneously increasing circulating Domain I adipokines and decreasing in circulating Domain III adipokines. The responses to bariatric surgery indicate that dietary nutrient deprivation is sufficient to produce a decisive shift in the balance of circulating adipokines to a cardioprotective profile. Changes in systemic inflammation following bariatric surgery are related to changes in inflammatory signaling within and disseminating from adipose tissue.

10. Current HFpEF drugs ameliorate adiposity, adipokines, and HFpEF

Current drug treatments for HFpEF cause shrinkage of visceral fat depots (disproportionate to the change in body weight), while simultaneously increasing circulating Domain I adipokines and decreasing in circulating Domain III adipokines.

11. Adiposity may identify patients who benefit most from neurohormonal antagonism

An expanded adipose tissue mass is the primary driver of neurohormonal activation, explaining why adiposity may identify patients most likely to respond to MRAs, SGLT2 inhibitors, and angiotensin receptor neprilysin inhibitors in clinical trials.

**12. Selective targeting of adipokines in adipose tissue influences cardiac structure and function**

Experimental interventions that target only adipose tissue so as to selectively increase or decrease its secretion of specific adipokines can lead (typically in an endocrine manner) to changes in cardiac or vascular structure and function and can influence the development of cardiomyopathy.

**ADIPOSE-SPECIFIC INTERVENTIONS THAT TARGET THE SECRETION OF SPECIFIC ADIPOKINES EXERT EFFECTS ON THE HEART, KIDNEYS AND VASCULATURE THAT ARE RELEVANT TO HFpEF.** Experimental studies have confirmed that signaling from adipose tissue to the heart and kidney drives changes in organ health that are relevant to HFpEF (Box 14).

**BOX 14. Adipose-Specific Interventions That Target the Secretion of Specific Adipokines Exert Endocrine Effects on the Heart, Kidneys and Vasculature**

The responses to bariatric surgery indicate that dietary nutrient deprivation is sufficient to produce a decisive shift in the balance of circulating adipokines to a new set point that would be expected to produce favorable biological effects in the heart.

**Domain I Adipokines**

Adipocyte-specific suppression of eNAMPT induces a systemic multiorgan metabolic dysfunction.

**Domain II Adipokines**

Adipocyte-specific overexpression of adiponectin produces favorable effects on the evolution of HFpEF, and transplantation of vaspin-expressing adipose tissue produces cardioprotective effects.

**Domain III Adipokines**

Adipocyte-specific secretion of chemerin exerts adverse vascular effects. Adipocyte-specific overexpression of PDGF-D promotes maladaptive cardiac remodeling, whereas adipocyte-specific silencing of PDGF-D decreases circulating PDGF-D levels and attenuates deleterious cardiac hypertrophic and fibrotic responses in experimental obesity.

Neurohormonal stimulation of white adipose tissue leads to galectin-3-mediated activation of cardiac fibroblasts. Conversely, adipocyte-specific silencing of autotaxin blocks the deleterious effects of obesity on the heart, preventing the development of cardiac hypertrophy, cardiomyopathy, and heart failure. Transplantation of adipose tissue lacking PAI-1 attenuates cardiac metabolic abnormalities in recipient mice fed a high-fat diet.

Genetic silencing of resistin—specifically in adipose tissue—reduces circulating levels of resistin and acts to preserve cardiac function during experimental pressure overload, despite having no influence on the cardiac expression of resistin.

Mice with selective deletion of LCN2 in adipose tissue—but not those with selective deletion of LCN2 in the kidney—are protected from aldosterone-induced renal injury. Adipocyte-specific up-regulation of the mineralocorticoid receptor leads to vascular dysfunction. Transplantation of perivascular adipose tissue in which angiotensin II signaling has been pharmacologically suppressed prevents vascular injury. Adipocyte-specific ablation of ANGPTL4 prevents vascular disease.

The suppression of systemic inflammation following bariatric surgery in people with obesity is not related to an effect on circulating inflammatory cells (e.g., monocytes), but instead, it is related to suppression of inflammation-related genes in adipose tissue.

Transplantation of bone marrow mesenchymal cells and adipocytes from mice with HFpEF leads to recapitulation of HFpEF in healthy recipient mice, but knockout of SPARC in transplanted bone marrow taken from mice with pressure overload prevents transmission of the cardiac fibrosis phenotype to recipient mice. Suppression of CCR2 in bone marrow-resident inflammatory cells ameliorates experimental cardiomyopathy. Transplantation of fat tissue (that is pretreated with an SGLT2 inhibitor) into recipient mice with experimental diet-induced obesity ameliorates their vascular abnormalities.

**Nutrient Surplus and Deprivation Signaling**

Selective SIRT1 up-regulation in adipose-derived stem cells alleviates diabetes-induced HFpEF.

Adipocyte-specific up-regulation of heme oxygenase-1 improves the biological profile of cardiac and vascular tissues in experimental obesity.

The effect of PPAR $\gamma$  agonism with rosiglitazone to induce cardiac hypertrophy is mediated by the drug's effect on adipose tissue rather than the heart, because the prohypertrophic action of the drug is attenuated by adipocyte-specific (but not by cardiomyocyte-specific) silencing of PPAR $\gamma$ .

For Domain I adipokines, adipocyte-specific suppression of eNAMPT induces a systemic multiorgan metabolic dysfunction.<sup>186-188</sup>

For Domain II adipokines, adipocyte-specific overexpression of adiponectin produces favorable effects on HFpEF.<sup>624-626</sup> Transplantation of vaspin-expressing adipose tissue produces cardioprotective effects in recipient mice.<sup>320</sup>

For Domain III adipokines, adipocyte-specific secretion of chemerin adversely affects vascular function.<sup>862</sup> Adipocyte-specific overexpression of PDGF-D promotes maladaptive cardiac remodeling, whereas adipocyte-specific silencing of PDGF-D decreases circulating PDGF-D levels and attenuates deleterious cardiac hypertrophic and fibrotic responses in experimental obesity.<sup>984</sup> Neurohormonal stimulation of white adipose tissue leads to galectin-3-mediated activation of cardiac fibroblasts.<sup>491</sup>

Experimental silencing of resistin—specifically in adipose tissue—reduces circulating levels of resistin and preserves cardiac function during pressure overload, but without any influence on cardiac expression of resistin.<sup>901</sup> Adipocyte-specific silencing of autotaxin blocks the deleterious effects of obesity on the heart, preventing the development of cardiac hypertrophy, cardiomyopathy, and heart failure.<sup>943</sup> Transplantation of adipose tissue lacking PAI-1 attenuates cardiac metabolic abnormalities in recipient mice fed a high-fat diet.<sup>105</sup>

Mice with selective deletion of LCN2 in adipose tissue—but not those with selective deletion of LCN2 in the kidney—are protected from aldosterone-induced renal injury.<sup>818</sup> Adipocyte-specific up-regulation of the mineralocorticoid receptor leads to vascular dysfunction.<sup>757</sup> Transplantation of perivascular adipose tissue in which angiotensin II signaling has been pharmacologically suppressed prevents vascular injury.<sup>752</sup> Adipocyte-specific ablation of ANGPTL4 prevents vascular disease.<sup>1358</sup>

The transplantation of bone marrow adipocytes from mice with HFpEF leads to recapitulation of HFpEF in healthy recipient mice,<sup>104</sup> but knockout of SPARC in transplanted bone marrow extracted from mice with pressure overload prevents the transmission of the cardiac fibrosis phenotype to recipient mice.<sup>1128</sup> Adipose tissue-specific suppression of CCL2 has favorable effects at distant sites,<sup>1266</sup> and suppression of CCR2 in inflammatory cells residing in the bone marrow acts to ameliorate experimental cardiomyopathy.<sup>1267</sup> Transplantation of fat tissue that has been pretreated with an SGLT2 inhibitor acts to ameliorate the vascular abnormalities in recipient mice with experimental diet-induced obesity.<sup>1642</sup>

With respect to the balance of intracellular nutrient deprivation and surplus signaling, selective SIRT1 up-regulation in adipose-derived stem cells alleviates diabetes-induced HFpEF.<sup>101</sup> Adipocyte-specific up-regulation of heme oxygenase-1 (which reinforces SIRT1 signaling<sup>102</sup>) improves the biological profile of cardiac and vascular tissues in experimental obesity.<sup>103</sup> The effect of PPAR $\gamma$  agonism with rosiglitazone to induce cardiac hypertrophy is mediated by the drug's effect on adipose tissue rather than the heart, because the prohypertrophic action of the drug is attenuated by adipocyte-specific (but not by cardiomyocyte-specific) silencing of PPAR $\gamma$ .<sup>1756,1757</sup>

Intriguingly, the crosstalk between adipose tissue and the heart is bidirectional, with cardiac-specific stresses and interventions leading to effects on adipose biology,<sup>129,141,142,247,796,821</sup> potentially representing a signal from the heart to adipocytes to fine-

tune the synthesis of adipokines, which can then respond (in an endocrine manner) to ameliorate or exacerbate conditions of cellular stress within the myocardium.<sup>247</sup>

**INTERVENTIONS THAT SHRINK THE MASS AND IMPROVE THE BIOLOGY OF VISCERAL ADIPOSE TISSUE HAVE FAVORABLE EFFECTS ON THE ADIPOKINE SECRETION PROFILE AND IN HFpEF.** In the clinical setting, the results with weight loss interventions provide the most persuasive support for the clinical relevance of the adipokine hypothesis of HFpEF. The weight loss that follows bariatric surgery not only produces an amelioration of adipose tissue hypertrophy and inflammation, but it also reverses most of the well-characterized abnormalities in adipokine signaling, with a remarkable restoration of Domain I adipokines along with normalization of Domain III adipokines. These responses are paralleled by exaggerated shrinkage of visceral fat depots (disproportionate to the decrease in body weight), suppression of systemic inflammation, amelioration of structural abnormalities in the left atrium and ventricle, favorable effects on symptoms, health status and exercise tolerance, and a reduction in the risk of worsening heart failure events.

The responses to bariatric surgery demonstrate that dietary nutrient deprivation is sufficient to produce a decisive shift in the balance of circulating adipokines to a cardioprotective profile. It is particularly noteworthy that the suppression of systemic inflammation following bariatric surgery in people with obesity is not related to an effect on circulating inflammatory cells, but instead, it is related to down-regulation of inflammation-related genes in adipose tissue.<sup>1519</sup>

Incretin receptor agonists as well as current FDA-approved drugs for HFpEF (MRAs, SGLT2 inhibitors, and angiotensin receptor neprilysin inhibitors) also cause a meaningful reduction in visceral adipose tissue mass that is disproportionately larger than the minimal change in body weight produced by these drugs. Furthermore, during treatment with these drugs, this shrinkage of visceral fat is accompanied by increases in Domain I adipokines and decreases in Domain III adipokines.

Interestingly, both bariatric surgery and current drugs for HFpEF lead to increases in several Domain II adipokines—FGF21, GDF-15, and ATGL; obesity may be accompanied by biological resistance to the effects of these proteins.<sup>251-253,280</sup> Drugs for HFpEF also increase circulating levels of several other Domain II adipokines (eg, irisin, apelin, HGF), whereas these adipokines are decreased by bariatric surgery. The

marked loss of weight with bariatric surgery may reduce the stimulus to the secretion of many Domain II adipokines. However, the action of currently prescribed drugs to up-regulate Domain II adipokines (simultaneous with suppression of Domain III adipokines) would be expected to produce unopposed favorable effects on adipose tissue and the heart.

The proposed framework identifies 2 generic drugs that might be usefully repurposed for HFpEF (ie, metformin and fenofibrate) as well as promising adipokine targets that can be exploited by existing novel pharmacological agents (ie, sotatercept and other activin antagonists, FGF21 analogs, leptin antagonists, and PDE9 inhibitors).

**ARE CURRENT ASSUMPTIONS OF EXCEPTIONAL HFpEF HETEROGENEITY JUSTIFIED?** The proposal of a single unifying hypothesis for HFpEF—based on adipose tissue dysfunction and its dissemination to the heart through secreted adipokines—may be viewed skeptically by those who have long believed that the pathogenesis of HFpEF is too complex to be described in a straight-forward manner that would be applicable to the vast majority of afflicted patients. Many investigators believe that HFpEF is an exceptionally heterogenous disorder and that evolution and progression of the disease is determined by distinct independent pathways, driven in different cohorts by numerous coexisting conditions, eg, sedentary aging, systemic and pulmonary hypertension, diabetes, coronary artery disease, aortic stiffness, cardiac hypertrophy and fibrosis, atrial fibrillation with atrial myopathy, microvascular abnormalities, systemic inflammation, natriuretic peptide deficiency, and chronic pulmonary or kidney disease.

However, the widespread belief that HFpEF is a heterogenous disorder lacks strong evidentiary support. The current impression of heterogeneity simply reflects the clinical appreciation that HFpEF is characterized by a large number of obvious comorbidities and pathophysiological abnormalities, whose presence and severity may vary from patient to patient. Yet, these same comorbidities and structural and functional derangements (along with their variability) are also seen in patients with HFrEF, in whom they are *not* believed to represent individual pathways, and instead, they are regarded as being consequences of neurohormonal activation. The comorbidities (or clusters of comorbidities) in HFpEF have not identified a particular group of responders in clinical trials. Furthermore, no evidence suggests that the treatment of hypertension, diabetes, coronary artery disease, elevated pulmonary artery

pressures, cardiac hypertrophy, or chronic kidney disease has any influence on outcomes in HFpEF. No unifying mechanism has been identified by which these comorbidities might exert convergent effects to promote systemic inflammation, coronary arterial endothelial dysfunction or microvascular rarefaction,<sup>19</sup> and myocardial hypertrophy and fibrosis.

Therefore, instead of considering the comorbidities of HFpEF as representing separate pathways or distinct mechanisms, the “adipokine hypothesis of HFpEF” suggests that these coexisting disorders are the expected clinical manifestations of a single underlying mechanism, ie, a nutrient excess-induced overabundant and dysfunctional visceral fat mass that transmits its biological derangements to distant sites through adipokines acting as intermediaries. Accordingly, the comorbidities of HFpEF do not cause HFpEF, but instead, HFpEF, its comorbidities, and the systemic inflammatory state are all caused by the action of adipokines on the heart, vasculature, and kidneys.

**A NEW CONCEPTUAL MODEL AS A LAUNCH POINT FOR RESEARCH AND DEBATE.** The adipokine hypothesis is presented herein as an intentionally bold proposal that warmly welcomes feedback and criticism. The framework is proposed with the intent of inviting discourse and debate, so as to motivate new ways of thinking and ignite new directions in research. This paper represents an early first step, because it does not cover hundreds of other adipose-secretory products that are likely to transmit the biological stress of inflamed adipocytes to the heart.

More work is needed to explore the role of adipokines in explaining the pathophysiological and clinical differences in the evolution and progression of HFpEF in men and women as well as the influence of aging.<sup>35</sup> When compared with men, women with visceral adiposity (identified by dual-energy x-ray absorptiometry) are more likely to be misclassified as not having obesity (defined by body mass index). In a 10-year survey of >9,000 people, 48% of women were misclassified as being nonobese by body mass index, but were found to have obesity by measurements of percent body fat.<sup>1816</sup> A similar pattern of discordance was not seen in men, and the biological importance of visceral adiposity in women in this study was confirmed by their markedly elevated levels of leptin. Circulating levels of leptin are better correlated with cardiovascular stress and systemic inflammation in women than in men,<sup>1817</sup> and the influence of leptin in women is heightened as people age.<sup>1818</sup>

According to the adipokine hypothesis, new treatments for HFpEF should not seek to achieve

weight loss for its own sake, but instead, they should act to ameliorate the dysfunctional adipose tissue biology that drives the pathogenesis of HFpEF—without producing off-target effects. Historically, certain weight-loss drugs have had independent adverse cardiovascular and neuropsychiatric actions, eg, sibutramine and rimonabant.<sup>1814,1815</sup> Similarly, amylin agonists can potentiate the weight loss produced by other incretin-based drugs,<sup>1812</sup> but increased amylin signaling may cause proteotoxic effects, pathological cardiomyocyte remodeling, and diastolic dysfunction.<sup>1813</sup>

In conclusion, the adipokine hypothesis of HFpEF is presented as a testable and falsifiable model for the conceptual organization, synthesis, and reconciliation of available experimental and clinical evidence. It seeks to provide a new coherent lens through which HFpEF can be investigated, understood, and

treated. Its ultimate value, if any, will be determined by its ability to galvanize new thinking, prompt decisive experiments, and improve the care of patients.

## DISCLOSURES

Dr Packer has received consulting fees from Abbvie, Actavis, Alnylam, Altimimmune, Ardelyx, Amgen, ARMO, AstraZeneca, Attralus, Bioapeutics, Boehringer Ingelheim, Caladrius, Casana, CSL Behring, Cytokinetics, Daiichi Sankyo, Eli Lilly and Company, Imara, Medtronic, Moderna, Novartis, Pharmacosmos, Regeneron, and Salamandra.

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## REFERENCES

1. Packer M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. *J Am Coll Cardiol*. 1992;20:248-254.
2. Packer M, Pitt B, Rouleau JL, Swedberg K, DeMets DL, Fisher L. Long-term effects of flosequinan on the morbidity and mortality of patients with severe chronic heart failure: primary results of the PROFILE trial after 24 years. *JACC Heart Fail*. 2017;5:399-407.
3. Hampton JR, van Veldhuisen DJ, Kleber FX, et al. Second Prospective Randomised Study of Ibopamine on Mortality and Efficacy (PRIME II) Investigators. Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure. *Lancet*. 1997;349:971-977.
4. Packer M, Carson P, Elkayam U, et al. Effect of amlodipine on the survival of patients with severe chronic heart failure due to a nonischemic cardiomyopathy: results of the PRAISE-2 study (Prospective Randomized Amlodipine Survival Evaluation 2). *JACC Heart Fail*. 2013;1:308-314.
5. Pitt B, Zannad F, Remme WJ, et al. Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999;341:709-717.
6. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993-1004.
7. Packer M, McMurray JJV, Krum H, et al. Long-term effect of endothelin receptor antagonism with bosentan on the morbidity and mortality of patients with severe chronic heart failure: primary results of the ENABLE trials. *JACC Heart Fail*. 2017;5:317-326.
8. Cohn JN, Pfeffer MA, Rouleau J, et al. Adverse mortality effect of central sympathetic inhibition with sustained-release moxonidine in patients with heart failure (MOXCON). *Eur J Heart Fail*. 2003;5:659-667.
9. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. *Circulation*. 2017;136:6-19.
10. Matsuzawa Y, Shimomura I, Kihara S, Funahashi T. Importance of adipocytokines in obesity-related diseases. *Horm Res*. 2003;60 (Suppl 3):56-59.
11. Swainson MG, Batterham AM, Tsakrildes C, Rutherford ZH, Hind K. Prediction of whole-body fat percentage and visceral adipose tissue mass from five anthropometric variables. *PLoS One*. 2017;12(5):e0177175. <https://doi.org/10.1371/journal.pone.0177175>
12. Peikert A, Vaduganathan M, Claggett BL, et al. Near-universal prevalence of central adiposity and its prognostic significance in heart failure with mildly reduced or preserved ejection fraction: the PARAGON-HF trial. *Eur Heart J*. 2025;ehaf057. <https://doi.org/10.1093/euroheartj/ehaf057>
13. Reddy YNV, Frantz RP, Hemnes AR, et al. Disentangling the impact of adiposity from insulin resistance in heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2025;85:1774-1788.
14. Oguntade AS, Taylor H, Lacey B, Lewington S. Adiposity, fat-free mass and incident heart failure in 500 000 individuals. *Open Heart*. 2024;11(2):e002711. <https://doi.org/10.1136/openhrt-2024-002711>
15. Sorimachi H, Obokata M, Takahashi N, et al. Pathophysiologic importance of visceral adipose tissue in women with heart failure and preserved ejection fraction. *Eur Heart J*. 2021;42:1595-1605.
16. Ramirez MF, Lau ES, Parekh JK, et al. Obesity-related biomarkers are associated with exercise intolerance and HFpEF. *Circ Heart Fail*. 2023;16 (11):e010618. <https://doi.org/10.1161/CIRCH-EARTFAILURE.123.010618>
17. Sorimachi H, Burkhoff D, Verbrugge FH, et al. Obesity, venous capacitance, and venous compliance in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2021;23:1648-1658.
18. Mohammed SF, Hussain S, Mirzoyev SA, Edwards WD, Maleszewski JJ, Redfield MM. Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. *Circulation*. 2015;131:550-559.
19. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol*. 2013;62:263-271.
20. Packer M. Leptin-aldosterone-neprilysin axis: identification of its distinctive role in the pathogenesis of the three phenotypes of heart failure in people with obesity. *Circulation*. 2018;137:1614-1631.
21. Packer M. Derangements in adrenergic-adipokine signalling establish a neurohormonal basis for obesity-related heart failure with a preserved ejection fraction. *Eur J Heart Fail*. 2018;20:873-878.
22. Packer M, Kitzman DW. Obesity-related heart failure with a preserved ejection fraction: the mechanistic rationale for combining inhibitors of aldosterone, neprilysin, and sodium-glucose cotransporter-2. *JACC Heart Fail*. 2018;6:633-639.
23. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;381:1609-1620.
24. Solomon SD, McMurray JJV, Vaduganathan M, et al. Finerenone in heart failure with mildly

- reduced or preserved ejection fraction. *N Engl J Med.* 2024;391:1475-1485.
- 25.** Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med.* 2021;385:1451-1461.
- 26.** Packer M, Zile MR, Kramer CM, et al. Tirzepatide for heart failure with preserved ejection fraction and obesity. *N Engl J Med.* 2025;392(5):427-437. <https://doi.org/10.1056/NEJMoa2410027>
- 27.** Kramer CM, Borlaug BA, Zile MR, et al. Tirzepatide reduces LV mass and paracardiac adipose tissue in obesity-related heart failure: SUMMIT CMR substudy. *J Am Coll Cardiol.* 2025;85(7):699-706.
- 28.** Packer M. The epicardial adipose inflammatory triad: coronary atherosclerosis, atrial fibrillation, and heart failure with a preserved ejection fraction. *Eur J Heart Fail.* 2018;20:1567-1569.
- 29.** Correia ETO, Barbetta LMDS, Costa OSD, Miranda PEH, Mesquita ET. Epicardial adipose tissue in heart failure phenotypes - a meta-analysis. *Arq Bras Cardiol.* 2022;118:625-633.
- 30.** Choy M, Huang Y, Peng Y, et al. Association between epicardial adipose tissue and incident heart failure mediating by alteration of natriuretic peptide and myocardial strain. *BMC Med.* 2023;21(1):117. <https://doi.org/10.1186/s12916-023-02836-4>
- 31.** van Woerden G, van Veldhuisen DJ, Manintveld OC, et al. Epicardial adipose tissue and outcome in heart failure with mid-range and preserved ejection fraction. *Circ Heart Fail.* 2022;15(3):e009238. <https://doi.org/10.1161/CIRCHEARTFAILURE.121.009238>
- 32.** Lau ES, Roshandelpoor A, Zarbafian S, et al. Eicosanoid and eicosanoid-related inflammatory mediators and exercise intolerance in heart failure with preserved ejection fraction. *Nat Commun.* 2023;14(1):7557. <https://doi.org/10.1038/s41467-023-43363-3>
- 33.** Malick A, Ali A, MacCannell ADV, Roberts LD. Brown and beige adipose tissue-derived metabolokine and lipokine inter-organ signalling in health and disease. *Exp Physiol.* 2025;110(7):918-935. <https://doi.org/10.1113/EPO92008>
- 34.** Matilainen J, Berg V, Vaittinen M, et al. Increased secretion of adipocyte-derived extracellular vesicles is associated with adipose tissue inflammation and the mobilization of excess lipid in human obesity. *J Transl Med.* 2024;22(1):623. <https://doi.org/10.1186/s12967-024-05249-w>
- 35.** Packer M, Lam CSP, Lund LH, Maurer MS, Borlaug BA. Characterization of the inflammatory-metabolic phenotype of heart failure with a preserved ejection fraction: a hypothesis to explain influence of sex on the evolution and potential treatment of the disease. *Eur J Heart Fail.* 2020;22:1551-1567.
- 36.** Bickel CA, Verbalis JG, Knepper MA, Ecelbarger CA. Increased renal Na-K-ATPase, NCC, and beta-ENaC abundance in obese Zucker rats. *Am J Physiol Renal Physiol.* 2001;281:F639-F648.
- 37.** Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity-induced hypertension: interaction of neurohumoral and renal mechanisms. *Circ Res.* 2015;116:991-1006.
- 38.** Huby AC, Antonova G, Groenendyk J, et al. Adipocyte-derived hormone leptin is a direct regulator of aldosterone secretion, which promotes endothelial dysfunction and cardiac fibrosis. *Circulation.* 2015;132:2134-2145.
- 39.** Briones AM, Nguyen Dinh, Cat A, Callera GE, et al. Adipocytes produce aldosterone through calcineurin-dependent signaling pathways: implications in diabetes mellitus-associated obesity and vascular dysfunction. *Hypertension.* 2012;59:1069-1078.
- 40.** Nagase M. Activation of the aldosterone/mineralocorticoid receptor system in chronic kidney disease and metabolic syndrome. *Clin Exp Nephrol.* 2010;14:303-314.
- 41.** Standeven KF, Hess K, Carter AM, et al. Neprilysin, obesity and the metabolic syndrome. *Int J Obes (Lond).* 2011;35:1031-1040.
- 42.** Poh KK, Shabbir A, Ngiam JN, et al. Plasma clearance of B-type natriuretic peptide (BNP) before and after bariatric surgery for morbid obesity. *Clin Chem.* 2021;67:662-671.
- 43.** Dudenbostel T, Calhoun DA. Use of aldosterone antagonists for treatment of uncontrolled resistant hypertension. *Am J Hypertens.* 2017;30(2):103-109.
- 44.** Jordan J, Stinkens R, Jax T, et al. Improved insulin sensitivity with angiotensin receptor neprilysin inhibition in individuals with obesity and hypertension. *Clin Pharmacol Ther.* 2017;101:254-263.
- 45.** Kennedy C, Hayes P, Cicero AFG, et al. Semaglutide and blood pressure: an individual patient data meta-analysis. *Eur Heart J.* 2024;45:4124-4134.
- 46.** Alpert MA, Karthikeyan K, Abdullah O, Ghadban R. Obesity and cardiac remodeling in adults: mechanisms and clinical implications. *Prog Cardiovasc Dis.* 2018;61:114-123.
- 47.** Fleenor BS, Carlini NA, Ouyang A, Du B, Harber MP. Greater aortic perivascular adipose tissue density is associated with aging, aortic stiffness, and central blood pressure in humans. *J Appl Physiol (1985).* 2023;134:703-709.
- 48.** Liu IF, Lin TC, Wang SC, et al. Long-term administration of Western diet induced metabolic syndrome in mice and causes cardiac microvascular dysfunction, cardiomyocyte mitochondrial damage, and cardiac remodeling involving caveolae and caveolin-1 expression. *Biol Direct.* 2023;18(1):9. <https://doi.org/10.1186/s13062-023-00363-z>
- 49.** Zhao H, Huang R, Jiang M, et al. Myocardial tissue-level characteristics of adults with metabolically healthy obesity. *JACC Cardiovasc Imaging.* 2023;16:889-901.
- 50.** Jhuo SJ, Lin YH, Liu IH, et al. Sodium glucose cotransporter 2 (SGLT2) inhibitor ameliorate metabolic disorder and obesity induced cardiomyocyte injury and mitochondrial remodeling. *Int J Mol Sci.* 2023;24(7):6842. <https://doi.org/10.3390/ijms24076842>
- 51.** Ruiz-Ramírez A, López-Acosta O, Barrios-Maya MA, El-Hafidi M. Cell death and heart failure in obesity: role of uncoupling proteins. *Oxid Med Cell Longev.* 2016;2016:9340654. <https://doi.org/10.1155/2016/9340654>
- 52.** Joseph LC, Subramanyam P, Radlicz C, et al. Mitochondrial oxidative stress during cardiac lipid overload causes intracellular calcium leak and arrhythmia. *Heart Rhythm.* 2016;13:1699-1706.
- 53.** El Saiedi SA, Mira MF, Sharaf SA, et al. Left ventricular diastolic dysfunction without left ventricular hypertrophy in obese children and adolescents: a Tissue Doppler Imaging and Cardiac Troponin I Study. *Cardiol Young.* 2018;28:76-84.
- 54.** Lyngbakken MN, Omland T, Nordstrand N, Norseth J, Hjelmesæth J, Hofsjø D. Effect of weight loss on subclinical myocardial injury: a clinical trial comparing gastric bypass surgery and intensive lifestyle intervention. *Eur J Prev Cardiol.* 2016;23:874-880.
- 55.** Zemancikova A, Torok J, Balis P, Valovic P, Ulicna O, Chomova M. Modulation of sympathetic-adrenergic contractions by perivascular adipose tissue in mesenteric arteries of rats with different level of body adiposity. *J Physiol Pharmacol.* 2020;71(4). <https://doi.org/10.26402/jpp.2020.4.14>
- 56.** Pascual M, Pascual DA, Soria F, et al. Effects of isolated obesity on systolic and diastolic left ventricular function. *Heart.* 2003;89:1152-1156.
- 57.** Alpert MA, Omran J, Bostick BP. Effects of obesity on cardiovascular hemodynamics, cardiac morphology, and ventricular function. *Curr Obes Rep.* 2016;5:424-434.
- 58.** Chalmers L, Kaskel FJ, Bamgbola O. The role of obesity and its bioclinical correlates in the progression of chronic kidney disease. *Adv Chronic Kidney Dis.* 2006;13:352-364.
- 59.** Agarwal A, Beddu S, Boucher R, et al. Evaluation of renal sodium handling in heart failure with preserved ejection fraction: a pilot study. *Physiol Rep.* 2024;12(9):e16033. <https://doi.org/10.1481/phy2.16033>
- 60.** Noumi B, Teruya S, Salomon S, Helmke S, Maurer MS. Blood volume measurements in patients with heart failure and a preserved ejection fraction: implications for diagnosing anemia. *Congest Heart Fail.* 2011;17:14-18.
- 61.** Tada A, Burkhoff D, Naser JA, et al. Dapagliflozin enhances arterial and venous compliance during exercise in heart failure with preserved ejection fraction: Insights From the CAMEO-DAPA trial. *Circulation.* 2024;150:997-1009.
- 62.** Kresoga KP, Rommel KP, Fengler K, et al. Renal sympathetic denervation in patients with heart failure with preserved ejection fraction. *Circ Heart Fail.* 2021;14(3):e007421. <https://doi.org/10.1161/CIRCHEARTFAILURE.120.007421>
- 63.** Málek F, Gajewski P, Zymlinski R, et al. Surgical ablation of the right greater splanchnic nerve for the treatment of heart failure with preserved ejection fraction: first-in-human clinical trial. *Eur J Heart Fail.* 2021;23:1134-1143.
- 64.** Edelmann F, Tomaschitz A, Wachter R, et al. Serum aldosterone and its relationship to left ventricular structure and geometry in patients

- with preserved left ventricular ejection fraction. *Eur Heart J.* 2012;33:203-212.
- 65.** Ke B, Tan X, Ren L, et al. Aldosterone dysregulation predicts the risk of mortality and rehospitalization in heart failure with a preserved ejection fraction. *Sci China Life Sci.* 2022;65:631-642.
- 66.** Ayuzawa N, Nagase M, Ueda K, et al. Rac1-mediated activation of mineralocorticoid receptor in pressure overload-induced cardiac injury. *Hypertension.* 2016;67:99-106.
- 67.** Faxén UL, Hage C, Andreasson A, et al. HFpEF and HFrEF exhibit different phenotypes as assessed by leptin and adiponectin. *Int J Cardiol.* 2017;228:709-716.
- 68.** Lanfear DE, Chow S, Padhukasasnam B, et al. Genetic and nongenetic factors influencing pharmacokinetics of B-type natriuretic peptide. *J Card Fail.* 2014;20:662-668.
- 69.** Goliasch G, Pavo N, Zotter-Tufaro C, et al. Soluble neprilysin does not correlate with outcome in heart failure with preserved ejection fraction. *Eur J Heart Fail.* 2016;18:89-93.
- 70.** Jackson AM, Jhund PS, Anand IS, et al. Sacubitril-valsartan as a treatment for apparent resistant hypertension in patients with heart failure and preserved ejection fraction. *Eur Heart J.* 2021;42:3741-3752.
- 71.** Pandey A, Garg S, Matulevicius SA, et al. Effect of mineralocorticoid receptor antagonists on cardiac structure and function in patients with diastolic dysfunction and heart failure with preserved ejection fraction: a meta-analysis and systematic review. *J Am Heart Assoc.* 2015;4(10):e002137. <https://doi.org/10.1161/JAHA.115.002137>
- 72.** Borlaug BA, Zile MR, Kramer CM, et al. Effects of tirzepatide on circulatory overload and end-organ damage in heart failure with preserved ejection fraction and obesity: a secondary analysis of the SUMMIT trial. *Nat Med.* 2025;31(2):544-551. <https://doi.org/10.1038/s41591-024-03374-z>
- 73.** Khadke S, Kumar A, Bhatti A, et al. GLP-1 receptor agonist in non-obese patients with type-2 diabetes mellitus and heart failure with preserved ejection fraction. *J Card Fail.* 2025;31(7):989-1001. <https://doi.org/10.1016/j.cardfail.2024.10.448>
- 74.** Ferreira JP, Claggett BL, Liu J, et al. High-sensitivity C-reactive protein in heart failure with preserved ejection fraction: findings from TOPCAT. *Int J Cardiol.* 2024;402:131818.
- 75.** Rosas PC, Neves LAA, Patel N, et al. Early pathological mechanisms in a mouse model of heart failure with preserved ejection fraction. *Am J Physiol Heart Circ Physiol.* 2024;327:H1524-H1543.
- 76.** Schiattarella GG, Altamirano F, Tong D, et al. Nitrosative stress drives heart failure with preserved ejection fraction. *Nature.* 2019;568:351-356.
- 77.** Yoshii A, McMillen TS, Wang Y, et al. Blunted cardiac mitophagy in response to metabolic stress contributes to HFpEF. *Circ Res.* 2024;135:1004-1017.
- 78.** Panico C, Felicetta A, Kunderfranco P, et al. Single-cell RNA sequencing reveals metabolic stress-dependent activation of cardiac macrophages in a model of dyslipidemia-induced diastolic dysfunction. *Circulation.* 2024;150:1517-1532.
- 79.** Obokata M, Reddy YNV, Melenovsky V, et al. Myocardial injury and cardiac reserve in patients with heart failure and preserved ejection fraction. *J Am Coll Cardiol.* 2018;72:29-40.
- 80.** Peikert A, Vaduganathan M, Mc Causland F, et al. Effects of sacubitril/valsartan versus valsartan on renal function in patients with and without diabetes and heart failure with preserved ejection fraction: insights from PARAGON-HF. *Eur J Heart Fail.* 2022;24:794-803.
- 81.** Zhao L, Zierath R, John JE, et al. Subclinical risk factors for heart failure with preserved and reduced ejection fraction among Black adults. *JAMA Netw Open.* 2022;5(9):e2231878. <https://doi.org/10.1001/jamanetworkopen.2022.31878>
- 82.** Rao VN, Zhao D, Allison MA, et al. Adiposity and incident heart failure and its subtypes: MESA (Multi-Ethnic Study of Atherosclerosis). *JACC Heart Fail.* 2018;6:999-1007.
- 83.** Oguntade AS, Islam N, Malouf R, et al. Body composition and risk of incident heart failure in 1 million adults: a systematic review and dose-response meta-analysis of prospective cohort studies. *J Am Heart Assoc.* 2023;12(13):e029062. <https://doi.org/10.1161/JAHA.122.029062>
- 84.** Packer M. Do most obese people with exercise intolerance and a normal ejection fraction have treatable heart failure? *Am J Med.* 2018;131:863-864.
- 85.** Gabreli I, Ma XH, Yang XM, et al. Removal of visceral fat prevents insulin resistance and glucose intolerance of aging: an adipokine-mediated process? *Diabetes.* 2002;51:2951-2958.
- 86.** Koutroumpakis E, Jozwik B, Aguilar D, Taegtmeyer H. Strategies of unloading the failing heart from metabolic stress. *Am J Med.* 2020;133:290-296.
- 87.** Gerstein HC, Bosch J, Dagenais GR, et al. ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med.* 2012;367:319-328.
- 88.** Abel ED, Peroni O, Kim JK. Adipose-selective targeting of the GLUT4 gene impairs insulin action in muscle and liver. *Nature.* 2001;409:729-733.
- 89.** Borlaug BA, Schaff HV, Asirvatham SJ, Koepf KE, Mauermann WJ, Rowse PG. Surgical pericardiectomy to treat heart failure with preserved ejection fraction: a first clinical study. *Eur Heart J.* 2023;44:4719-4721.
- 90.** Al-Samarraie SHA, Ayaz-Güner S, Acar MB, et al. Mesenchymal stem cells from adipose tissue prone to lose their stemness associated markers in obesity related stress conditions. *Sci Rep.* 2024;14(1):19702. <https://doi.org/10.1038/s41598-024-70127-w>
- 91.** Lehr S, Hartwig S, Lamers D, et al. Identification and validation of novel adipokines released from primary human adipocytes. *Mol Cell Proteomics.* 2012;11(1):M111.010504. <https://doi.org/10.1074/mcp.M111.010504>
- 92.** Zhong J, Krawczyk SA, Chaerkady R, et al. Temporal profiling of the secretome during adipogenesis in humans. *J Proteome Res.* 2010;9:5228-5238.
- 93.** Packer M. Role of deranged energy deprivation signaling in the pathogenesis of cardiac and renal disease in states of perceived nutrient overabundance. *Circulation.* 2020;141:2095-2105.
- 94.** Packer M. Longevity genes, cardiac ageing, and the pathogenesis of cardiomyopathy: implications for understanding the effects of current and future treatments for heart failure. *Eur Heart J.* 2020;41:3856-3861.
- 95.** Packer M. Cardioprotective effects of sirtuin-1 and its downstream effectors: potential role in mediating the heart failure benefits of SGLT2 (sodium-glucose cotransporter 2) inhibitors. *Circ Heart Fail.* 2020;13(9):e007197. <https://doi.org/10.1161/CIRCHEARTFAILURE.120.007197>
- 96.** Cao Y, Han S, Lu H, et al. Targeting mTOR signaling by dietary polyphenols in obesity prevention. *Nutrients.* 2022;14(23):5171. <https://doi.org/10.3390/nut14235171>
- 97.** Zhang S, Sun S, Wei X, et al. Short-term moderate caloric restriction in a high-fat diet alleviates obesity via AMPK/SIRT1 signaling in white adipocytes and liver. *Food Nutr Res.* 2022;66. <https://doi.org/10.29219/fnr.v66.7909>
- 98.** Chattopadhyay M, Mukherjee S, Chatterjee SK, et al. Impairment of energy sensors, SIRT1 and AMPK, in lipid induced inflamed adipocyte is regulated by Fetuin A. *Cell Signal.* 2018;42:67-76.
- 99.** Polak P, Cybulski N, Feige JN, Auwerx J, Rueegg MA, Hall MN. Adipose-specific knockout of raptor results in lean mice with enhanced mitochondrial respiration. *Cell Metab.* 2008;8:399-410.
- 100.** Uchinaka A, Yoneda M, Yamada Y, Murohara T, Nagata K. Effects of mTOR inhibition on cardiac and adipose tissue pathology and glucose metabolism in rats with metabolic syndrome. *Pharmacol Res Perspect.* 2017;5(4):e00331. <https://doi.org/10.1002/prp2.331>
- 101.** Chen TS, Chuang SY, Shen CY, et al. Antioxidant Sirt1/Akt axis expression in resveratrol pre-treated adipose-derived stem cells increases regenerative capability in a rat model with cardiomyopathy induced by diabetes mellitus. *J Cell Physiol.* 2021;236:4290-4302.
- 102.** Lakhani HV, Zehra M, Pillai S, Shapiro JL, Sodhi K. Dysregulation of HO-1-SIRT1 axis is associated with AngII-induced adipocyte dysfunction. *J Clin Med Sci.* 2024;8(2):1000275.
- 103.** Singh SP, Greenberg M, Glick Y, et al. Adipocyte specific HO-1 gene therapy is effective in antioxidant treatment of insulin resistance and vascular function in an obese mice model. *Antioxidants (Basel).* 2020;9(1):40. <https://doi.org/10.3390/antiox9010040>
- 104.** Nakayama Y, Fujii K, Oshima T, et al. Heart failure promotes multimorbidity through innate immune memory. *Sci Immunol.* 2024;9(95):eade3814. <https://doi.org/10.1126/sciimmuno.ade3814>

- 105.** Liu S, Li Y, Fan X, Li K, et al. Transplantation of adipose tissue lacking PAI-1 improves glucose tolerance and attenuates cardiac metabolic abnormalities in high-fat diet-induced obesity. *Adipocyte*. 2020;9:170-178.
- 106.** Inoue T, Takemori K, Mizuguchi N, et al. Heart-bound adiponectin, not serum adiponectin, inversely correlates with cardiac hypertrophy in stroke-prone spontaneously hypertensive rats. *Exp Physiol*. 2017;102:1435-1447.
- 107.** Li X, Zhang D, Vatner DF, et al. Mechanisms by which adiponectin reverses high fat diet-induced insulin resistance in mice. *Proc Natl Acad Sci U S A*. 2020;117:32584-32593.
- 108.** Kita S, Maeda N, Shimomura I. Interorgan communication by exosomes, adipose tissue, and adiponectin in metabolic syndrome. *J Clin Invest*. 2019;129:4041-4049.
- 109.** Koentges C, König A, Pfeil K, et al. Myocardial mitochondrial dysfunction in mice lacking adiponectin receptor 1. *Basic Res Cardiol*. 2015;110(4):37. <https://doi.org/10.1007/s00395-015-0495-4>
- 110.** Tanida M, Shen J, Horii Y, et al. Effects of adiponectin on the renal sympathetic nerve activity and blood pressure in rats. *Exp Biol Med (Maywood)*. 2007;232:390-397.
- 111.** Czerwieńska B, Lelek M, Gojowy D, et al. Effect of renal denervation on the plasma adiponectin concentration in patients with resistant hypertension. *J Clin Med*. 2023;12(6):2114. <https://doi.org/10.3390/jcm12062114>
- 112.** Li P, Sun F, Cao HM, et al. Expression of adiponectin receptors in mouse adrenal glands and the adrenocortical Y-1 cell line: adiponectin regulates steroidogenesis. *Biochem Biophys Res Commun*. 2009;390(4):1208-1213. <https://doi.org/10.1016/j.bbrc.2009.10.122>
- 113.** Guo C, Ricciuti V, Lian BQ, et al. Mineralocorticoid receptor blockade reverses obesity-related changes in expression of adiponectin, peroxisome proliferator-activated receptor-gamma, and proinflammatory adipokines. *Circulation*. 2008;117:2253-2261.
- 114.** Tanaka K, Wilson RM, Essick EE, et al. Effects of adiponectin on calcium-handling proteins in heart failure with preserved ejection fraction. *Circ Heart Fail*. 2014;7:976-985.
- 115.** Sam F, Duhaney TA, Sato K, et al. Adiponectin deficiency, diastolic dysfunction, and diastolic heart failure. *Endocrinology*. 2010;151:322-331.
- 116.** Cnop M, Havel PJ, Utzschneider KM, et al. Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. *Diabetologia*. 2003;46:459-469.
- 117.** Huang H, Han Y, Jose PA, Zeng C. Loss of adiponectin-induced renal sodium excretion in hypertension. *J Am Soc Hypertens*. 2016;10(Suppl 1):e4. <https://doi.org/10.1016/j.jash.2016.06.013>
- 118.** Wang LL, Miller D, Wanders D, et al. Adiponectin downregulation is associated with volume overload-induced myocyte dysfunction in rats. *Acta Pharmacol Sin*. 2016;37:187-195.
- 119.** Lin H, Lian WS, Chen HH, Lai PF, Cheng CF. Adiponectin ameliorates iron-overload cardiomyopathy through the PPARalpha-PGC-1-dependent signaling pathway. *Mol Pharmacol*. 2013;84:275-285.
- 120.** Liao Y, Takashima S, Maeda N, et al. Exacerbation of heart failure in adiponectin-deficient mice due to impaired regulation of AMPK and glucose metabolism. *Cardiovasc Res*. 2005;67:705-713.
- 121.** Norvik JV, Schirmer H, Ytrehus K, et al. Low adiponectin is associated with diastolic dysfunction in women: a cross-sectional study from the Tromso Study. *BMC Cardiovasc Disord*. 2017;17(1):79. <https://doi.org/10.1186/s12872-017-0509-2>
- 122.** Ybarra J, Resmini E, Planas F, et al. Relationship between adiponectin and left atrium size in uncomplicated obese patients: adiponectin, a link between fat and heart. *Obes Surg*. 2009;19:1324-1332.
- 123.** Bidulescu A, Liu J, Musani SK, et al. Association of adiponectin with left ventricular mass in blacks: the Jackson Heart Study. *Circ Heart Fail*. 2011;4:747-753.
- 124.** Peters KE, Davis WA, Beilby J, Hung J, Bruce DG, Davis TME. The relationship between circulating adiponectin, ADIPOQ variants and incident cardiovascular disease in type 2 diabetes: The Fremantle Diabetes Study. *Diabetes Res Clin Pract*. 2018;143:62-70.
- 125.** Tocylowski K, Hirnle T, Harasiuk D, et al. Plasma concentration and expression of adipokines in epicardial and subcutaneous adipose tissue are associated with impaired left ventricular filling pattern. *J Transl Med*. 2019;17(1):310. <https://doi.org/10.1186/s12967-019-2060-7>
- 126.** Wang LL, Miller D, Wanders D, et al. Adiponectin downregulation is associated with volume overload-induced myocyte dysfunction in rats. *Acta Pharmacol Sin*. 2016;37:187-195.
- 127.** Tan W, Wang Y, Cheng S, et al. AdipoRon ameliorates the progression of heart failure with preserved ejection fraction via mitigating lipid accumulation and fibrosis. *J Adv Res*. 2024;68:299-315. <https://doi.org/10.1016/j.jare.2024.02.015>
- 128.** Wang Y, Lau WB, Gao E, Tao L, et al. Cardiomyocyte-derived adiponectin is biologically active in protecting against myocardial ischemia-reperfusion injury. *Am J Physiol Endocrinol Metab*. 2010;298:E663-E670.
- 129.** Khan RS, Kato TS, Chokshi A, et al. Adipose tissue inflammation and adiponectin resistance in patients with advanced heart failure: correction after ventricular assist device implantation. *Circ Heart Fail*. 2012;5(3):340-348.
- 130.** Skurk C, Wittchen F, Suckau L, et al. Description of a local cardiac adiponectin system and its deregulation in dilated cardiomyopathy. *Eur Heart J*. 2008;29:1168-1180.
- 131.** Seldin MM, Tan SY, Wong GW. Metabolic function of the CTRP family of hormones. *Rev Endocr Metab Disord*. 2014;15:111-123.
- 132.** Wong GW, Krawczyk SA, Kitidis-Mitrokostas C, et al. Identification and characterization of CTRP9, a novel secreted glycoprotein, from adipose tissue that reduces serum glucose in mice and forms heterotrimers with adiponectin. *FASEB J*. 2009;23:241-258.
- 133.** Peterson JM, Wei Z, Seldin MM, Byerly MS, Ajia S, Wong GW. CTRP9 transgenic mice are protected from diet-induced obesity and metabolic dysfunction. *Am J Physiol Regul Integr Comp Physiol*. 2013;305:R522-R533.
- 134.** Kambara T, Shibata R, Ohashi K, et al. C1q/tumor necrosis factor-related protein 9 protects against acute myocardial injury through an adiponectin receptor 1-AMPK-dependent mechanism. *Mol Cell Biol*. 2015;35:2173-2185.
- 135.** Liu Y, Wu P, Xu X, et al. C1q/TNF-related protein 3 alleviates heart failure via attenuation of oxidative stress in myocardial infarction rats. *Peptides*. 2023;163:170980. <https://doi.org/10.1016/j.peptides.2023.170980>
- 136.** Zheng Q, Yuan Y, Yi W, et al. C1q/TNF-related proteins, a family of novel adipokines, induce vascular relaxation through the adiponectin receptor-1/AMPK/eNOS/nitric oxide signaling pathway. *Arterioscler Thromb Vasc Biol*. 2011;31:2616-2623.
- 137.** Zhang Q, Pei L, Fu J, Zhao R. The role of CTRP9 on inhibition the high-glucose-induced apoptosis of myocardial cells via Wnt/beta-catenin signal pathway. *Cell Mol Biol (Noisy-le-grand)*. 2022;68:59-66.
- 138.** Deng W, Li C, Zhang Y, et al. Serum C1q/TNF-related protein-3 (CTRP3) levels are decreased in obesity and hypertension and are negatively correlated with parameters of insulin resistance. *Diabetol Metab Syndr*. 2015;7:33. <https://doi.org/10.1186/s13098-015-0029-0>
- 139.** Hwang YC, Woo Oh S, Park SW, Park CY. Association of serum C1q/TNF-related protein-9 (CTRP9) concentration with visceral adiposity and metabolic syndrome in humans. *Int J Obes (Lond)*. 2014;38:1207-1212.
- 140.** Gao C, Zhao S, Lian K, et al. C1q/TNF-related protein 3 (CTRP3) and 9 (CTRP9) concentrations are decreased in patients with heart failure and are associated with increased morbidity and mortality. *BMC Cardiovasc Disord*. 2019;19(1):139. <https://doi.org/10.1186/s12872-019-1117-0>
- 141.** Yi W, Sun Y, Yuan Y, et al. C1q/tumor necrosis factor-related protein-3, a newly identified adipokine, is a novel antiapoptotic, proangiogenic, and cardioprotective molecule in the ischemic mouse heart. *Circulation*. 2012;125:3159-3169.
- 142.** Kambara T, Ohashi K, Shibata R, et al. CTRP9 protein protects against myocardial injury following ischemia-reperfusion through AMP-activated protein kinase (AMPK)-dependent mechanism. *J Biol Chem*. 2012;287:18965-18973.
- 143.** Yan W, Guo Y, Tao L, et al. C1q/tumor necrosis factor-related protein-9 regulates the fate of implanted mesenchymal stem cells and mobilizes their protective effects against ischemic heart injury via multiple novel signaling pathways. *Circulation*. 2017;136:2162-2177.
- 144.** Appari M, Breitbart A, Brandes F, et al. C1q-TNF-related protein-9 promotes cardiac hypertrophy and failure. *Circ Res*. 2017;120:66-77.
- 145.** Ma ZG, Yuan YP, Zhang X, et al. C1q-tumour necrosis factor-related protein-3 exacerbates

- cardiac hypertrophy in mice. *Cardiovasc Res.* 2019;115:1067-1077.
- 146.** Li X, Jiang L, Yang M, Wu YW, Sun SX, Sun JZ. Expression of CTRP3, a novel adipokine, in rats at different pathogenic stages of type 2 diabetes mellitus and the impacts of GLP-1 receptor agonist on it. *J Diabetes Res.* 2014;2014:398518. <https://doi.org/10.1155/2014/398518>
- 147.** Watanabe T, Watanabe-Kominato K, Takahashi Y, Kojima M, Watanabe R. Adipose tissue-derived omentin-1 function and regulation. *Compr Physiol.* 2017;7:765-781.
- 148.** Deng X, Luo H, He J, Deng W, Wang D. Omentin-1 ameliorates pulmonary arterial hypertension by inhibiting endoplasmic reticulum stress through AMPKalpha signaling. *Clin Exp Hypertens.* 2024;46(1):2332695. <https://doi.org/10.1080/10641963.2024.2332695>
- 149.** Yang H, Song S, Li J, et al. Omentin-1 drives cardiomyocyte cell cycle arrest and metabolic maturation by interacting with BMP7. *Cell Mol Life Sci.* 2023;80(7):186. <https://doi.org/10.1007/s00018-023-04829-1>
- 150.** Wan S, Cui Z, Wu L, et al. Ginsenoside Rd promotes omentin secretion in adipose through TBK1-AMPK to improve mitochondrial biogenesis via WNT5A/Ca(2+) pathways in heart failure. *Redox Biol.* 2023;60:102610. <https://doi.org/10.1016/j.redox.2023.102610>
- 151.** Fernández-Trasancos Á, Agra RM, García-Acuña JM, Fernández ÁL, González-Juanatey JR, Eiras S. Omentin treatment of epicardial fat improves its anti-inflammatory activity and paracrine benefit on smooth muscle cells. *Obesity (Silver Spring).* 2017;25(6):1042-1049.
- 152.** Matsuo K, Shibata R, Ohashi K, et al. Omentin functions to attenuate cardiac hypertrophic response. *J Mol Cell Cardiol.* 2015;79:195-202.
- 153.** Kataoka Y, Shibata R, Ohashi K, et al. Omentin prevents myocardial ischemic injury through AMP-activated protein kinase- and Akt-dependent mechanisms. *J Am Coll Cardiol.* 2014;63:2722-2733.
- 154.** Okamura Y, Adachi K, Niijima R, et al. Human omentin-1 reduces vascular insulin resistance and hypertension in Otsuka Long-Evans Tokushima Fatty rats. *Naunyn Schmiedebergs Arch Pharmacol.* 2024;397:3379-3387.
- 155.** de Souza Batista CM, Yang RZ, Lee MJ, et al. Omentin plasma levels and gene expression are decreased in obesity. *Diabetes.* 2007;56:1655-1661.
- 156.** Huang Y, Lin Y, Zhang S, et al. Circulating omentin-1 levels are decreased in dilated cardiomyopathy patients with overt heart failure. *Dis Markers.* 2016;2016:6762825. <https://doi.org/10.1155/2016/6762825>
- 157.** Narumi T, Watanabe T, Kadokawa S, et al. Impact of serum omentin-1 levels on cardiac prognosis in patients with heart failure. *Cardiovasc Diabetol.* 2014;13:84. <https://doi.org/10.1186/1475-2840-13-84>
- 158.** Su Z, Tian S, Liang W, Wu L. Association between omentin-1 and heart failure with preserved ejection fraction in Chinese elderly patients. *Clin Cardiol.* 2023;47(2):e24181. <https://doi.org/10.1002/clc.24181>
- 159.** Yan P, Li L, Yang M, et al. Effects of the long-acting human glucagon-like peptide-1 analog liraglutide on plasma omentin-1 levels in patients with type 2 diabetes mellitus. *Diabetes Res Clin Pract.* 2011;92:368-374.
- 160.** Song Y, Ma Y, Zhang K, et al. Secreted frizzled-related protein 5: A promising therapeutic target for metabolic diseases via regulation. *Biochem Biophys Res Commun.* 2023;677:70-76.
- 161.** Hong P, Wang L, Wang H, Shi M, Guo B. Effect of secreted frizzled-related protein 5 in mice with heart failure. *Evid Based Complement Alternat Med.* 2022;2022:1606212. <https://doi.org/10.1155/2022/1606212>
- 162.** Lv C, Jiang Y, Wang H, Chen B. Sfrp5 expression and secretion in adipocytes are up-regulated during differentiation and are negatively correlated with insulin resistance. *Cell Biol Int.* 2012;36:851-855.
- 163.** Mori H, Prestwich TC, Reid MA, et al. Secreted frizzled-related protein 5 suppresses adipocyte mitochondrial metabolism through WNT inhibition. *J Clin Invest.* 2012;122:2405-2416.
- 164.** Ouchi N, Higuchi A, Ohashi K, et al. Sfrp5 is an anti-inflammatory adipokine that modulates metabolic dysfunction in obesity. *Science.* 2010;329:454-457.
- 165.** Huang X, Yan Y, Zheng W, et al. Secreted Frizzled-related protein 5 protects against cardiac rupture and improves cardiac function through inhibiting mitochondrial dysfunction. *Front Cardiovasc Med.* 2021;8:e682409. <https://doi.org/10.3389/fcvm.2021.682409>
- 166.** Nakamura K, Sano S, Fuster JJ, et al. Secreted frizzled-related protein 5 diminishes cardiac inflammation and protects the heart from ischemia/reperfusion injury. *J Biol Chem.* 2016;291:2566-2575.
- 167.** Deng D, Tian D, Wang Y, Bai Y, Diao Z, Liu W. Secreted frizzled-related protein 5 protects against renal fibrosis by inhibiting Wnt/beta-catenin pathway. *Open Med (Wars).* 2024;19(1):20240934. <https://doi.org/10.1515/med-2024-0934>
- 168.** Xu Q, Wang H, Li Y, et al. Plasma Sfrp5 levels correlate with determinants of the metabolic syndrome in Chinese adults. *Diabetes Metab Res Rev.* 2017;33(6). <https://doi.org/10.1002/dmrr.2896>
- 169.** Carstensen-Kirberg M, Kannenberg JM, Huth C, et al. Inverse associations between serum levels of secreted frizzled-related protein-5 (SFRP5) and multiple cardiometabolic risk factors: KORA F4 study. *Cardiovasc Diabetol.* 2017;16(1):109. <https://doi.org/10.1186/s12933-017-0591-x>
- 170.** Kelly CJ, Chu M, Untaru R, et al. Association of circulating plasma secreted frizzled-related protein 5 (sfrp5) levels with cardiac function. *J Cardiovasc Dev Dis.* 2023;10(7):274. <https://doi.org/10.3390/jcdd10070274>
- 171.** Wu J, Zheng H, Liu X, et al. Prognostic value of secreted frizzled-related protein 5 in heart failure patients with and without type 2 diabetes mellitus. *Circ Heart Fail.* 2020;13(9):e007054. <https://doi.org/10.1161/CIRCHEARTFAILURE.120.007054>
- 172.** Kelly C, Nesbitt A, Croft A, et al. Low expression of secreted frizzled receptor protein 5 (Sfrp5) is human right atrial appendage is associated with diastolic dysfunction. *Heart Lung Circ.* 2019. <https://doi.org/10.1016/j.hlc.2019.06.111>
- 173.** Li Q, Wang X, Guo A, et al. The promising significance of liraglutide combined with dapagliflozin or empagliflozin in the prevention of early diabetic nephropathy. *Am J Transl Res.* 2022;14:5622-5629.
- 174.** Tan X, Wang X, Chu H, Liu H, Yi X, Xiao Y. SFRP5 correlates with obesity and metabolic syndrome and increases after weight loss in children. *Clin Endocrinol (Oxf).* 2014;81:363-369.
- 175.** Hu W, Li L, Yang M, et al. Circulating Sfrp5 is a signature of obesity-related metabolic disorders and is regulated by glucose and liraglutide in humans. *J Clin Endocrinol Metab.* 2013;98:290-298.
- 176.** Haider DG, Schindler K, Schaller G, Prager G, Wolzt M, Ludvik B. Increased plasma visfatin concentrations in morbidly obese subjects are reduced after gastric banding. *J Clin Endocrinol Metab.* 2006;91:1578-1581.
- 177.** Yoon MJ, Yoshida M, Johnson S, et al. SIRT1-mediated eNAMPT secretion from adipose tissue regulates hypothalamic NAD+ and function in mice. *Cell Metab.* 2015;21:706-717.
- 178.** Costantino S, Mengozzi A, Velagapudi S, et al. Treatment with recombinant Sirt1 rewires the cardiac lipidome and rescues diabetes-related metabolic cardiomyopathy. *Cardiovasc Diabetol.* 2023;22(1):312. <https://doi.org/10.1186/s12933-023-02057-2>
- 179.** Mengozzi A, Costantino S, Paneni F, et al. Targeting SIRT1 rescues age- and obesity-induced microvascular dysfunction in ex vivo human vessels. *Circ Res.* 2022;131:476-491.
- 180.** Yoshida M, Satoh A, Lin JB, et al. Extracellular vesicle-contained eNAMPT delays aging and extends lifespan in mice. *Cell Metab.* 2019;30(2):329-342.e5.
- 181.** Torretta S, Colombo G, Travelli C, et al. The cytokine nicotinamide phosphoribosyltransferase (eNAMPT; PBEF; visfatin) acts as a natural antagonist of C-C chemokine receptor type 5 (CCR5). *Cells.* 2020;9(2):496. <https://doi.org/10.3390/cells9020496>
- 182.** Chiao YA, Chakraborty AD, Light CM, et al. NAD+ redox imbalance in the heart exacerbates diabetic cardiomyopathy. *Circ Heart Fail.* 2021;14(8):e008170. [https://doi.org/10.1161/CIRCH-EARTFAILURE.120.008170](https://doi.org/10.1161/CIRCH- EARTFAILURE.120.008170)
- 183.** Revollo JR, Körner A, Mills KF, et al. Nampt/PBEF/Visfatin regulates insulin secretion in beta cells as a systemic NAD biosynthetic enzyme. *Cell Metab.* 2007;6:363-375.
- 184.** Jukarainen S, Heinonen S, Rämö JT, et al. Obesity is associated with low NAD(+)/SIRT pathway expression in adipose tissue of BMI-discordant monozygotic twins. *J Clin Endocrinol Metab.* 2016;101:275-283.

- 185.** Rappou E, Jukarainen S, Rinnankoski-Tuikka R, et al. Weight loss is associated with increased NAD(+)SIRT1 expression but reduced PARP activity in white adipose tissue. *J Clin Endocrinol Metab.* 2016;101:1263-1273.
- 186.** Franczyk MP, Qi N, Stromsdorfer KL, et al. Importance of adipose tissue NAD<sup>+</sup> biology in regulating metabolic flexibility. *Endocrinology.* 2021;162(3):bqab006. <https://doi.org/10.1210/endocr/bqab006>
- 187.** Stromsdorfer KL, Yamaguchi S, Yoon MJ, et al. NAMPT-mediated NAD(+) biosynthesis in adipocytes regulates adipose tissue function and multi-organ insulin sensitivity in mice. *Cell Rep.* 2016;16:1851-1860.
- 188.** Yamaguchi S, Franczyk MP, Chondronikola M, et al. Adipose tissue NAD(+) biosynthesis is required for regulating adaptive thermogenesis and whole-body energy homeostasis in mice. *Proc Natl Acad Sci U S A.* 2019;116:23822-23828.
- 189.** Yano M, Akazawa H, Oka T, et al. Monocyte-derived extracellular Nampt-dependent biosynthesis of NAD(+) protects the heart against pressure overload. *Sci Rep.* 2015;5:15857. <https://doi.org/10.1038/srep15857>
- 190.** Oka SI, Byun J, Huang CY, et al. Nampt potentiates antioxidant defense in diabetic cardiomyopathy. *Circ Res.* 2021;129:114-130.
- 191.** Doan KV, Luongo TS, Ts'olo TT, et al. Cardiac NAD(+) depletion in mice promotes hypertrophic cardiomyopathy and arrhythmias prior to impaired bioenergetics. *Nat Cardiovasc Res.* 2024;3:1236-1248.
- 192.** Hsu CP, Oka S, Shao D, Hariharan N, Sadoshima J. Nicotinamide phosphoribosyltransferase regulates cell survival through NAD<sup>+</sup> synthesis in cardiac myocytes. *Circ Res.* 2009;105:481-491.
- 193.** Misner DL, Kauss MA, Singh J, et al. Cardiotoxicity associated with nicotinamide phosphoribosyltransferase inhibitors in rodents and in rat and human-derived cell lines. *Cardiovasc Toxicol.* 2017;17:307-318.
- 194.** Berezina TA, Berezin OO, Novikov EV, Lichtenauer M, Berezin AE. Irisin predicts poor clinical outcomes in patients with heart failure with preserved ejection fraction and low levels of N-terminal pro-B-type natriuretic peptide. *Bio-molecules.* 2024;14(12):1615. <https://doi.org/10.3390/biom14121615>
- 195.** Tong D, Schiattarella GG, Jiang N, et al. NAD (+) repletion reverses heart failure with preserved ejection fraction. *Circ Res.* 2021;128:1629-1641.
- 196.** Abdellatif M, Trummer-Herbst V, Koser F, et al. Nicotinamide for the treatment of heart failure with preserved ejection fraction. *Sci Transl Med.* 2021;13(580):eabd7064. <https://doi.org/10.1126/scitranslmed.abd7064>
- 197.** Bao Y, Bing C, Hunter L, Jenkins JR, Wabitsch M, Trayhurn P. Zinc-alpha2-glycoprotein, a lipid mobilizing factor, is expressed and secreted by human (SGBS) adipocytes. *FEBS Lett.* 2005;579:41-47.
- 198.** Gong FY, Zhang SJ, Deng JY, et al. Zinc-alpha2-glycoprotein is involved in regulation of body weight through inhibition of lipogenic enzymes in adipose tissue. *Int J Obes (Lond).* 2009;33:1023-1030.
- 199.** Russell ST, Tisdale MJ. Role of beta-adrenergic receptors in the anti-obesity and anti-diabetic effects of zinc-alpha2-glycoprotein (ZAG). *Biochim Biophys Acta.* 2012;1821:590-599.
- 200.** Elattar S, Dimri M, Satyanarayana A. The tumor secretory factor ZAG promotes white adipose tissue browning and energy wasting. *FASEB J.* 2018;32:4727-4743.
- 201.** Cabassi A, Tedeschi S. Zinc-alpha2-glycoprotein as a marker of fat catabolism in humans. *Curr Opin Clin Nutr Metab Care.* 2013;16:267-271.
- 202.** Mracek T, Gao D, Tzanavari T, et al. Downregulation of zinc-{alpha}2-glycoprotein in adipose tissue and liver of obese ob/ob mice and by tumour necrosis factor-alpha in adipocytes. *J Endocrinol.* 2010;204:165-172.
- 203.** Marrades MP, Martínez JA, Moreno-Aliaga MJ. ZAG, a lipid mobilizing adipokine, is downregulated in human obesity. *J Physiol Biochem.* 2008;64:61-66.
- 204.** Mracek T, Ding Q, Tzanavari T, et al. The adipokine zinc-alpha2-glycoprotein (ZAG) is downregulated with fat mass expansion in obesity. *Clin Endocrinol (Oxf).* 2010;72:334-341.
- 205.** Yang M, Liu R, Li S, Luo Y, et al. Zinc-alpha2-glycoprotein is associated with insulin resistance in humans and is regulated by hyperglycemia, hyperinsulinemia, or liraglutide administration: cross-sectional and interventional studies in normal subjects, insulin-resistant subjects, and subjects with newly diagnosed diabetes. *Diabetes Care.* 2013;36:1074-1082.
- 206.** Ceperuelo-Mallafré V, Näf S, Escoté X, et al. Circulating and adipose tissue gene expression of zinc-alpha2-glycoprotein in obesity: its relationship with adipokine and lipolytic gene markers in subcutaneous and visceral fat. *J Clin Endocrinol Metab.* 2009;94:5062-5069.
- 207.** Sörensen-Zender I, Bhayana S, Susnik N, et al. Zinc-alpha2-glycoprotein exerts antifibrotic effects in kidney and heart. *J Am Soc Nephrol.* 2015;26:2659-2668.
- 208.** Zhou X, Deng C, Chen L, et al. Zinc-alpha2-glycoprotein modulates blood pressure by regulating renal lipid metabolism reprogramming-mediated urinary Na<sup>+</sup> excretion in hypertension. *Cardiovasc Res.* 2024;120:2134-2146.
- 209.** Soltani L, Kheirouri S, Enamzadeh E. Elevated serum levels of S100A1 and zinc alpha2-glycoprotein in patients with heart failure. *Nutr Metab Cardiovasc Dis.* 2021;31:162-168.
- 210.** Zhu HJ, Wang XQ, Pan H, et al. Serum levels of the adipokine zinc-alpha2-glycoprotein are decreased in patients with hypertension. *ISRN Endocrinol.* 2014;2014:374090. <https://doi.org/10.1155/2014/374090>
- 211.** Bilovol OM, Knyazkova II, Al-Travneh OV, Bogun MV, Berezin AE. Altered cytokine profile predicts early stage of left ventricular remodeling in hypertensive patients with type 2 diabetes mellitus. *Diabetes Metab Syndr.* 2020;14:109-116.
- 212.** Kabil SL, Mahmoud NM. Canagliflozin protects against non-alcoholic steatohepatitis in type-2 diabetic rats through zinc alpha-2 glycoprotein up-regulation. *Eur J Pharmacol.* 2018;828:135-145.
- 213.** Liao X, Wang X, Li H, et al. Sodium-glucose cotransporter 2 (SGLT2) inhibitor increases circulating zinc-alpha2-glycoprotein levels in patients with type 2 diabetes. *Sci Rep.* 2016;6:32887. <https://doi.org/10.1038/srep32887>
- 214.** Yang M, Liu R, Li S, et al. Zinc-alpha2-glycoprotein is associated with insulin resistance in humans and is regulated by hyperglycemia, hyperinsulinemia, or liraglutide administration: cross-sectional and interventional studies in normal subjects, insulin-resistant subjects, and subjects with newly diagnosed diabetes. *Diabetes Care.* 2013;36:1074-1082.
- 215.** Geissler A, Ryzhov S, Sawyer DB. Neuregulins: protective and reparative growth factors in multiple forms of cardiovascular disease. *Clin Sci (Lond).* 2020;134:2623-2643.
- 216.** Lenihan DJ, Anderson SA, Lenneman CG, et al. A phase i, single ascending dose study of cimaglermin alfa (neuregulin 1beta3) in patients with systolic dysfunction and heart failure. *JACC Basic Transl Sci.* 2016;1:576-586.
- 217.** Zeng F, Wang Y, Kloepfer LA, Wang S, Harris RC. ErbB4 deletion predisposes to development of metabolic syndrome in mice. *Am J Physiol Endocrinol Metab.* 2018;315:E583-E593.
- 218.** Villarroya J, Cereijo R, Gavalda-Navarro A, Peyrou M, Giralt M, Villarroya F. New insights into the secretory functions of brown adipose tissue. *J Endocrinol.* 2019;243:R19-R27.
- 219.** Martins FF, Souza-Mello V, Aguilera MB, Mandarim-de-Lacerda CA. Brown adipose tissue as an endocrine organ: updates on the emerging role of batokines. *Horm Mol Biol Clin Investig.* 2022;44:219-227.
- 220.** Liu Y, Chen M. Neuregulin 4 as a novel adipokine in energy metabolism. *Front Physiol.* 2023;13:1106380. <https://doi.org/10.3389/fphys.2022.1106380>
- 221.** Díaz-Sáez F, Blanco-Sinfreu C, Archilla-Ortega A, et al. Neuregulin 4 downregulation induces insulin resistance in 3T3-L1 adipocytes through inflammation and autophagic degradation of GLUT4 vesicles. *Int J Mol Sci.* 2021;22(23):12960. <https://doi.org/10.3390/ijms222312960>
- 222.** Díaz-Sáez F, Balcells C, Rosselló L, et al. Neuregulin 4 downregulation alters mitochondrial morphology and induces oxidative stress in 3T3-L1 adipocytes. *Int J Mol Sci.* 2024;25(21):11718. <https://doi.org/10.3390/ijms252111718>
- 223.** Chen Z, Wang GX, Ma SL, et al. Nrg4 promotes fuel oxidation and a healthy adipokine profile to ameliorate diet-induced metabolic disorders. *Mol Metab.* 2017;6:863-872.
- 224.** Wang R, Zhou W, Zhu X, et al. Differences in neuregulin 4 expression in children: effects of fat depots and obese status. *Endocr Res.* 2020;45(3):190-201. <https://doi.org/10.1080/07435800.2020.1721528>
- 225.** Ziqibu K, Dladla PV, Mthembu SXH, Nkambule B, Mazibuko-Mbeje SE. Low circulating levels of neuregulin 4 as a potential biomarker associated with the severity and prognosis of

- obesity-related metabolic diseases: a systematic review.** *Adipocyte.* 2024;13(1):2390833. <https://doi.org/10.1080/21623945.2024.2390833>
- 226.** Guo D, Liu J, Zhang P, et al. Adiposity measurements and metabolic syndrome are linked through circulating neuregulin 4 and adiponectin levels in obese adults. *Front Physiol.* 2021;12:667330. <https://doi.org/10.3389/fphys.2021.667330>
- 227.** Tutunchi H, Ostadrakhimi A, Hosseinzadeh-Attar MJ, et al. A systematic review of the association of neuregulin 4, a brown fat-enriched secreted factor, with obesity and related metabolic disturbances. *Obes Rev.* 2020;21(2):e12952. <https://doi.org/10.1111/obr.12952>
- 228.** Wang R, Yang F, Qing L, Huang R, Liu Q, Li XC. Decreased serum neuregulin 4 levels associated with non-alcoholic fatty liver disease in children with obesity. *Clin Obes.* 2019;9(1):e12289. <https://doi.org/10.1111/cob.12289>
- 229.** Kralisch S, Hoffmann A, Klöting N, et al. The brown fat-secreted adipokine neuregulin 4 is decreased in human and murine chronic kidney disease. *Eur J Endocrinol.* 2019;181:151–159.
- 230.** Yang C, Zhu D, Liu C, et al. Lipid metabolic reprogramming mediated by circulating Nrg4 alleviates metabolic dysfunction-associated steatotic liver disease during the early recovery phase after sleeve gastrectomy. *BMC Med.* 2024;22(1):164. <https://doi.org/10.1186/s12916-024-03377-0>
- 231.** Zhu B, Mei W, Jiao T, et al. Neuregulin 4 alleviates hepatic steatosis via activating AMPK/mTOR-mediated autophagy in aged mice fed a high fat diet. *Eur J Pharmacol.* 2020;884:173350. <https://doi.org/10.1016/j.ejphar.2020.173350>
- 232.** Wang W, Zhang Y, Yang C, et al. Transplantation of neuregulin 4-overexpressing adipose-derived mesenchymal stem cells ameliorates insulin resistance by attenuating hepatic steatosis. *Exp Biol Med (Maywood).* 2019;244:565–578.
- 233.** Ma Y, Gao M, Liu D. Preventing high fat diet-induced obesity and improving insulin sensitivity through neuregulin 4 gene transfer. *Sci Rep.* 2016;6:26242. <https://doi.org/10.1038/srep26242>
- 234.** Wang GX, Zhao XY, Meng ZX, et al. The brown fat-enriched secreted factor Nrg4 preserves metabolic homeostasis through attenuation of hepatic lipogenesis. *Nat Med.* 2014;20:1436–1443.
- 235.** Wei H, Guo X, Yan J, et al. Neuregulin-4 alleviates isoproterenol (ISO)-induced cardiac remodeling by inhibiting inflammation and apoptosis via AMPK/NF-kappaB pathway. *Int Immunopharmacol.* 2024;143(Pt 2):113301. <https://doi.org/10.1016/j.intimp.2024.113301>
- 236.** Wang P, Guo X, Wang H, Wang L, Ma M, Guo B. Neuregulin-4 protects cardiomyocytes against high-glucose-induced ferroptosis via the AMPK/NRF2 signalling pathway. *Biol Direct.* 2024;19(1):62. <https://doi.org/10.1186/s13062-024-00505-x>
- 237.** Wang H, Wang L, Hu F, et al. Neuregulin-4 attenuates diabetic cardiomyopathy by regulating autophagy via the AMPK/mTOR signalling pathway. *Cardiovasc Diabetol.* 2022;21(1):205. <https://doi.org/10.1186/s12933-022-01643-0>
- 238.** Shi J, Xu W, Zheng R, Miao H, Hu Q. Neuregulin 4 attenuate tubulointerstitial fibrosis and advanced glycosylation end products accumulation in diabetic nephropathy rats via regulating TNF-R1 signaling. *Am J Transl Res.* 2019;11:5501–5513.
- 239.** Yang Z, Yaling W, Tao L, Mingyue R, Yongjun L. Cardioprotective effect of NRG-4 gene expression on spontaneous hypertension rats and its mechanism through mediating the activation of ErbB signaling pathway. *Cell Mol Biol (Noisy-le-grand).* 2022;68(1):89–101.
- 240.** Hanssen MJ, Broeders E, Samms RJ, et al. Serum FGF21 levels are associated with brown adipose tissue activity in humans. *Sci Rep.* 2015;5:10275. <https://doi.org/10.1038/srep10275>
- 241.** Yang C, Wang C, Ye M, et al. Control of lipid metabolism by adipocyte FGFR1-mediated adipohepatic communication during hepatic stress. *Nutr Metab (Lond).* 2012;9(1):94. <https://doi.org/10.1186/1743-7075-9-94>
- 242.** Chau MD, Gao J, Yang Q, Wu Z, Gromada J. Fibroblast growth factor 21 regulates energy metabolism by activating the AMPK-SIRT1-PGC-1alpha pathway. *Proc Natl Acad Sci U S A.* 2010;107:12553–12558.
- 243.** Holland WL, Adams AC, Brozinick JT, et al. An FGF21-adiponectin-ceramide axis controls energy expenditure and insulin action in mice. *Cell Metab.* 2013;17:790–797.
- 244.** Szczepańska E, Gietka-Czernel M. FGF21: a novel regulator of glucose and lipid metabolism and whole-body energy balance. *Horm Metab Res.* 2022;54:203–211.
- 245.** Jain U, Srivastava P, Sharma A, Sinha S, Johari S. Impaired fibroblast growth factor 21 (FGF21) associated with visceral adiposity leads to insulin resistance: the core defect in diabetes mellitus. *Curr Diabetes Rev.* 2025;21(5):e260424229342. <https://doi.org/10.2174/011573399826591523116043813>
- 246.** Jimenez V, Jambrina C, Casana E, et al. FGF21 gene therapy as treatment for obesity and insulin resistance. *EMBO Mol Med.* 2018;10(8):e8791. <https://doi.org/10.15252/emmm.201708791>
- 247.** Liu SQ, Roberts D, Kharitonov A, et al. Endocrine protection of ischemic myocardium by FGF21 from the liver and adipose tissue. *Sci Rep.* 2013;3:2767. <https://doi.org/10.1038/srep02767>
- 248.** Yang H, Feng A, Lin S, et al. Fibroblast growth factor-21 prevents diabetic cardiomyopathy via AMPK-mediated antioxidation and lipid-lowering effects in the heart. *Cell Death Dis.* 2018;9(2):227. <https://doi.org/10.1038/s41419-018-0307-5>
- 249.** Planavila A, Redondo-Angulo I, Ribas F, et al. Fibroblast growth factor 21 protects the heart from oxidative stress. *Cardiovasc Res.* 2015;106:19–31.
- 250.** Planavila A, Redondo I, Hondares E, et al. Fibroblast growth factor 21 protects against cardiac hypertrophy in mice. *Nat Commun.* 2013;4:2019. <https://doi.org/10.1038/ncomms3019>
- 251.** Patel V, Adya R, Chen J, et al. Novel insights into the cardio-protective effects of FGF21 in lean and obese rat hearts. *PLoS One.* 2014;9(2):e87102. <https://doi.org/10.1371/journal.pone.0087102>
- 252.** Kaur N, Gare SR, Ruiz-Velasco A, et al. FGF21/FGFR1-beta-KL cascade in cardiomyocytes modulates angiogenesis and inflammation under metabolic stress. *Helicon.* 2023;9(4):e14952. <https://doi.org/10.1016/j.heliyon.2023.e14952>
- 253.** Yue C, Li R, Li C, et al. Ultrasound-targeted microbubble destruction technology delivering beta-klotho to the heart enhances FGF21 sensitivity and attenuates heart remodeling post-myocardial infarction. *Int J Mol Med.* 2024;53(6):54. <https://doi.org/10.3892/ijmm.2024.5378>
- 254.** Berti L, Irmeler M, Zdichavsky M, et al. Fibroblast growth factor 21 is elevated in metabolically unhealthy obesity and affects lipid deposition, adipogenesis, and adipokine secretion of human abdominal subcutaneous adipocytes. *Mol Metab.* 2015;4:519–527.
- 255.** Zhang X, Yeung DC, Karpisek M, et al. Serum FGF21 levels are increased in obesity and are independently associated with the metabolic syndrome in humans. *Diabetes.* 2008;57:1246–1253.
- 256.** Gan J, Duan Z, Tang L, et al. Fibroblast growth factor 21 resistance is associated with body shape in patients with type 2 diabetes complicating hypertension. *Front Cardiovasc Med.* 2023;10:1168047. <https://doi.org/10.3389/fcm.2023.1168047>
- 257.** Gao RY, Hsu BG, Wu DA, Hou JS, Chen MC. Serum fibroblast growth factor 21 levels are positively associated with metabolic syndrome in patients with type 2 diabetes. *Int J Endocrinol.* 2019;2019:5163245. <https://doi.org/10.1155/2019/5163245>
- 258.** Chou RH, Huang PH, Hsu CY, et al. Circulating fibroblast growth factor 21 is associated with diastolic dysfunction in heart failure patients with preserved ejection fraction. *Sci Rep.* 2016;6:33953. <https://doi.org/10.1038/srep33953>
- 259.** Fan L, Gu L, Yao Y, Ma G. High serum fibroblast growth factor 21 levels were related to the prognosis and ventricular remodeling of heart failure patients with mildly reduced and reduced ejection fraction. *Perfusion.* 2024;39(2):285–293.
- 260.** Sommakkia S, Almaw NH, Lee SH, et al. FGF21 (fibroblast growth factor 21) defines a potential cardiohepatic signaling circuit in end-stage heart failure. *Circ Heart Fail.* 2022;15(3):e008910. <https://doi.org/10.1161/CIRCHEARTFAILURE.121.008910>
- 261.** Valdecantos MP, Ruiz L, Folgueira C, et al. The dual GLP-1/glucagon receptor agonist G49 mimics bariatric surgery effects by inducing metabolic rewiring and inter-organ crosstalk. *Nat Commun.* 2024;15(1):10342. <https://doi.org/10.1038/s41467-024-54080-w>
- 262.** Di Vincenzo A, Crescenzi M, Granzotto M, et al. Treatment with dapagliflozin increases FGF-21 gene expression and reduces triglycerides content in myocardial tissue of genetically obese mice. *J Endocrinol Invest.* 2024;47:1777–1786.

- 263.** Loomba R, Sanyal AJ, Kowdley KV, et al. Randomized, controlled trial of the FGF21 analogue pegozafermin in NASH. *N Engl J Med.* 2023;389:998-1008.
- 264.** Ding Q, Mracek T, Gonzalez-Muniesa P, et al. Identification of macrophage inhibitory cytokine-1 analogue in adipose tissue and its secretion as an adipokine by human adipocytes. *Endocrinology.* 2009;150:1688-1696.
- 265.** Takeuchi K, Yamaguchi K, Takahashi Y, et al. Hepatocyte-specific GDF15 overexpression improves high-fat diet-induced obesity and hepatic steatosis in mice via hepatic FGF21 induction. *Sci Rep.* 2024;14(1):23993. <https://doi.org/10.1038/s41598-024-75107-8>
- 266.** Wang T, Liu J, McDonald C, et al. GDF15 is a heart-derived hormone that regulates body growth. *EMBO Mol Med.* 2017;9:1150-1164.
- 267.** Day EA, Ford RJ, Smith BK, et al. Metformin-induced increases in GDF15 are important for suppressing appetite and promoting weight loss. *Nat Metab.* 2019;1:1202-1208.
- 268.** Chrysovergis K, Wang X, Kosak J, et al. NAG-1/GDF-15 prevents obesity by increasing thermogenesis, lipolysis and oxidative metabolism. *Int J Obes (Lond).* 2014;38:1555-1564.
- 269.** Šrámková V, Koc M, Krauzová E, et al. Expression of lipogenic markers is decreased in subcutaneous adipose tissue and adipocytes of older women and is negatively linked to GDF15 expression. *J Physiol Biochem.* 2019;75:253-262.
- 270.** Kim HJ, Kang SU, Kim HJ, Lee YS, Kim CH. GDF15 inhibits early-stage adipocyte differentiation by enhancing HOP2 expression and suppressing C/EBP $\alpha$  expression. *Mol Cell Endocrinol.* 2025;598:112461. <https://doi.org/10.1016/j.mce.2025.112461>
- 271.** Moon JS, Goeminne LJE, Kim JT, et al. Growth differentiation factor 15 protects against the aging-mediated systemic inflammatory response in humans and mice. *Aging Cell.* 2020;19(8):e13195. <https://doi.org/10.1111/acel.13195>
- 272.** Campderros L, Moure R, Cairo M, et al. Brown adipocytes secrete GDF15 in response to thermogenic activation. *Obesity (Silver Spring).* 2019;27:1606-1616.
- 273.** Wang D, Townsend LK, DesOrmeaux GJ, et al. GDF15 promotes weight loss by enhancing energy expenditure in muscle. *Nature.* 2023;619:143-150.
- 274.** Jena J, García-Peña LM, Pereira RO. The roles of FGF21 and GDF15 in mediating the mitochondrial integrated stress response. *Front Endocrinol (Lausanne).* 2023;14:1264530. <https://doi.org/10.3389/fendo.2023.1264530>
- 275.** Keipert S, Ost M. Stress-induced FGF21 and GDF15 in obesity and obesity resistance. *Trends Endocrinol Metab.* 2021;32:904-915.
- 276.** Macia L, Tsai VW, Nguyen AD, et al. Macrophage inhibitory cytokine 1 (MIC-1/GDF15) decreases food intake, body weight and improves glucose tolerance in mice on normal & obesogenic diets. *PLoS One.* 2012;7(4):e34868. <https://doi.org/10.1371/journal.pone.0034868>
- 277.** Tsai VW, Zhang HP, Manandhar R, et al. Treatment with the TGF- $\beta$  superfamily cytokine MIC-1/GDF15 reduces the adiposity and corrects the metabolic dysfunction of mice with diet-induced obesity. *Int J Obes (Lond).* 2018;42(3):561-571.
- 278.** Tran T, Yang J, Gardner J, Xiong Y. GDF15 deficiency promotes high fat diet-induced obesity in mice. *PLoS One.* 2018;13(8):e0201584. <https://doi.org/10.1371/journal.pone.0201584>
- 279.** Groarke JD, Crawford J, Collins SM, et al. Ponsegrromab for the treatment of cancer cachexia. *N Engl J Med.* 2024;391:2291-2303.
- 280.** Eddy AC, Trask AJ. Growth differentiation factor-15 and its role in diabetes and cardiovascular disease. *Cytokine Growth Factor Rev.* 2021;57:11-18.
- 281.** Choi MJ, Jung SB, Lee SE, et al. An adipocyte-specific defect in oxidative phosphorylation increases systemic energy expenditure and protects against diet-induced obesity in mouse models. *Diabetologia.* 2020;63:837-852.
- 282.** Kusminski CM, Ghaben AL, Morley TS, et al. A novel model of diabetic complications: adipocyte mitochondrial dysfunction triggers massive beta-cell hyperplasia. *Diabetes.* 2020;69:313-330.
- 283.** Lee SH, Lee JY, Lim KH, Lee YS, Koh JM. Associations between plasma growth and differentiation factor-15 with aging phenotypes in muscle, adipose tissue, and bone. *Calciif Tissue Int.* 2022;110:236-243.
- 284.** Ho LC, Wu HT, Hung HC, et al. Growth differentiation factor-15 is independently associated with metabolic syndrome and hyperglycemia in non-elderly subjects. *Biofactors.* 2023;49:119-126.
- 285.** Dostálová I, Roubíček T, Bártlová M, et al. Increased serum concentrations of macrophage inhibitory cytokine-1 in patients with obesity and type 2 diabetes mellitus: the influence of very low calorie diet. *Eur J Endocrinol.* 2009;161:397-404.
- 286.** Carballo-Casla A, García-Esquinas E, Buño-Soto A, et al. Metabolic syndrome and growth differentiation factor in older adults. *Geroscience.* 2022;44:867-880.
- 287.** Miyake M, Zhang J, Yasue A, et al. Integrated stress response regulates GDF15 secretion from adipocytes, preferentially suppresses appetite for a high-fat diet and improves obesity. *iScience.* 2021;24(12):103448. <https://doi.org/10.1016/j.isci.2021.103448>
- 288.** Griner SE, Wang KJ, Joshi JP, Nahta R. Mechanisms of adipocytokine-mediated trastuzumab resistance in HER2-positive breast cancer cell lines. *Curr Pharmacogenomics Person Med.* 2013;11:31-41.
- 289.** Zou A, Xiao T, Chi B, et al. Engineered exosomes with growth differentiation factor-15 overexpression enhance cardiac repair after myocardial injury. *Int J Nanomedicine.* 2024;19:3295-3314.
- 290.** Heger J, Schiegnitz E, von Waldthausen D, Anwar MM, Piper HM, Euler G. Growth differentiation factor 15 acts anti-apoptotic and pro-hypertrophic in adult cardiomyocytes. *J Cell Physiol.* 2010;224:120-126.
- 291.** Xu J, Kimball TR, Lorenz JN, et al. GDF15/MIC-1 functions as a protective and anti-hypertrophic factor released from the myocardium in association with SMAD protein activation. *Circ Res.* 2006;98:342-350.
- 292.** Ren Q, Lin P, Wang Q, Zhang B, Feng L. Chronic peripheral ghrelin injection exerts anti-fibrotic effects by increasing growth differentiation factor 15 in rat hearts with myocardial fibrosis induced by isoproterenol. *Physiol Res.* 2020;69:439-450.
- 293.** Chan JSF, Tabatabaei Dakhili SA, Lorenzana-Carrillo MA, et al. Growth differentiation factor 15 alleviates diastolic dysfunction in mice with experimental diabetic cardiomyopathy. *Cell Rep.* 2024;43(8):114573. <https://doi.org/10.1016/j.celrep.2024.114573>
- 294.** Chen L, Yin Y, Liu G. Metformin alleviates bevacizumab-induced vascular endothelial injury by up-regulating GDF15 and activating the PI3K/AKT/FOXO/PPARgamma signaling pathway. *Ann Transl Med.* 2021;9(20):1547. <https://doi.org/10.21037/atm-21-4764>
- 295.** Lee J, Jin YJ, Lee MS, Kim YM, Lee H. Macrophage inhibitory cytokine-1 promotes angiogenesis by eliciting the GFRAL-mediated endothelial cell signaling. *J Cell Physiol.* 2021;236:4008-4023.
- 296.** Wimalanathan T, Paus MF, Brox Skrane J, et al. Associations between growth differentiation factor 15, cardiac troponin T, and N-terminal pro-B-type natriuretic peptide, and future myocardial fibrosis assessed by cardiac magnetic resonance imaging: data from the Akershus Cardiac Examination 1950 Study. *J Appl Lab Med.* 2025;10(2):392-405. <https://doi.org/10.1093/jalm/jfae145>
- 297.** Fluschnik N, Ojeda F, Zeller T, Jørgensen T, et al. Predictive value of long-term changes of growth differentiation factor-15 over a 27-year-period for heart failure and death due to coronary heart disease. *PLoS One.* 2018;13(5):e0197497. <https://doi.org/10.1371/journal.pone.0197497>
- 298.** Fernandez C, Rysä J, Ström K, Nilsson J, et al. Circulating protein biomarkers predict incident hypertensive heart failure independently of N-terminal pro-B-type natriuretic peptide levels. *ESC Heart Fail.* 2020;7:1891-1899.
- 299.** deFilippi CR, Tran H, Gattani R, et al. Association of cardiac troponin T and growth differentiation factor 15 with replacement and interstitial cardiac fibrosis in community dwelling adults: The Multi-Ethnic Study of Atherosclerosis. *Front Cardiovasc Med.* 2023;10:1104715. <https://doi.org/10.3389/fcvn.2023.1104715>
- 300.** Dinh W, Füth R, Lankisch M, et al. Growth-differentiation factor-15: a novel biomarker in patients with diastolic dysfunction? *Arg Bras Cardiol.* 2011;97:65-75.
- 301.** Meessen JMTA, Cesaroni G, Mureddu GF, et al. IGFBP7 and GDF-15, but not PINP, are associated with cardiac alterations and 10-year outcome in an elderly community-based study. *BMC Cardiovasc Disord.* 2021;21(1):328. <https://doi.org/10.1186/s12872-021-02138-8>
- 302.** Baessler A, Strack C, Rousseva E, et al. Growth-differentiation factor-15 improves reclassification for the diagnosis of heart failure

- with normal ejection fraction in morbid obesity. *Eur J Heart Fail.* 2012;14:1240-1248.
- 303.** Mitic VT, Stojanovic DR, Deljanin Ilic MZ, et al. Cardiac remodeling biomarkers as potential circulating markers of left ventricular hypertrophy in heart failure with preserved ejection fraction. *Tohoku J Exp Med.* 2020;250:233-242.
- 304.** Kanagala P, Arnold JR, Singh A, et al. Characterizing heart failure with preserved and reduced ejection fraction: An imaging and plasma biomarker approach. *PLoS One.* 2020;15(4):e0232280.
- 305.** Kempf T, von Haehling S, Peter T, et al. Prognostic utility of growth differentiation factor-15 in patients with chronic heart failure. *J Am Coll Cardiol.* 2007;50:1054-1060.
- 306.** Mendez Fernandez AB, Ferrero-Gregorri A, Garcia-Osuna A, et al. Growth differentiation factor 15 as mortality predictor in heart failure patients with non-reduced ejection fraction. *ESC Heart Fail.* 2020;7:2223-2229.
- 307.** Sakamoto D, Matsuoka Y, Nakatani D, et al. Role and prognostic value of growth differentiation factor 15 in patient of heart failure with preserved ejection fraction: insights from the PURSUIT-HFpEF registry. *Open Heart.* 2025;12(1):e003008. <https://doi.org/10.1136/openheart-2024-003008>
- 308.** Wang C, Gu Z, Guo Y. Meta-analysis of the applied value of the growth differentiation factor 15 detection in HFpEF diagnosis. *Acta Cardiol.* 2023;78:1120-1128.
- 309.** Omar M, Jensen J, Kistorp C, et al. The effect of empagliflozin on growth differentiation factor 15 in patients with heart failure: a randomized controlled trial (Empire HF Biomarker). *Cardiovasc Diabetol.* 2022;21(1):34. <https://doi.org/10.1186/s12933-022-01463-2>
- 310.** Ferreira JP, Packer M, Butler J, et al. Growth differentiation factor-15 and the effect of empagliflozin in heart failure: findings from the EMPEROR program. *Eur J Heart Fail.* 2024;26:155-164.
- 311.** Hida K, Wada J, Eguchi J, et al. Visceral adipose tissue-derived serine protease inhibitor: a unique insulin-sensitizing adipocytokine in obesity. *Proc Natl Acad Sci U S A.* 2005;102:10610-10615.
- 312.** Klöting N, Berndt J, Kralisch S, et al. Vaspin gene expression in human adipose tissue: association with obesity and type 2 diabetes. *Biochem Biophys Res Commun.* 2006;339:430-436.
- 313.** Weiner J, Rohde K, Krause K, et al. Brown adipose tissue (BAT) specific vaspin expression is increased after obesogenic diets and cold exposure and linked to acute changes in DNA-methylation. *Mol Metab.* 2017;6:482-493.
- 314.** Youn BS, Klöting N, Kratzsch J, et al. Serum vaspin concentrations in human obesity and type 2 diabetes. *Diabetes.* 2008;57:372-377.
- 315.** Li Q, Chen R, Moriya J, et al. A novel adipocytokine, visceral adipose tissue-derived serine protease inhibitor (vaspin), and obesity. *J Int Med Res.* 2008;36:625-629.
- 316.** Feng R, Li Y, Wang C, Luo C, Liu L, Chuo F, Li Q, Sun C. Higher vaspin levels in subjects with obesity and type 2 diabetes mellitus: a meta-analysis. *Diabetes Res Clin Pract.* 2014;106:88-94.
- 317.** Rapöhn I, Elias I, Weiner J, et al. Over-expressing high levels of human vaspin limits high fat diet-induced obesity and enhances energy expenditure in a transgenic mouse. *Front Endocrinol (Lausanne).* 2023;14:1146454.
- 318.** Chang HM, Lee HJ, Park HS, et al. Effects of weight reduction on serum vaspin concentrations in obese subjects: modification by insulin resistance. *Obesity (Silver Spring).* 2010;18:2105-2110.
- 319.** Zieger K, Weiner J, Krause K, et al. Vaspin suppresses cytokine-induced inflammation in 3T3-L1 adipocytes via inhibition of NFκB pathway. *Mol Cell Endocrinol.* 2018;460:181-188.
- 320.** Zhang D, Zhu H, Zhan E, et al. Vaspin mediates the intraorgan crosstalk between heart and adipose tissue in lipodystrophic mice. *Front Cell Dev Biol.* 2021;9:647131. <https://doi.org/10.3389/fcell.2021.647131>
- 321.** Ji M, Li Y, Liu Y, Ma G. Vaspin ameliorates cardiac remodeling by suppressing phosphoinositide 3-kinase/protein kinase B pathway to improve oxidative stress in heart failure rats. *J Cardiovasc Pharmacol.* 2022;80:442-452.
- 322.** Nakatsuka A, Wada J, Iseda I, et al. Vaspin is an adipokine ameliorating ER stress in obesity as a ligand for cell-surface GRP78/MTJ-1 complex. *Diabetes.* 2012;61:2823-2832.
- 323.** Li X, Ke X, Li Z, Li B. Vaspin prevents myocardial injury in rats model of diabetic cardiomyopathy by enhancing autophagy and inhibiting inflammation. *Biochem Biophys Res Commun.* 2019;514:1-8.
- 324.** Ke X, Hao Y, Li B, et al. Vaspin prevents tumor necrosis factor-alpha-induced apoptosis in cardiomyocytes by promoting autophagy. *J Cardiovasc Pharmacol.* 2018;77:257-267.
- 325.** Zhu Y, Gu Z, Shi J, Chen C, Xu H, Lu Q. Vaspin attenuates atrial abnormalities by promoting ULK1/FUND1-mediated mitophagy. *Oxid Med Cell Longev.* 2022;2022:3187463.
- 326.** Yang F, Xue L, Han Z, et al. Vaspin alleviates myocardial ischaemia/reperfusion injury via activating autophagic flux and restoring lysosomal function. *Biochem Biophys Res Commun.* 2018;503:501-507.
- 327.** Jung CH, Lee MJ, Kang YM, et al. Vaspin inhibits cytokine-induced nuclear factor-κB activation and adhesion molecule expression via AMP-activated protein kinase activation in vascular endothelial cells. *Cardiovasc Diabetol.* 2014;13:41. <https://doi.org/10.1186/1475-2840-13-41>
- 328.** Li H, Peng W, Zhuang J, Lu Y, et al. Vaspin attenuates high glucose-induced vascular smooth muscle cells proliferation and chemokinesis by inhibiting the MAPK, PI3K/Akt, and NF-κB signaling pathways. *Atherosclerosis.* 2013;228:61-68.
- 329.** Kameshima S, Yamada K, Morita T, Okada M, Yamawaki H. Visceral adipose tissue-derived serine protease inhibitor augments acetylcholine-induced relaxation via the inhibition of acetylcholine esterase activity in rat isolated mesenteric artery. *Acta Physiol (Oxf).* 2016;216:203-210.
- 330.** Jung CH, Lee WJ, Hwang JY, et al. Vaspin increases nitric oxide bioavailability through the reduction of asymmetric dimethylarginine in vascular endothelial cells. *PLoS One.* 2012;7(12):e52346. <https://doi.org/10.1371/journal.pone.0052346>
- 331.** Zhang B, Peng W, Wang K, Li H, Xu Y. Vaspin as a prognostic marker in patients with acute myocardial infarction. *Heart Lung Circ.* 2016;25:257-264.
- 332.** Zhou X, Chen Y, Tao Y, Zhang W, Xu W, Lu X. Serum vaspin as a predictor of adverse cardiac events in acute myocardial infarction. *J Am Heart Assoc.* 2019;8(2):e010934. <https://doi.org/10.1161/JAHA.118.010934>
- 333.** Chen M, Deng D, Fang Z, et al. Fenofibrate increases serum vaspin by upregulating its expression in adipose tissue. *Endocrine.* 2014;45:409-421.
- 334.** Ferreira JP, Vasques-Nóvoa F, Ferrão D, et al. Fenofibrate and heart failure outcomes in patients with type 2 diabetes: analysis from ACCORD. *Diabetes Care.* 2022;45:1584-1591.
- 335.** Ramanjaneya M, Chen J, Brown JE, et al. Identification of nesfatin-1 in human and murine adipose tissue: a novel depot-specific adipokine with increased levels in obesity. *Endocrinology.* 2010;151:3169-3180.
- 336.** Ramanjaneya M, Addison M, Randeva HS. Possible role of NUCB2/nesfatin-1 in adipogenesis. *Curr Pharm Des.* 2013;19:6976-6980.
- 337.** Könczöl K, Pintér O, Ferenczi S, et al. Nesfatin-1 exerts long-term effect on food intake and body temperature. *Int J Obes (Lond).* 2012;36:1514-1521.
- 338.** Li Z, Gao L, Tang H, Yin Y, et al. Peripheral effects of nesfatin-1 on glucose homeostasis. *PLoS One.* 2013;8(8):e71513. <https://doi.org/10.1371/journal.pone.0071513>
- 339.** Riva M, Nitert MD, Voss U, et al. Nesfatin-1 stimulates glucagon and insulin secretion and beta cell NUCB2 is reduced in human type 2 diabetic subjects. *Cell Tissue Res.* 2011;346:393-405.
- 340.** Gonzalez R, Perry RL, Gao X, et al. Nutrient responsive nesfatin-1 regulates energy balance and induces glucose-stimulated insulin secretion in rats. *Endocrinology.* 2011;152:3628-3637.
- 341.** Tagaya Y, Osaki A, Miura A, et al. Secreted nucleobindin-2 inhibits 3T3-L1 adipocyte differentiation. *Protein Pept Lett.* 2012;19:997-1004.
- 342.** Gharanei S, Ramanjaneya M, Patel AH, et al. NUCB2/nesfatin-1 reduces obesogenic diet induced inflammation in mice subcutaneous white adipose tissue. *Nutrients.* 2022;14(7):1409. <https://doi.org/10.3390/nu14071409>
- 343.** Steffen TL, Stafford JD, Samson WK, Yosten GLC. Nesfatin-1 is a regulator of inflammation with implications during obesity and metabolic syndrome. *Appetite.* 2024;203:107669. <https://doi.org/10.1016/j.appet.2024.107669>
- 344.** Wang Y, Li Z, Zhang X, Xiang X, Li Y, Mulholland MW, Zhang W. Nesfatin-1 promotes

- brown adipocyte phenotype. *Sci Rep.* 2016;6:34747. <https://doi.org/10.1038/srep34747>
- 345.** Mori Y, Shimizu H, Kushima H, et al. Increased blood pressure in nesfatin/nucleobindin-2-transgenic mice. *Hypertens Res.* 2017;40:861-867.
- 346.** Tanida M, Gotoh H, Yamamoto N, et al. Hypothalamic nesfatin-1 stimulates sympathetic nerve activity via hypothalamic erk signaling. *Diabetes.* 2015;64:3725-3736.
- 347.** Tanida M, Mori M. Nesfatin-1 stimulates renal sympathetic nerve activity in rats. *Neuro-report.* 2011;22:309-312.
- 348.** Rajeswari JJ, Unniappan S. Tissue-specific modulation of gluco- and growth-regulatory factor abundance by nesfatin-1 and nesfatin-1-like peptide in goldfish. *Animals (Basel).* 2023;13(9):1437. <https://doi.org/10.3390/ani13091437>
- 349.** Li M, Li K, Ren Y. Nesfatin-1 protects H9c2 cardiomyocytes against cobalt chloride-induced hypoxic injury by modulating the MAPK and Notch1 signaling pathways. *J Biol Res (Thessalon).* 2021;28(1):21. <https://doi.org/10.1186/s40709-021-00147-4>
- 350.** Fan Z, Dong J, Mu Y, Liu X. Nesfatin-1 protects against diabetic cardiomyopathy in the streptozotocin-induced diabetic mouse model via the p38-MAPK pathway. *Bioengineered.* 2022;13:14670-14681.
- 351.** Su RY, Geng XY, Yang Y, Yin HS. Nesfatin-1 inhibits myocardial ischaemia/reperfusion injury through activating Akt/ERK pathway-dependent attenuation of endoplasmic reticulum stress. *J Cell Mol Med.* 2021;25:5050-5059.
- 352.** Sharifi M, Nazarinia D, Ramezani F, Azizi Y, Naderi N, Aboutaleb N. Necroptosis and RhoA/ROCK pathways: molecular targets of Nesfatin-1 in cardioprotection against myocardial ischemia/reperfusion injury in a rat model. *Mol Biol Rep.* 2021;48:2507-2518.
- 353.** Naseroleslami M, Sharifi M, Rakhshan K, Mokhtari B, Aboutaleb N. Nesfatin-1 attenuates injury in a rat model of myocardial infarction by targeting autophagy, inflammation, and apoptosis. *Arch Physiol Biochem.* 2023;129:122-130.
- 354.** Tasatargil A, Kuscu N, Dalaklioglu S, et al. Cardioprotective effect of nesfatin-1 against isoproterenol-induced myocardial infarction in rats: Role of the Akt/GSK-3beta pathway. *Peptides.* 2017;95:1-9. <https://doi.org/10.1016/j.peptides.2017.07.003>
- 355.** Kerkutluoglu M, Gunes H, Onus AE, Dagli M, Yucel O. Predictive value of nesfatin-1 in heart failure mortality. *Turk J Biochem.* 2023 Jul 31. <https://doi.org/10.1515/tjb-2022-0227>
- 356.** Boström P, Wu J, Jedrychowski MP, et al. A PGCI- $\alpha$ -dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature.* 2012;481:463-468.
- 357.** Moreno-Navarrete JM, Ortega F, Serrano M, et al. Irisin is expressed and produced by human muscle and adipose tissue in association with obesity and insulin resistance. *J Clin Endocrinol Metab.* 2013;98:E769-E778.
- 358.** Pérez-Sotelo D, Roca-Rivada A, Baamonde I, et al. Lack of adipocyte-Fndc5/irisin expression and secretion reduces thermogenesis and enhances adipogenesis. *Sci Rep.* 2017;7(1):16289. <https://doi.org/10.1038/s41598-017-16602-z>
- 359.** Zhang Y, Xie C, Wang H, et al. Irisin exerts dual effects on browning and adipogenesis of human white adipocytes. *Am J Physiol Endocrinol Metab.* 2016;311:E530-E541.
- 360.** Lee P, Linderman JD, Smith S, et al. Irisin and FGF21 are cold-induced endocrine activators of brown fat function in humans. *Cell Metab.* 2014;19:302-309.
- 361.** Xiong XQ, Chen D, Sun HJ, et al. FNDC5 overexpression and irisin ameliorate glucose/lipid metabolic derangements and enhance lipolysis in obesity. *Biochim Biophys Acta.* 2015;1852:1867-1875.
- 362.** Crujeiras AB, Pardo M, Arturo RR, et al. Longitudinal variation of circulating irisin after an energy restriction-induced weight loss and following weight regain in obese men and women. *Am J Hum Biol.* 2014;26:198-207.
- 363.** Pardo M, Crujeiras AB, Amil M, et al. Association of irisin with fat mass, resting energy expenditure, and daily activity in conditions of extreme body mass index. *Int J Endocrinol.* 2014;2014:857270. <https://doi.org/10.1155/2014/857270>
- 364.** Campolo J, Corradi E, Rizzardi A, et al. Irisin and markers of metabolic derangement in non-diabetic Caucasian subjects with stage I-II obesity during early aging. *PLoS One.* 2020;15(2):e0229152. <https://doi.org/10.1371/journal.pone.0229152>
- 365.** Tabak O, Simsek G, Erdenen F, et al. The relationship between circulating irisin, retinol binding protein-4, adiponectin and inflammatory mediators in patients with metabolic syndrome. *Arch Endocrinol Metab.* 2017;61:515-523.
- 366.** Shoukry A, Shalaby SM, El-Arabi Bdeir S, Mahmoud AA, Mousa MM, Khalifa A. Circulating serum irisin levels in obesity and type 2 diabetes mellitus. *IUBMB Life.* 2016;68:544-556.
- 367.** Crujeiras AB, Pardo M, Casanueva FF. Irisin: 'fat' or artefact. *Clin Endocrinol (Oxf).* 2015;82:467-474.
- 368.** Lee YJ, Heo Y, Choi JH, et al. Association of circulating irisin concentrations with weight loss after Roux-en-Y gastric bypass surgery. *Int J Environ Res Public Health.* 2019;16(4):660. <https://doi.org/10.3390/ijerph16040660>
- 369.** Shantavasinkul PC, Omotosho P, Corsino L, Muehlbauer MJ, Chatranukulchai P, Torquati A. Changes of circulating irisin and high-sensitivity C-reactive protein levels in morbidly obese individuals with type 2 diabetes after Roux-en-Y gastric bypass. *J Laparoendosc Adv Surg Tech A.* 2022;32(8):817-822.
- 370.** Tang YJ, Zhang Z, Yan T, et al. Irisin attenuates type 1 diabetic cardiomyopathy by anti-ferroptosis via SIRT1-mediated deacetylation of p53. *Cardiovasc Diabetol.* 2024;23(1):116. <https://doi.org/10.1186/s12933-024-02183-5>
- 371.** Wang B, Xu H, Shang S, Liu L, Sun C, Du W. Irisin improves ROS-induced mitohormesis imbalance in H9c2 cells. *Mol Med Rep.* 2024;30(6):240. <https://doi.org/10.3892/mmr.2024.13364>
- 372.** Peng Q, Ding R, Wang X, Yang P, Jiang F, Chen X. Effect of irisin on pressure overload-induced cardiac remodeling. *Arch Med Res.* 2021;52:182-190.
- 373.** Lin C, Guo Y, Xia Y, et al. FNDC5/Irisin attenuates diabetic cardiomyopathy in a type 2 diabetes mouse model by activation of integrin alphaV/beta5-AKT signaling and reduction of oxidative/nitrosative stress. *J Mol Cell Cardiol.* 2021;160:27-41.
- 374.** Deng J, Zhang N, Chen F, et al. Irisin ameliorates high glucose-induced cardiomyocytes injury via AMPK/mTOR signal pathway. *Cell Biol Int.* 2020;44:2315-2325.
- 375.** Zhuo C, Xin J, Huang W, et al. Irisin protects against doxorubicin-induced cardiotoxicity by improving AMPK-Nrf2 dependent mitochondrial fusion and strengthening endogenous antioxidant defense mechanisms. *Toxicology.* 2023;494:153597. <https://doi.org/10.1016/j.tox.2023.153597>
- 376.** Zhang X, Hu C, Kong CY, et al. FNDC5 alleviates oxidative stress and cardiomyocyte apoptosis in doxorubicin-induced cardiotoxicity via activating AKT. *Cell Death Differ.* 2020;27:540-555.
- 377.** Li X, Zhang DQ, Wang X, et al. Irisin alleviates high glucose-induced hypertrophy in H9c2 cardiomyoblasts by inhibiting endoplasmic reticulum stress. *Peptides.* 2022;152:170774. <https://doi.org/10.1016/j.peptides.2022.170774>
- 378.** Li RL, Wu SS, Wu Y, et al. Irisin alleviates pressure overload-induced cardiac hypertrophy by inducing protective autophagy via mTOR-independent activation of the AMPK-ULK1 pathway. *J Mol Cell Cardiol.* 2018;121:242-255.
- 379.** Song R, Zhao X, Cao R, Liang Y, Zhang DQ, Wang R. Irisin improves insulin resistance by inhibiting autophagy through the PI3K/Akt pathway in H9c2 cells. *Gene.* 2021;769:145209. <https://doi.org/10.1016/j.gene.2020.145209>
- 380.** Liu X, Mujahid H, Rong B, et al. Irisin inhibits high glucose-induced endothelial-to-mesenchymal transition and exerts a dose-dependent bidirectional effect on diabetic cardiomyopathy. *J Cell Mol Med.* 2018;22:808-822.
- 381.** Ho MY, Wen MS, Yeh JK, et al. Excessive irisin increases oxidative stress and apoptosis in murine heart. *Biochem Biophys Res Commun.* 2018;503:2493-2498.
- 382.** Kawashima T, Inuzuka Y, Okuda J, et al. Constitutive SIRT1 overexpression impairs mitochondria and reduces cardiac function in mice. *J Mol Cell Cardiol.* 2011;51:1026-1036.
- 383.** Yu Q, Kou W, Xu X, et al. FNDC5/Irisin inhibits pathological cardiac hypertrophy. *Clin Sci (Lond).* 2019;133(5):611-627.
- 384.** Zhang W, Chang L, Zhang C, et al. Central and peripheral irisin differentially regulate blood pressure. *Cardiovasc Drugs Ther.* 2015;29:121-127.
- 385.** Matsuo Y, Gleitsmann K, Mangner N, et al. Fibronectin type III domain containing 5 expression in skeletal muscle in chronic heart failure-

- relevance of inflammatory cytokines. *J Cachexia Sarcopenia Muscle*. 2015;6:62-72.
- 386.** Abd El-Mottaleb NA, Galal HM, El Maghraby KM, Gadallah AI. Serum irisin level in myocardial infarction patients with or without heart failure. *Can J Physiol Pharmacol*. 2019;97:932-938.
- 387.** Huerta-Delgado AS, Roffe-Vazquez DN, Luna-Ceron E, et al. Association of irisin levels with cardiac magnetic resonance, inflammatory, and biochemical parameters in patients with chronic heart failure versus controls. *Magn Reson Imaging*. 2022;93:62-72.
- 388.** Grzeszczuk M, Mrozowska M, Kmiecik A, et al. The effect of hypoxia on irisin expression in HL-1 cardiomyocytes. *Vivo*. 2024;38:2126-2133.
- 389.** Silvestrini A, Bruno C, Vergani E, et al. Circulating irisin levels in heart failure with preserved or reduced ejection fraction: a pilot study. *PLoS One*. 2019;14(1):e0210320. <https://doi.org/10.1371/journal.pone.0210320>
- 390.** Berezin AA, Obradovic AB, Fushtey IM, Berezina TA, Lichtenauer M, Berezin AE. Low plasma levels of irisin predict acutely decompensated heart failure in type 2 diabetes mellitus patients with chronic heart failure. *J Cardiovasc Dev Dis*. 2023;10(4):136. <https://doi.org/10.3390/jcd10040136>
- 391.** Berezin AA, Lichtenauer M, Boxhammer E, Fushtey IM, Berezin AE. Serum levels of irisin predict cumulative clinical outcomes in heart failure patients with type 2 diabetes mellitus. *Front Physiol*. 2022;13:922775. <https://doi.org/10.3389/fphys.2022.922775>
- 392.** Deng J, Zhang T, Li M, et al. Irisin-pretreated BMSCs secrete exosomes to alleviate cardiomyocytes pyroptosis and oxidative stress to hypoxia/reoxygenation injury. *Curr Stem Cell Res Ther*. 2023;18:843-852.
- 393.** Yan W, Chen Y, Guo Y, et al. Irisin promotes cardiac homing of intravenously delivered MSCs and protects against ischemic heart injury. *Adv Sci (Weinh)*. 2022;9(7):e2103697. <https://doi.org/10.1002/advs.202103697>
- 394.** Yang R, Roshani D, Gao B, Li P, Shang N. Metallothionein: a comprehensive review of its classification, structure, biological functions, and applications. *Antioxidants (Basel)*. 2024;13(7):825. <https://doi.org/10.3390/antiox13070825>
- 395.** Li Y, Lee SH, Piao M, Kim HS, Lee KY. Metallothionein 3 inhibits 3T3-L1 adipocyte differentiation via reduction of reactive oxygen species. *Antioxidants (Basel)*. 2023;12(3):640. <https://doi.org/10.3390/antiox12030640>
- 396.** Baldini F, Fabbri R, Eberhagen C, et al. Adipocyte hypertrophy parallels alterations of mitochondrial status in a cell model for adipose tissue dysfunction in obesity. *Life Sci*. 2021;265:118812. <https://doi.org/10.1016/j.lfs.2020.118812>
- 397.** Sato M, Kawakami T, Kondoh M, et al. Development of high-fat-diet-induced obesity in female metallothionein-null mice. *FASEB J*. 2010;24:2375-2384.
- 398.** Szrok S, Stelmanska E, Turyn J, Bielicka-Gieldon A, Sledzinski T, Swierczynski J. Metallothioneins 1 and 2, but not 3, are regulated by nutritional status in rat white adipose tissue. *Genes Nutr*. 2016;11:18. <https://doi.org/10.1186/s12263-016-0533-3>
- 399.** Lynes MA, Zaffuto K, Unfricht DW, Marusov G, Samson JS, Yin X. The physiological roles of extracellular metallothionein. *Exp Biol Med (Maywood)*. 2006;231:1548-1554.
- 400.** Beattie JH, Black DJ, Wood AM, Trayhurn P. Cold-induced expression of the metallothionein-1 gene in brown adipose tissue of rats. *Am J Physiol*. 1996;270:R971-R977.
- 401.** Do MS, Nam SY, Hong SE, et al. Metallothionein gene expression in human adipose tissue from lean and obese subjects. *Horm Metab Res*. 2002;34:348-351.
- 402.** Trayhurn P, Duncan JS, Wood AM, Beattie JH. Metallothionein gene expression and secretion in white adipose tissue. *Am J Physiol Regul Integr Comp Physiol*. 2000;279:R2329-R2335.
- 403.** Wang B, Jenkins JR, Trayhurn P. Expression and secretion of inflammation-related adipokines by human adipocytes differentiated in culture: integrated response to TNF-alpha. *Am J Physiol Endocrinol Metab*. 2005;288:E731-E740.
- 404.** Beattie JH, Wood AM, Newman AM, et al. Obesity and hyperleptinemia in metallothionein (-I and -II) null mice. *Proc Natl Acad Sci U S A*. 1998;95:358-363.
- 405.** Zhang H, Zhou W, Wang X, et al. Exacerbation by knocking-out metallothionein gene of obesity-induced cardiac remodeling is associated with the activation of CARD9 signaling. *Int J Biol Sci*. 2025;21:1032-1046.
- 406.** Wang S, Gu J, Xu Z, et al. Zinc rescues obesity-induced cardiac hypertrophy via stimulating metallothionein to suppress oxidative stress-activated BCL10/CARD9/p38 MAPK pathway. *J Cell Mol Med*. 2017;21:1182-1192.
- 407.** Guo R, Ma H, Gao F, Zhong L, Ren J. Metallothionein alleviates oxidative stress-induced endoplasmic reticulum stress and myocardial dysfunction. *J Mol Cell Cardiol*. 2009;47:228-237.
- 408.** Yang X, Doser TA, Fang CX, et al. Metallothionein prolongs survival and antagonizes senescence-associated cardiomyocyte diastolic dysfunction: role of oxidative stress. *FASEB J*. 2006;20:1024-1026.
- 409.** Yang L, Wang J, Yang J, et al. Antioxidant metallothionein alleviates endoplasmic reticulum stress-induced myocardial apoptosis and contractile dysfunction. *Free Radic Res*. 2015;49:1187-1198.
- 410.** Guo J, Guo Q, Fang H, et al. Cardioprotection against doxorubicin by metallothionein is associated with preservation of mitochondrial biogenesis involving PGC-1alpha pathway. *Eur J Pharmacol*. 2014;737:117-124.
- 411.** Yang L, Hu N, Jiang S, et al. Heavy metal scavenger metallothionein attenuates ER stress-induced myocardial contractile anomalies: role of autophagy. *Toxicol Lett*. 2014;225:333-341.
- 412.** Dong F, Li Q, Sreejayan N, Nunn JM, Ren J. Metallothionein prevents high-fat diet induced cardiac contractile dysfunction: role of peroxisome proliferator activated receptor gamma coactivator 1alpha and mitochondrial biogenesis. *Diabetes*. 2007;56:2201-2212.
- 413.** Li FJ, Fu S, Ye H, et al. Metallothionein alleviates glutathione depletion-induced oxidative cardiomyopathy through CISD1-dependent regulation of ferroptosis in murine hearts. *Am J Pathol*. 2024;194:912-926.
- 414.** Xue M, Joo YA, Li S, et al. Metallothionein protects the heart against myocardial infarction via the mTORC2/FoxO3a/Bim pathway. *Antioxid Redox Signal*. 2019;31:403-419.
- 415.** Wang J, Song Y, Elsherif L, et al. Cardiac metallothionein induction plays the major role in the prevention of diabetic cardiomyopathy by zinc supplementation. *Circulation*. 2006;113:544-554.
- 416.** Baba HA, Grabellus F, August C, et al. Reversal of metallothionein expression is different throughout the human myocardium after prolonged left-ventricular mechanical support. *J Heart Lung Transplant*. 2000;19:668-674.
- 417.** Bell LN, Cai L, Johnstone BH, Traktuev DO, March KL, Considine RV. A central role for hepatocyte growth factor in adipose tissue angiogenesis. *Am J Physiol Endocrinol Metab*. 2008;294:E336-E344.
- 418.** Yamaji D, Soliman MM, Kamikawa A, et al. Species-specific control of hepatocyte growth factor expression and production in adipocytes in a differentiation-dependent manner. *Domest Anim Endocrinol*. 2018;62:39-48.
- 419.** Ito T, Yamaji D, Kamikawa A, et al. Progesterone dose-dependently modulates hepatocyte growth factor production in 3T3-L1 mouse pre-adipocytes. *Endocr J*. 2017;64:777-785.
- 420.** Yin J, Lee JH, Zhang J, Gao Z, Polotsky VY, Ye J. Regulation of hepatocyte growth factor expression by NF-kappaB and PPARgamma in adipose tissue. *Am J Physiol Endocrinol Metab*. 2014;306:E929-E936.
- 421.** Saiki A, Watanabe F, Murano T, Miyashita Y, Shirai K. Hepatocyte growth factor secreted by cultured adipocytes promotes tube formation of vascular endothelial cells in vitro. *Int J Obes (Lond)*. 2006;30:1676-1684.
- 422.** Kusunoki H, Taniyama Y, Otsu R, Rakugi H, Morishita R. Anti-inflammatory effects of hepatocyte growth factor on the vicious cycle of macrophages and adipocytes. *Hypertens Res*. 2014;37:500-506.
- 423.** Muratsu J, Iwabayashi M, Sanada F, et al. Hepatocyte growth factor prevented high-fat diet-induced obesity and improved insulin resistance in mice. *Sci Rep*. 2017;7(1):130. <https://doi.org/10.1038/s41598-017-00199-4>
- 424.** Cui Q, Fu S, Li Z. Hepatocyte growth factor inhibits TGF-β1-induced myofibroblast differentiation in tendon fibroblasts: role of AMPK signaling pathway. *J Physiol Sci*. 2013;63:163-170.
- 425.** Varela-Rey M, Beraza N, Lu SC, Mato JM, Martínez-Chantar ML. Role of AMP-activated protein kinase in the control of hepatocyte priming and proliferation during liver regeneration. *Exp Biol Med (Maywood)*. 2011;236:402-408.
- 426.** Chanda D, Li T, Song KH, et al. Hepatocyte growth factor family negatively regulates hepatic gluconeogenesis via induction of orphan nuclear

- receptor small heterodimer partner in primary hepatocytes. *J Biol Chem.* 2009;284:28510-28521.
- 427.** Araújo TG, Oliveira AG, Carvalho BM, et al. Hepatocyte growth factor plays a key role in insulin resistance-associated compensatory mechanisms. *Endocrinology.* 2012;153:5760-5769.
- 428.** Coudriet GM, Stoops J, Orr AV, et al. A noncanonical role for plasminogen activator inhibitor type 1 in obesity-induced diabetes. *Am J Pathol.* 2019;189:1413-1422.
- 429.** Huang Y, Liu Y, Ma Y, et al. Associations of visceral adipose tissue, circulating protein biomarkers, and risk of cardiovascular diseases: a mendelian randomization analysis. *Front Cell Dev Biol.* 2022;10:840866. <https://doi.org/10.3389/fcell.2022.840866>
- 430.** Faber DR, van der Graaf Y, Westerink J, et al. Hepatocyte growth factor and interferon- $\gamma$  inducible protein-10 are related to visceral adiposity. *Eur J Clin Invest.* 2013;43:369-378.
- 431.** Balaban YH, Sumer H, Simsek H, Us D, Tatar G. Metabolic syndrome, non-alcoholic steatohepatitis (NASH), and hepatocyte growth factor (HGF). *Ann Hepatol.* 2006;5:109-114.
- 432.** Rehman J, Considine RV, Bovenkerk JE, et al. Obesity is associated with increased levels of circulating hepatocyte growth factor. *J Am Coll Cardiol.* 2003;41:1408-1413.
- 433.** Faber DR, Moll FL, Vink A, et al. Adipose tissue quantity and composition contribute to adipokine concentrations in the subclavian vein and the inferior mesenteric vein. *Int J Obes (Lond).* 2012;36:1078-1085.
- 434.** Bell LN, Ward JL, Degawa-Yamauchi M, et al. Adipose tissue production of hepatocyte growth factor contributes to elevated serum HGF in obesity. *Am J Physiol Endocrinol Metab.* 2006;291:E843-E848.
- 435.** Wiewiora M, Mertas A, Gluck M, Nowowiejska-Wiewiora A, Czuba Z, Piecuch J. Effect of weight loss surgery on biomarkers of angiogenesis in obese patients. *Obes Surg.* 2020;30:3417-3425.
- 436.** Girerd N, Levy D, Duarte K, et al. Protein biomarkers of new-onset heart failure: insights from the Heart Omics and Ageing Cohort, the Atherosclerosis Risk in Communities Study, and the Framingham Heart Study. *Circ Heart Fail.* 2023;16(5):e009694. <https://doi.org/10.1161/CIRCHEARTFAILURE.122.009694>
- 437.** Ferraro RA, Ogunmoroti O, Zhao D, et al. Hepatocyte growth factor and incident heart failure subtypes: the Multi-Ethnic Study of Atherosclerosis (MESA). *J Card Fail.* 2021;27:981-990.
- 438.** Ferraro RA, Ogunmoroti O, Zhao D, et al. Hepatocyte growth factor and 10-year change in left ventricular structure: the Multi-Ethnic Study of Atherosclerosis (MESA). *CJC Open.* 2023;5:364-372.
- 439.** Chen HL, Zhu XT, Zhang W, Cheng XB, Hu ZP. Hepatocyte growth factor and B-type natriuretic peptide as independent predictors of mortality in HFpEF patients. *Front Cardiovasc Med.* 2025;12:1512411. <https://doi.org/10.3389/fcvm.2025.1512411>
- 440.** Pérez-Calvo JL, Morales-Rull JL, Gimeno-Orna JA, et al. Usefulness of the hepatocyte growth factor as a predictor of mortality in patients hospitalized with acute heart failure regardless of ejection fraction. *Am J Cardiol.* 2016;118:543-549.
- 441.** Rychlik I, Richter B, Hohensinner PJ, et al. Hepatocyte growth factor is a strong predictor of mortality in patients with advanced heart failure. *Heart.* 2011;97:1158-1163.
- 442.** Lamblin N, Susen S, Dagorn J, et al. Prognostic significance of circulating levels of angiogenic cytokines in patients with congestive heart failure. *Am Heart J.* 2005;150:137-143.
- 443.** Ueno S, Ikeda U, Hojo Y, et al. Serum hepatocyte growth factor levels are increased in patients with congestive heart failure. *J Card Fail.* 2001;7:329-334.
- 444.** Jin H, Yang R, Li W, et al. Early treatment with hepatocyte growth factor improves cardiac function in experimental heart failure induced by myocardial infarction. *J Pharmacol Exp Ther.* 2003;304:654-660.
- 445.** Yi X, Li X, Zhou Y, et al. Hepatocyte growth factor regulates the TGF- $\beta$ 1-induced proliferation, differentiation and secretory function of cardiac fibroblasts. *Int J Mol Med.* 2014;34:381-390.
- 446.** Yan L, Zhu TB, Wang LS, et al. Inhibitory effect of hepatocyte growth factor on cardiomyocytes apoptosis is partly related to reduced calcium sensing receptor expression during a model of simulated ischemia/reperfusion. *Mol Biol Rep.* 2011;38:2695-2701.
- 447.** Gallo S, Spilinga M, Albano R, et al. Activation of the MET receptor attenuates doxorubicin-induced cardiotoxicity in vivo and in vitro. *Br J Pharmacol.* 2020;177:3107-3122.
- 448.** Yang J, Yan B, Zhang H, et al. Estimating the causal effects of genetically predicted plasma proteome on heart failure. *Front Cardiovasc Med.* 2023;10:978918. <https://doi.org/10.3389/fcvm.2023.978918>
- 449.** Hu ZP, Bao Y, Chen DN, et al. Effects of recombinant adenovirus hepatocyte growth factor gene on myocardial remodeling in spontaneously hypertensive rats. *J Cardiovasc Pharmacol Ther.* 2013;18:476-480.
- 450.** Jayasankar V, Woo YJ, Bish LT, et al. Gene transfer of hepatocyte growth factor attenuates postinfarction heart failure. *Circulation.* 2003;108:II230-II236.
- 451.** Li Y, Takemura G, Kosai K, et al. Post-infarction treatment with an adenoviral vector expressing hepatocyte growth factor relieves chronic left ventricular remodeling and dysfunction in mice. *Circulation.* 2003;107:2499-2506.
- 452.** Sala V, Gatti S, Gallo S, et al. A new transgenic mouse model of heart failure and cardiac cachexia raised by sustained activation of met tyrosine kinase in the heart. *Biomed Res Int.* 2016;2016:9549036. <https://doi.org/10.1155/2016/9549036>
- 453.** Sala V, Gallo S, Gatti S, et al. Cardiac concentric hypertrophy promoted by activated Met receptor is mitigated in vivo by inhibition of Erk1,2 signalling with Pimasertib. *J Mol Cell Cardiol.* 2016;93:84-97.
- 454.** Leo C, Sala V, Morello M, et al. Activated Met signalling in the developing mouse heart leads to cardiac disease. *PLoS One.* 2011;6(2):e14675. <https://doi.org/10.1371/journal.pone.0014675>
- 455.** Meng H, Chen B, Tao Z, et al. Safety and efficacy of adenovirus carrying hepatocyte growth factor gene by percutaneous endocardial injection for treating post-infarct heart failure: a phase IIa clinical trial. *Curr Gene Ther.* 2018;18:125-130.
- 456.** Famulla S, Lamers D, Hartwig S, Passlack W, Horrighs A, Cramer A, Lehr S, Sell H, Eckel J. Pigment epithelium-derived factor (PEDF) is one of the most abundant proteins secreted by human adipocytes and induces insulin resistance and inflammatory signaling in muscle and fat cells. *Int J Obes (Lond).* 2011;35:762-772.
- 457.** Xu M, Chen X, Yu Z, Li X. Receptors that bind to PEDF and their therapeutic roles in retinal diseases. *Front Endocrinol (Lausanne).* 2023;14:1116136. <https://doi.org/10.3389/fendo.2023.1116136>
- 458.** Haemerle G, Lass A, Zimmermann R, et al. Defective lipolysis and altered energy metabolism in mice lacking adipose triglyceride lipase. *Science.* 2006;312:734-737.
- 459.** Zhang M, Tombra-Tink J, Yang S, Zhang X, Li X, Barnstable CJ. PEDF is an endogenous inhibitor of VEGF-R2 angiogenesis signaling in endothelial cells. *Exp Eye Res.* 2021;213:108828. <https://doi.org/10.1016/j.exer.2021.108828>
- 460.** Khan SA, Sathyaranayanan A, Mashek MT, Ong KT, Wollaston-Hayden EE, Mashek DG. ATGL-catalyzed lipolysis regulates SIRT1 to control PGC-1alpha/PPAR-alpha signaling. *Diabetes.* 2015;64:418-426.
- 461.** Fougerat A, Schoiswohl G, Polizzi A, et al. ATGL-dependent white adipose tissue lipolysis controls hepatocyte PPARalpha activity. *Cell Rep.* 2022;39(10):110910. <https://doi.org/10.1016/j.celrep.2022.110910>
- 462.** Haemerle G, Lass A, Woelkart G, et al. ATGL-mediated fat catabolism regulates cardiac mitochondrial function via PPAR-alpha and PGC-1. *Nat Med.* 2011;17:1076-1085.
- 463.** Marzolla V, Feraco A, Gorini S, et al. The novel non-steroidal MR antagonist finerenone improves metabolic parameters in high-fat diet-fed mice and activates brown adipose tissue via AMPK-ATGL pathway. *FASEB J.* 2020;34:12450-12465.
- 464.** Mouisel E, Bodon A, Noll C, et al. Cold-induced thermogenesis requires neutral-lipase-mediated intracellular lipolysis in brown adipocytes. *Cell Metab.* 2025;37:429-440.e5.
- 465.** Desai A, Loureiro ZY, DeSouza T, Yang Q, Solivan-Rivera J, Corvera S. cAMP driven UCP1 induction in human adipocytes requires ATGL-catalyzed lipolysis. *Mol Metab.* 2024;90:102051. <https://doi.org/10.1016/j.molmet.2024.102051>
- 466.** Matsui T, Nishino Y, Ojima A, Maeda S, Tahara N, Yamagishi SI. Pigment epithelium-derived factor improves metabolic derangements

- and ameliorates dysregulation of adipocytokines in obese type 2 diabetic rats. *Am J Pathol.* 2014;184:1094-1103.
- 467.** Maeda S, Matsui T, Takeuchi M, Yamagishi S. Pigment epithelium-derived factor (PEDF) blocks advanced glycation end products (AGEs)-RAGE-induced suppression of adiponectin mRNA level in adipocytes by inhibiting NADPH oxidase-mediated oxidative stress generation. *Int J Cardiol.* 2011;152:408-410.
- 468.** Crowe S, Wu LE, Economou C, et al. Pigment epithelium-derived factor contributes to insulin resistance in obesity. *Cell Metab.* 2009;10:40-47.
- 469.** Ahmadian M, Duncan RE, Varady KA, et al. Adipose overexpression of desnutrin promotes fatty acid use and attenuates diet-induced obesity. *Diabetes.* 2009;58:855-866.
- 470.** Toluso B, Gigante MR, Alivernini S, et al. Chemerin and PEDF are metaflammation-related biomarkers of disease activity and obesity in rheumatoid arthritis. *Front Med (Lausanne).* 2018;5:207. <https://doi.org/10.3389/fmed.2018.00207>
- 471.** Tryggestad JB, Wang JJ, Zhang SX, Thompson DM, Short KR. Elevated plasma pigment epithelium-derived factor in children with type 2 diabetes mellitus is attributable to obesity. *Pediatr Diabetes.* 2015;16:600-605.
- 472.** Gattu AK, Birkenfeld AL, Jornayvaz F, et al. Insulin resistance is associated with elevated serum pigment epithelium-derived factor (PEDF) levels in morbidly obese patients. *Acta Diabetol.* 2012;49:S161-S169.
- 473.** Sabater M, Moreno-Navarrete JM, Ortega FJ, et al. Circulating pigment epithelium-derived factor levels are associated with insulin resistance and decrease after weight loss. *J Clin Endocrinol Metab.* 2010;95:4720-4728.
- 474.** Choi KM, Hwang SY, Hong HC, et al. C1q/TNF-related protein-3 (CTRP-3) and pigment epithelium-derived factor (PEDF) concentrations in patients with type 2 diabetes and metabolic syndrome. *Diabetes.* 2012;61:2932-2936.
- 475.** Nakamura K, Yamagishi S, Adachi H, Kurita-Nakamura Y, Matsui T, Inoue H. Serum levels of pigment epithelium-derived factor (PEDF) are positively associated with visceral adiposity in Japanese patients with type 2 diabetes. *Diabetes Metab Res Rev.* 2009;25:52-56.
- 476.** Rychli K, Niessner A, Hohensinner PJ, et al. Prognostic value of pigment epithelium-derived factor in patients with advanced heart failure. *Chest.* 2010;138:656-664.
- 477.** Zhao Q, Liu Z, Huang B, et al. PEDF improves cardiac function in rats subjected to myocardial ischemia/reperfusion injury by inhibiting ROS generation via PEDF-R. *Int J Mol Med.* 2018;41:3243-3252.
- 478.** Zhou Z, Wang Z, Guan Q, et al. PEDF inhibits the activation of NLRP3 inflammasome in hypoxic cardiomyocytes through PEDF receptor/phospholipase A2. *Int J Mol Sci.* 2016;17(12):2064. <https://doi.org/10.3390/ijms17122064>
- 479.** Kuo HF, Liu PL, Chong IW, et al. Pigment epithelium-derived factor mediates autophagy and apoptosis in myocardial hypoxia/reoxygenation injury. *PLoS One.* 2016;11(5):e0156059. <https://doi.org/10.1371/journal.pone.0156059>
- 480.** Li Y, Liu Z, Zhang Y, et al. PEDF protects cardiomyocytes by promoting FUNDC1-mediated mitophagy via PEDF-R under hypoxic condition. *Int J Mol Med.* 2018;41:3394-3404.
- 481.** Liang J, Luo Q, Shen N, et al. PEDF protects endothelial barrier integrity during acute myocardial infarction via 67LR. *Int J Mol Sci.* 2023;24:2787.
- 482.** Zhang H, Wang Z, Feng SJ, et al. PEDF improves cardiac function in rats with acute myocardial infarction via inhibiting vascular permeability and cardiomyocyte apoptosis. *Int J Mol Sci.* 2015;16:5618-5634.
- 483.** Huang B, Miao H, Yuan Y, et al. PEDF decreases cardiomyocyte edema during oxygen-glucose deprivation and recovery via inhibiting lactate accumulation and expression of AQP1. *Int J Mol Med.* 2019;43:1979-1990.
- 484.** Hui HL, Jiang B, Zhou YY, et al. PEDF inhibits VEGF-induced vascular leakage through binding to VEGFR2 in acute myocardial infarction. *J Biomol Struct Dyn.* 2024;1:1-13. <https://doi.org/10.1080/07391102.2024.2314260>
- 485.** Ueda S, Yamagishi S, Matsui T, Jinnouchi Y, Imaizumi T. Administration of pigment epithelium-derived factor inhibits left ventricular remodeling and improves cardiac function in rats with acute myocardial infarction. *Am J Pathol.* 2011;178:591-598.
- 486.** Zhang H, Hui H, Li Z, et al. Pigment epithelium-derived factor attenuates myocardial fibrosis via inhibiting Endothelial-to-Mesenchymal Transition in rats with acute myocardial infarction. *Sci Rep.* 2017;7:41932. <https://doi.org/10.1038/srep41932>
- 487.** Wölkart G, Schrammel A, Dörffel K, Haemmerle G, Zechner R, Mayer B. Cardiac dysfunction in adipose triglyceride lipase deficiency: treatment with a PPARalpha agonist. *Br J Pharmacol.* 2012;165:380-389.
- 488.** Kienesberger PC, Pulinkkunnil T, Nagendran J, et al. Early structural and metabolic cardiac remodelling in response to inducible adipose triglyceride lipase ablation. *Cardiovasc Res.* 2013;99:442-451.
- 489.** Parajuli N, Takahara S, Matsumura N, et al. Atglistatin ameliorates functional decline in heart failure via adipocyte-specific inhibition of adipose triglyceride lipase. *Am J Physiol Heart Circ Physiol.* 2018;315:H879-H884.
- 490.** Thiele A, Luettges K, Ritter D, et al. Pharmacological inhibition of adipose tissue adipose triglyceride lipase by Atglistatin prevents catecholamine-induced myocardial damage. *Cardiovasc Res.* 2022;118:2488-2505.
- 491.** Takahara S, Ferdaoussi M, Srnic N, et al. Inhibition of ATGL in adipose tissue ameliorates isoproterenol-induced cardiac remodeling by reducing adipose tissue inflammation. *Am J Physiol Heart Circ Physiol.* 2021;320:H432-H446.
- 492.** Salatzki J, Foryst-Ludwig A, Bentle K, et al. Adipose tissue ATGL modifies the cardiac lipidome in pressure-overload-induced left ventricular failure. *PLoS Genet.* 2018;14(1):e1007171. <https://doi.org/10.1371/journal.pgen.1007171>
- 493.** Foryst-Ludwig A, Kreissl MC, Benz V, et al. Adipose tissue lipolysis promotes exercise-induced cardiac hypertrophy involving the lipokine C16:1n7-palmiteoleate. *J Biol Chem.* 2015;290:23603-23615.
- 494.** Devron CA. Fatty acids and expression of adipokines. *Biochim Biophys Acta.* 2005;1740:287-292.
- 495.** Wei J, Nelson MD, Szczepaniak EW, et al. Myocardial steatosis as a possible mechanistic link between diastolic dysfunction and coronary microvascular dysfunction in women. *Am J Physiol Heart Circ Physiol.* 2016;310:H14-H19.
- 496.** Mao T, Wang Y. PEDF overexpression ameliorates cardiac lipotoxicity in diabetic cardiomyopathy via regulation of energy metabolism. *Diabetes Metab Syndr Obes.* 2025;18:217-231.
- 497.** Cui X, Jing J, Wu R, et al. Adipose tissue-derived neurotrophic factor 3 regulates sympathetic innervation and thermogenesis in adipose tissue. *Nat Commun.* 2021;12(1):5362. <https://doi.org/10.1038/s41467-021-25766-2>
- 498.** Nonomura T, Tsuchida A, Ono-Kishino M, Nakagawa T, Taiji M, Noguchi H. Brain-derived neurotrophic factor regulates energy expenditure through the central nervous system in obese diabetic mice. *Int J Exp Diabetes Res.* 2001;2:201-209.
- 499.** Colitti M, Montanari T. Brain-derived neurotrophic factor modulates mitochondrial dynamics and thermogenic phenotype on 3T3-L1 adipocytes. *Tissue Cell.* 2020;66:101388. <https://doi.org/10.1016/j.tice.2020.101388>
- 500.** White UA, Stephens JM. The gp130 receptor cytokine family: regulators of adipocyte development and function. *Curr Pharm Des.* 2011;17:340-346.
- 501.** Ryan VH, German AJ, Wood IS, Hunter L, Morris P, Trayhurn P. NGF gene expression and secretion by canine adipocytes in primary culture: upregulation by the inflammatory mediators LPS and TNFalpha. *Horm Metab Res.* 2008;40:861-868.
- 502.** Zvonic S, Cornelius P, Stewart WC, Mynatt RL, Stephens JM. The regulation and activation of ciliary neurotrophic factor signaling proteins in adipocytes. *J Biol Chem.* 2003;278:2228-2235.
- 503.** Ott V, Fasshauer M, Dalski A, Klein HH, Klein J. Direct effects of ciliary neurotrophic factor on brown adipocytes: evidence for a role in peripheral regulation of energy homeostasis. *J Endocrinol.* 2002;173:R1-R8.
- 504.** Dahl-Jørgensen A, Ostergaard K, Pedersen EB, Zimmer J. Serum and CNTF stimulate oligodendroglia and reduce fiber outgrowth from striatal cultures. *Exp Neurol.* 1999;157:88-95.
- 505.** Razavi S, Razavi MR, Kheirollahi-Kouhestani M, Mardani M, Mostafavi FS. Co-culture with neurotrophic factor secreting cells induced from adipose-derived stem cells:

- promotes neurogenic differentiation. *Biochem Biophys Res Commun.* 2013;440:381-387.
- 506.** Kim KS, Lee HJ, An J, et al. Transplantation of human adipose tissue-derived stem cells delays clinical onset and prolongs life span in ALS mouse model. *Cell Transplant.* 2014;23:1585-1597.
- 507.** Bulló M, Peeraully MR, Trayhurn P, Folch J, Salas-Salvadó J. Circulating nerve growth factor levels in relation to obesity and the metabolic syndrome in women. *Eur J Endocrinol.* 2007;157:303-310.
- 508.** Perugini J, Di Mercurio E, Giuliani A, et al. Ciliary neurotrophic factor is increased in the plasma of patients with obesity and its levels correlate with diabetes and inflammation indices. *Sci Rep.* 2022;12(1):8331. <https://doi.org/10.1038/s41598-022-11942-x>
- 509.** Popa-Wagner A, Furczyk K, Richter J, Irmisch G, Thome J. Neurotrophin levels at admission did not change significantly upon alcohol deprivation and were positively correlated with the BMI and LDL levels. *J Mol Psychiatry.* 2013;1(1):20. <https://doi.org/10.1186/2049-9256-1-20>
- 510.** Akbarian SA, Salehi-Abargouei A, Pourmasoumi M, Kelishadi R, Nikpour P, Heidari-Beni M. Association of brain-derived neurotrophic factor gene polymorphisms with body mass index: A systematic review and meta-analysis. *Adv Med Sci.* 2018;63(1):43-56.
- 511.** Liu QS, Gao M, Zhu SY, et al. The novel mechanism of recombinant human ciliary neurotrophic factor on the anti-diabetes activity. *Basic Clin Pharmacol Toxicol.* 2007;101:78-84.
- 512.** Perugini J, Di Mercurio E, Tossetta G, et al. Biological effects of ciliary neurotrophic factor on hMADS adipocytes. *Front Endocrinol (Lausanne).* 2019;10:768. <https://doi.org/10.3389/fendo.2019.00768>
- 513.** Crowe S, Turpin SM, Ke F, Kemp BE, Watt MJ. Metabolic remodeling in adipocytes promotes ciliary neurotrophic factor-mediated fat loss in obesity. *Endocrinology.* 2008;149:2546-2556.
- 514.** Watt MJ, Dzamko N, Thomas WG, et al. CNTF reverses obesity-induced insulin resistance by activating skeletal muscle AMPK. *Nat Med.* 2006;12:541-548.
- 515.** Gloaguen I, Costa P, Demartis A, et al. Ciliary neurotrophic factor corrects obesity and diabetes associated with leptin deficiency and resistance. *Proc Natl Acad Sci U S A.* 1997;94:6456-6461.
- 516.** Blüher S, Moschos S, Bullen J Jr, et al. Ciliary neurotrophic factor Ax15 alters energy homeostasis, decreases body weight, and improves metabolic control in diet-induced obese and UCP1-DTA mice. *Diabetes.* 2004;53:2787-2796.
- 517.** Miller RG, Petajan JH, Bryan WW, et al, rhCNTF ALS Study Group. A placebo-controlled trial of recombinant human ciliary neurotrophic (rhCNTF) factor in amyotrophic lateral sclerosis. *Ann Neurol.* 1996;39:256-260.
- 518.** Ettinger MP, Littlejohn TW, Schwartz SL, et al. Recombinant variant of ciliary neurotrophic factor for weight loss in obese adults: a randomized, dose-ranging study. *JAMA.* 2003;289:1826-1832.
- 519.** Ichimura-Shimizu M, Kojima M, Suzuki S, et al. Brain-derived neurotrophic factor knock-out mice develop non-alcoholic steatohepatitis. *J Pathol.* 2023;261:465-476.
- 520.** Jo D, Son Y, Yoon G, Song J, Kim OY. Role of adiponectin and brain derived neurotrophic factor in metabolic regulation involved in adiposity and body fat browning. *J Clin Med.* 2020;10(1):56. <https://doi.org/10.3390/jcm10010056>
- 521.** Cannava A, Jun S, Rengo G, et al. beta3AR-dependent brain-derived neurotrophic factor (BDNF) generation limits chronic postischemic heart failure. *Circ Res.* 2023;132:867-881.
- 522.** Yan F, Chen Z, Cui W. H3K9me2 regulation of BDNF expression via G9a partakes in the progression of heart failure. *BMC Cardiovasc Disord.* 2022;22(1):182. <https://doi.org/10.1186/s12872-022-02621-w>
- 523.** Hang P, Zhao J, Sun L, et al. Brain-derived neurotrophic factor attenuates doxorubicin-induced cardiac dysfunction through activating Akt signalling in rats. *J Cell Mol Med.* 2017;21:685-696.
- 524.** Lam NT, Currie PD, Lieschke GJ, Rosenthal NA, Kaye DM. Nerve growth factor stimulates cardiac regeneration via cardiomyocyte proliferation in experimental heart failure. *PLoS One.* 2012;7(12):e53210. <https://doi.org/10.1371/journal.pone.0053210>
- 525.** He B, Ye F, Zhou X, Li H, et al. Exogenous nerve growth factor supplementation elevates myocardial immunoreactivity and attenuates cardiac remodeling in pressure-overload rats. *Acta Biochim Biophys Sin (Shanghai).* 2012;44:931-938.
- 526.** Meloni M, Descamps B, Caporali A, et al. Nerve growth factor gene therapy using adenovirus-associated viral vectors prevents cardiomyopathy in type 1 diabetic mice. *Diabetes.* 2012;61:229-240.
- 527.** Zhao J, Du J, Pan Y, et al. Activation of cardiac TrkB receptor by its small molecular agonist 7,8-dihydroxyflavone inhibits doxorubicin-induced cardiotoxicity via enhancing mitochondrial oxidative phosphorylation. *Free Radic Biol Med.* 2019;130:557-567.
- 528.** Wang J, Wu N, Zhang J, et al. Ciliary neurotrophic factor attenuates myocardial infarction-induced oxidative stress and ferroptosis via PI3K/Akt signaling. *J Mol Histol.* 2025;56(2):90. <https://doi.org/10.1007/s10735-025-10359-w>
- 529.** Zhong P, Zeng G, et al. Ciliary neurotrophic factor overexpression protects the heart against pathological remodelling in angiotensin II-infused mice. *Biochem Biophys Res Commun.* 2021;547:15-22.
- 530.** Bi W, Wang J, Jiang Y, et al. Neurotrophin-3 contributes to benefits of human embryonic stem cell-derived cardiovascular progenitor cells against reperfused myocardial infarction. *Stem Cells Transl Med.* 2021;10:756-772.
- 531.** Kawaguchi-Manabe H, Ieda M, Kimura K, et al. A novel cardiac hypertrophic factor, neurotrophin-3, is paradoxically downregulated in cardiac hypertrophy. *Life Sci.* 2007;81:385-392.
- 532.** Kaye DM, Vaddadi G, Gruskin SL, Du XJ, Esler MD. Reduced myocardial nerve growth factor expression in human and experimental heart failure. *Circ Res.* 2000;86:E80-E84.
- 533.** Kreusser MM, Buss SJ, Krebs J, et al. Differential expression of cardiac neurotrophic factors and sympathetic nerve ending abnormalities within the failing heart. *J Mol Cell Cardiol.* 2008;44:380-387.
- 534.** Fang CX, Dong F, Thomas DP, Ma H, He L, Ren J. Hypertrophic cardiomyopathy in high-fat diet-induced obesity: role of suppression of forkhead transcription factor and atrophy gene transcription. *Am J Physiol Heart Circ Physiol.* 2008;295:H1206-H1215.
- 535.** Fukushima A, Kinugawa S, Homma T, et al. Serum brain-derived neurotropic factor level predicts adverse clinical outcomes in patients with heart failure. *J Card Fail.* 2015;21:300-306.
- 536.** Boucher J, Masri B, Daviaud D, et al. Apelin, a newly identified adipokine up-regulated by insulin and obesity. *Endocrinology.* 2005;146:1764-1771.
- 537.** Higuchi K, Masaki T, Gotoh K, et al. Apelin, an APJ receptor ligand, regulates body adiposity and favors the messenger ribonucleic acid expression of uncoupling proteins in mice. *Endocrinology.* 2007;148:2690-2697.
- 538.** Than A, He HL, Chua SH, et al. Apelin enhances brown adipogenesis and browning of white adipocytes. *J Biol Chem.* 2015;290:14679-14691.
- 539.** Guo M, Chen F, Lin T, et al. Apelin-13 decreases lipid storage in hypertrophic adipocytes in vitro through the upregulation of AQP7 expression by the PI3K signaling pathway. *Med Sci Monit.* 2014;20:1345-1352.
- 540.** Than A, Cheng Y, Foh LC, et al. Apelin inhibits adipogenesis and lipolysis through distinct molecular pathways. *Mol Cell Endocrinol.* 2012;362:227-241.
- 541.** Than A, Zhang X, Leow MK, Poh CL, Chong SK, Chen P. Apelin attenuates oxidative stress in human adipocytes. *J Biol Chem.* 2014;289:3763-3774.
- 542.** Zhu S, Sun F, Li W, et al. Apelin stimulates glucose uptake through the PI3K/Akt pathway and improves insulin resistance in 3T3-L1 adipocytes. *Mol Cell Biochem.* 2011;353:305-313.
- 543.** Yamamoto T, Habata Y, Matsumoto Y, et al. Apelin-transgenic mice exhibit a resistance against diet-induced obesity by increasing vascular mass and mitochondrial biogenesis in skeletal muscle. *Biochim Biophys Acta.* 2011;1810:853-862.
- 544.** Mund C, Kelleluu CK, Rattan R, Mahapatra S, Lamare AA, Jena S. Study of serum apelin and insulin resistance in type 2 diabetes mellitus patients with or without obesity. *Cureus.* 2023;15(8):e43401. <https://doi.org/10.7759/cureus.43401>
- 545.** Cavallo MG, Sentinelli F, Barchetta I, et al. Altered glucose homeostasis is associated with increased serum apelin levels in type 2 diabetes mellitus. *PLoS One.* 2012;7(12):e51236. <https://doi.org/10.1371/journal.pone.0051236>
- 546.** Khajeh E, Panahi N, Golpaie A, et al. Plasma apelin and asymmetric dimethylarginine (ADMA)

- levels shortly after laparoscopic greater curvature plication. *Obes Surg.* 2017;27:1596-1603.
- 547.** Berry MF, Pirolli TJ, Jayasankar V, et al. Apelin has in vivo inotropic effects on normal and failing hearts. *Circulation.* 2004;110:II187-II193.
- 548.** Schinzari F, Veneziani A, Mores N, et al. Beneficial effects of apelin on vascular function in patients with central obesity. *Hypertension.* 2017;69:942-949.
- 549.** Pchelitski D, Foussal C, Alfarano C, et al. Apelin prevents cardiac fibroblast activation and collagen production through inhibition of sphingosine kinase 1. *Eur Heart J.* 2012;33:2360-2369.
- 550.** Kuba K, Zhang L, Imai Y, et al. Impaired heart contractility in Apelin gene-deficient mice associated with aging and pressure overload. *Circ Res.* 2007;101:e32-e42.
- 551.** Wang W, McKinnie SM, Patel VB, et al. Loss of Apelin exacerbates myocardial infarction adverse remodeling and ischemia-reperfusion injury: therapeutic potential of synthetic Apelin analogues. *J Am Heart Assoc.* 2013;2(4):e000249. <https://doi.org/10.1161/JAHA.113.000249>
- 552.** Alfarano C, Foussal C, Lairez O, et al. Transition from metabolic adaptation to maladaptation of the heart in obesity: role of apelin. *Int J Obes (Lond).* 2015;39:312-320.
- 553.** Ayari H, Chraibi A. Apelin-13 decreases epithelial sodium channel (ENaC) expression and activity in kidney collecting duct cells. *Cell Physiol Biochem.* 2022;56:1-12.
- 554.** Flahault A, Girault-Sotias PE, Keck M, et al. A metabolically stable apelin-17 analog decreases AVP-induced antidiuresis and improves hypotremia. *Nat Commun.* 2021;12(1):305. <https://doi.org/10.1038/s41467-020-20560-y>
- 555.** Földes G, Horvay F, Szokodi I, et al. Circulating and cardiac levels of apelin, the novel ligand of the orphan receptor APJ, in patients with heart failure. *Biochem Biophys Res Commun.* 2003;308:480-485.
- 556.** Gao LR, Xu RY, Zhang NK, et al. Increased apelin following bone marrow mononuclear cell transplantation contributes to the improvement of cardiac function in patients with severe heart failure. *Cell Transplant.* 2009;18:1311-1318.
- 557.** Goiedescu CM, Chiorescu RM, Diana ML, et al. ACE2 and Apelin-13: biomarkers with a prognostic value in congestive heart failure. *Dis Markers.* 2021;2021:5569410. <https://doi.org/10.1155/2021/5569410>
- 558.** Chandrasekaran B, Kalra PR, Donovan J, Hooper J, Clague JR, McDonagh TA. Myocardial apelin production is reduced in humans with left ventricular systolic dysfunction. *J Card Fail.* 2010;16:556-561.
- 559.** Zhang T, Wang X, Wang Z, et al. Canagliflozin ameliorates ventricular remodeling through apelin/angiotensin-converting enzyme 2 signaling in heart failure with preserved ejection fraction rats. *Pharmacology.* 2023;108(5):478-491.
- 560.** Berezin AA, Fushtey IM, Berezin AE. Discriminative utility of Apelin-to-NT-pro-brain natriuretic peptide ratio for heart failure with preserved ejection fraction among type 2 diabetes mellitus patients. *J Cardiovasc Dev Dis.* 2022;9(1):23. <https://doi.org/10.3390/jcd9010023>
- 561.** Gargalovic P, Wong P, Onorato J, et al. In vitro and in vivo evaluation of a small-molecule APJ (apelin receptor) agonist, BMS-986224, as a potential treatment for heart failure. *Circ Heart Fail.* 2021;14(3):e007351. <https://doi.org/10.1161/CIRCHEARTFAILURE.120.007351>
- 562.** Winkle P, Goldsmith S, Koren MJ, et al. A first-in-human study of AMG 986, a novel apelin receptor agonist, in healthy subjects and heart failure patients. *Cardiovasc Drugs Ther.* 2023;37:743-755.
- 563.** Qi T, Hay DL. Structure-function relationships of the N-terminus of receptor activity-modifying proteins. *Br J Pharmacol.* 2010;159:1059-1068.
- 564.** Clark AJ, Mullooly N, Safitri D, et al. CGRP, adrenomedullin and adrenomedullin 2 display endogenous GPCR agonist bias in primary human cardiovascular cells. *Commun Biol.* 2021;4(1):776. <https://doi.org/10.1038/s42403-021-02293-w>
- 565.** Li Y, Jiang C, Wang X, Zhang Y, Shibahara S, Takahashi K. Adrenomedullin is a novel adipokine: adrenomedullin in adipocytes and adipose tissues. *Peptides.* 2007;28:1129-1143.
- 566.** Paulmyer-Lacroix O, Desbriere R, Poggi M, et al. Expression of adrenomedullin in adipose tissue of lean and obese women. *Eur J Endocrinol.* 2006;155:177-185.
- 567.** Nambu T, Arai H, Komatsu Y, et al. Expression of the adrenomedullin gene in adipose tissue. *Regul Pept.* 2005;132:17-22.
- 568.** Kim J, Lee SK, Kim D, et al. Altered expression of adrenomedullin 2 and its receptor in the adipose tissue of obese patients. *J Clin Endocrinol Metab.* 2020;105(1):dgz066. <https://doi.org/10.1210/clem/dgz066>
- 569.** Vila G, Riedl M, Maier C, et al. Plasma MR-proADM correlates to BMI and decreases in relation to leptin after gastric bypass surgery. *Obesity (Silver Spring).* 2009;17:1184-1188.
- 570.** Nomura I, Kato J, Tokashiki M, Kitamura K. Increased plasma levels of the mature and intermediate forms of adrenomedullin in obesity. *Regul Pept.* 2009;158:127-131.
- 571.** Fukai N, Yoshimoto T, Sugiyama T, et al. Concomitant expression of adrenomedullin and its receptor components in rat adipose tissues. *Am J Physiol Endocrinol Metab.* 2005;288:E56-E62.
- 572.** Koyama T, Kuriyama N, Uehara R. Midregional proadrenomedullin can reflect the accumulation of visceral adipose tissue—a key to explaining the obesity paradox. *Int J Environ Res Public Health.* 2020;17(11):3968. <https://doi.org/10.3390/ijerph17113968>
- 573.** Go AG, Chow KH, Hwang IS, Tang F. Adrenomedullin and its receptor components in adipose tissues: Differences between white and brown fats and the effects of adrenergic stimulation. *Peptides.* 2007;28:920-927.
- 574.** Zhang H, Zhang SY, Jiang C, et al. Intermedin/adrenomedullin 2 polypeptide promotes adipose tissue browning and reduces high-fat diet-induced obesity and insulin resistance in mice. *Int J Obes (Lond).* 2016;40:852-860.
- 575.** Dai HB, Wang FZ, Kang Y, et al. Adrenomedullin attenuates inflammation in white adipose tissue of obese rats through receptor-mediated PKA pathway. *Obesity (Silver Spring).* 2021;29:86-97.
- 576.** Kita T, Tokashiki M, Kitamura K. Aldosterone antisecretagogue and antihypertensive actions of adrenomedullin in patients with primary aldosteronism. *Hypertens Res.* 2010;33:374-379.
- 577.** Gupta P, Harte AL, da Silva NF, et al. Expression of calcitonin gene-related peptide, adrenomedullin, and receptor modifying proteins in human adipose tissue and alteration in their expression with menopause status. *Menopause.* 2007;14:1031-1038.
- 578.** Danaher RN, Loomes KM, Leonard BL, et al. Evidence that alpha-calcitonin gene-related peptide is a neurohormone that controls systemic lipid availability and utilization. *Endocrinology.* 2008;149:154-160.
- 579.** Etefagh HH, Shahmiri SS, Melali H, Sayadi M, Ansari H, Shahzamani A, Deyhimi MS. Bariatric surgery in migraine patients: CGRP level and weight loss. *Obes Surg.* 2022;32:3635-3640.
- 580.** Cui N, Sakurai T, Kamiyoshi A, et al. Adrenomedullin-RAMP2 and -RAMP3 systems regulate cardiac homeostasis during cardiovascular stress. *Endocrinology.* 2021;162(3):bqab001. <https://doi.org/10.1210/endocr/bqab001>
- 581.** Niu P, Shindo T, Iwata H, et al. Protective effects of endogenous adrenomedullin on cardiac hypertrophy, fibrosis, and renal damage. *Circulation.* 2004;109:1789-1794.
- 582.** Bell D, Campbell M, Wang X, Earle JA, Cosby SL, McDermott BJ. Adrenomedullin gene delivery is cardio-protective in a model of chronic nitric oxide deficiency combining pressure overload, oxidative stress and cardiomyocyte hypertrophy. *Cell Physiol Biochem.* 2010;26:383-394.
- 583.** Zhao Y, Sakurai T, Kamiyoshi A, et al. Adrenomedullin 2/intermedin exerts cardioprotective effects by regulating cardiomyocyte mitochondrial function. *Hypertension.* 2025;82:e6-e21.
- 584.** Aubdool AA, Thakore P, Argunhan F, et al. A novel  $\alpha$ -calcitonin gene-related peptide analogue protects against end-organ damage in experimental hypertension, cardiac hypertrophy, and heart failure. *Circulation.* 2017;136:367-383.
- 585.** Li J, Levick SP, DiPette DJ, Janicki JS, Supowit SC. Alpha-calcitonin gene-related peptide is protective against pressure overload-induced heart failure. *Regul Pept.* 2013;185:20-28.
- 586.** Kumar A, Supowit S, Potts JD, DiPette DJ. Alpha-calcitonin gene-related peptide prevents pressure-overload induced heart failure: role of apoptosis and oxidative stress. *Physiol Rep.* 2019;7(21):e14269. <https://doi.org/10.14814/phy2.14269>
- 587.** Wang HY, Wang FZ, Chang R, et al. Adrenomedullin improves hypertension and vascular remodeling partly through the receptor-mediated AMPK pathway in rats with obesity-related hypertension. *Int J Mol Sci.* 2023;24(4):3943. <https://doi.org/10.3390/ijms24043943>

- 588.** Shekhar YC, Anand IS, Sarma R, Ferrari R, Wahi PL, Poole-Wilson PA. Effects of prolonged infusion of human alpha calcitonin gene-related peptide on hemodynamics, renal blood flow and hormone levels in congestive heart failure. *Am J Cardiol.* 1991;67:732-736.
- 589.** Nagaya N, Satoh T, Nishikimi T, et al. Hemodynamic, renal, and hormonal effects of adrenomedullin infusion in patients with congestive heart failure. *Circulation.* 2000;101:498-503.
- 590.** Bhandari SS, Davies JE, Struck J, Ng LL. The midregional portion of proadrenomedullin is an independent predictor of left ventricular mass index in hypertension. *Metabolism.* 2010;59:7-13.
- 591.** Metwalley KA, Farghaly HS, Sherief T. Plasma adrenomedullin level in children with obesity: relationship to left ventricular function. *World J Pediatr.* 2018;14:84-91.
- 592.** Takvorian KS, Wang D, Courchesne P, et al. The association of protein biomarkers with incident heart failure with preserved and reduced ejection fraction. *Circ Heart Fail.* 2023;16(1):e009446. <https://doi.org/10.1161/CIRCHARTFAILURE.121.009446>
- 593.** Kresoja KP, Rommel KP, Wachter R, et al. Proteomics to improve phenotyping in obese patients with heart failure with preserved ejection fraction. *Eur J Heart Fail.* 2021;23:1633-1644.
- 594.** Obokata M, Kane GC, Reddy YNV, et al. The neurohormonal basis of pulmonary hypertension in heart failure with preserved ejection fraction. *Eur Heart J.* 2019;40:3707-3717.
- 595.** Stahrenberg R, Duvinage A, Mende M, et al. Determinants of submaximal exercise capacity in patients at risk for heart failure with preserved ejection fraction—results from the DIAST-CHF study. *ESC Heart Fail.* 2015;2:76-84.
- 596.** Obokata M, Reddy YNV, Melenovsky V, Sorimachi H, Jarolim P, Borlaug BA. Uncoupling between intravascular and distending pressures leads to underestimation of circulatory congestion in obesity. *Eur J Heart Fail.* 2022;24:353-361.
- 597.** Jensen J, Schou M, Kistorp C, et al. MR-proANP and incident cardiovascular disease in patients with type 2 diabetes with and without heart failure with preserved ejection fraction. *Cardiovasc Diabetol.* 2020;19(1):180. <https://doi.org/10.1186/s12933-020-01155-9>
- 598.** Myhre PL, Liu Y, Kulac IJ, et al. Changes in mid-regional pro-adrenomedullin during treatment with sacubitril/valsartan. *Eur J Heart Fail.* 2023;25:1396-1405.
- 599.** Schnelle M, Leha A, Eeidizadeh A, et al. Plasma biomarker profiling in heart failure patients with preserved ejection fraction before and after spironolactone treatment: results from the Aldo-DHF trial. *Cells.* 2021;10(10):2796. <https://doi.org/10.3390/cells10102796>
- 600.** Kong Y, Wang N, Tong Z, et al. Role of complement factor D in cardiovascular and metabolic diseases. *Front Immunol.* 2024;15:1453030. <https://doi.org/10.3389/fimmu.2024.1453030>
- 601.** Gilani A, Stoll L, Homan EA, Lo JC. Adipose signals regulating distal organ health and disease. *Diabetes.* 2024;73:169-177.
- 602.** Rezvani R, Shadmehr Foumani Moghadam MR, Cianflone K. Acylation stimulating protein/C3adesArg in the metabolic states: role of adipocyte dysfunction in obesity complications. *J Physiol.* 2024;602:773-790.
- 603.** Kalant D, Phélix S, Fielding BA, Frayn KN, Cianflone K, Sniderman AD. Increased post-prandial fatty acid trapping in subcutaneous adipose tissue in obese women. *J Lipid Res.* 2000;41:1963-1968.
- 604.** Cui W, Lapointe M, Gauvreau D, Kalant D, Cianflone K. Recombinant C3adesArg/acylation stimulating protein (ASP) is highly bioactive: a critical evaluation of CSL2 binding and 3T3-L1 adipocyte activation. *Mol Immunol.* 2009;46:3207-3217.
- 605.** Paglialunga S, Fisette A, Yan Y, et al. Acylation-stimulating protein deficiency and altered adipose tissue in alternative complement pathway knockout mice. *Am J Physiol Endocrinol Metab.* 2008;294:E521-E529.
- 606.** Bamberg CE, Mackay CR, Lee H, et al. The C5a receptor (C5aR) C5L2 is a modulator of C5aR-mediated signal transduction. *J Biol Chem.* 2010;285:7633-7644.
- 607.** Croker DE, Monk PN, Halai R, et al. Discovery of functionally selective C5aR2 ligands: novel modulators of C5a signalling. *Immunol Cell Biol.* 2016;94:787-795.
- 608.** Lo JC, Ljubicic S, Leibiger B, et al. Adipsin is an adipokine that improves beta cell function in diabetes. *Cell.* 2014;158:41-53.
- 609.** Gómez-Banoy N, Guseh JS, Li G, et al. Adipsin preserves beta cells in diabetic mice and associates with protection from type 2 diabetes in humans. *Nat Med.* 2019;25:1739-1747.
- 610.** McLaren RE, Cui W, Lu H, Simard S, Cianflone K. Association of adipocyte genes with ASP expression: a microarray analysis of subcutaneous and omental adipose tissue in morbidly obese subjects. *BMC Med Genomics.* 2010;3:3. <https://doi.org/10.1186/1755-8794-3-3>
- 611.** Ma L, Gilani A, Rubio-Navarro A, et al. Adipsin and adipocyte-derived C3aR1 regulate thermogenic fat in a sex-dependent fashion. *JCI Insight.* 2024;9(11):e178925. <https://doi.org/10.1172/jci.insight.178925>
- 612.** Fisette A, Munkonda MN, Oikonomopoulou K, Paglialunga S, Lambris JD, Cianflone K. C5L2 receptor disruption enhances the development of diet-induced insulin resistance in mice. *Immunobiology.* 2013;218:127-133.
- 613.** Gauvreau D, Gupta A, Fisette A, Tom FQ, Cianflone K. Deficiency of C5L2 increases macrophage infiltration and alters adipose tissue function in mice. *PLoS One.* 2013;8(4):e60795. <https://doi.org/10.1371/journal.pone.0060795>
- 614.** Roy C, Gupta A, Fisette A, et al. C5a receptor deficiency alters energy utilization and fat storage. *PLoS One.* 2013;8(5):e62531. <https://doi.org/10.1371/journal.pone.0062531>
- 615.** Poursharifi P, Lapointe M, Fisette A, et al. C5aR and C5L2 act in concert to balance immunometabolism in adipose tissue. *Mol Cell Endocrinol.* 2014;382:325-333.
- 616.** Wen Y, Wang H, McLaren R, Wu J, Lu H, Cianflone K. Palmitate and oleate induction of acylation stimulating protein resistance in 3T3-L1 adipocytes and preadipocytes. *J Cell Biochem.* 2008;104:391-401.
- 617.** Fisette A, Lapointe M, Cianflone K. Obesity-inducing diet promotes acylation stimulating protein resistance. *Biochem Biophys Res Commun.* 2013;437:403-407.
- 618.** Milek M, Moulla Y, Kern M, et al. Adipsin serum concentrations and adipose tissue expression in people with obesity and type 2 diabetes. *Int J Mol Sci.* 2022;23(4):2222. <https://doi.org/10.3390/ijms23042222>
- 619.** Ramirez MF, Pan AS, Parekh JK, et al. Sex differences in protein biomarkers and measures of fat distribution. *J Am Heart Assoc.* 2024;13(22):e000223. <https://doi.org/10.1161/JAHA.124.000223>
- 620.** Lee YJ, Kim JJ, Kim J, Cho DW, Won JY. The correlation between waist circumference and the pro-inflammatory adipokines in diabetic retinopathy of type 2 diabetes patients. *Int J Mol Sci.* 2023;24(3):2036. <https://doi.org/10.3390/ijms24032036>
- 621.** Schrover IM, van der Graaf Y, Spiering W, Visseren FL, SMART study group. The relation between body fat distribution, plasma concentrations of adipokines and the metabolic syndrome in patients with clinically manifest vascular disease. *Eur J Prev Cardiol.* 2018;25:1548-1557.
- 622.** Faraj M, Havel PJ, Phélix S, Blank D, Sniderman AD, Cianflone K. Plasma acylation-stimulating protein, adiponectin, leptin, and ghrelin before and after weight loss induced by gastric bypass surgery in morbidly obese subjects. *J Clin Endocrinol Metab.* 2003;88:1594-1602.
- 623.** Wang Y, Li Q, Zhou S, Tan P. Contents of exosomes derived from adipose tissue and their regulation on inflammation, tumors, and diabetes. *Front Endocrinol (Lausanne).* 2024;15:1374715. <https://doi.org/10.3389/fendo.2024.1374715>
- 624.** Zhang X, Duan Y, Zhang X, et al. Adipsin alleviates cardiac microvascular injury in diabetic cardiomyopathy through Csk-dependent signaling mechanism. *BMC Med.* 2023;21(1):197. <https://doi.org/10.1186/s12916-023-02887-7>
- 625.** Jiang MY, Man WR, Zhang XB, et al. Adipsin inhibits Irak2 mitochondrial translocation and improves fatty acid beta-oxidation to alleviate diabetic cardiomyopathy. *Mit Med Res.* 2023;10(1):63. <https://doi.org/10.1186/s40779-023-00493-5>
- 626.** Man W, Song X, Xiong Z, et al. Exosomes derived from pericardial adipose tissues attenuate cardiac remodeling following myocardial infarction by adipsin-regulated iron homeostasis. *Front Cardiovasc Med.* 2022;9:1003282. <https://doi.org/10.3389/fcm.2022.1003282>
- 627.** Shahini N, Michelsen AE, Nilsson PH, et al. The alternative complement pathway is dysregulated in patients with chronic heart failure. *Sci Rep.* 2017;7:42532. <https://doi.org/10.1038/srep42532>
- 628.** Ren J, Chen L, Chen X, Zhang N, Sun X, Song J. Acylation-stimulating protein and heart failure progression in arrhythmogenic right

- ventricular cardiomyopathy. *ESC Heart Fail.* 2023;10:492-501.
- 629.** de la Encarnación A, Alquézar C, Martín-Requero Á. Increased Wnt signaling and reduced viability in a neuronal model of progranulin-deficient frontotemporal lobar degeneration. *Mol Neurobiol.* 2016;53:7107-7118.
- 630.** Schmid A, Roderfeld M, Gehl J, et al. C1q/TNF-related protein 3 (CTRP-3) deficiency of adipocytes affects white adipose tissue mass but not systemic CTRP-3 concentrations. *Int J Mol Sci.* 2021;22(4):1670. <https://doi.org/10.3390/ijms22041670>
- 631.** Zhu Y, Ohama T, Kawase R, et al. Progranulin deficiency leads to enhanced age-related cardiac hypertrophy through complement C1q-induced beta-catenin activation. *J Mol Cell Cardiol.* 2020;138:197-211.
- 632.** Yoo HJ, Hwang SY, Hong HC, et al. Implication of progranulin and C1q/TNF-related protein-3 (CTRP3) on inflammation and atherosclerosis in subjects with or without metabolic syndrome. *PLoS One.* 2013;8(2):e55744. <https://doi.org/10.1371/journal.pone.0055744>
- 633.** Lee CH, Park CB, Kim HK, et al. Macrophage-specific progranulin deficiency prevents diet-induced obesity through the inhibition of hypothalamic and adipose tissue inflammation. *Diabetes Metab J.* 2025;49(4):784-797. <https://doi.org/10.4093/dmj.2024.0486>
- 634.** Sasaki T, Shimazawa M, Kanamori H, et al. Effects of progranulin on the pathological conditions in experimental myocardial infarction model. *Sci Rep.* 2020;10(1):11842. <https://doi.org/10.1038/s41598-020-68804-7>
- 635.** Sasaki T, Kuse Y, Nakamura S, Shimazawa M, Hara H. Progranulin deficiency exacerbates cardiac remodeling after myocardial infarction. *FASEB Biadv.* 2023;5:395-411.
- 636.** Singh S, Bruder A, Costa RM, et al. Vascular contractility relies on integrity of progranulin pathway: insights into mitochondrial function. *J Am Heart Assoc.* 2025;14(3):e037640. <https://doi.org/10.1161/JAHA.124.037640>
- 637.** Verdonschot JAJ, Ferreira JP, Pellicori P, et al. Proteomic mechanistic profile of patients with diabetes at risk of developing heart failure: insights from the HOMAGE trial. Heymans SRB; HOMAGE "Heart Omics in AGEing" consortium. *Cardiovasc Diabetol.* 2021;20(1):163. <https://doi.org/10.1186/s12933-021-01357-9>
- 638.** Klimczak-Tomanik D, Bouwens E, Schuurman AS, et al. Temporal patterns of macrophage- and neutrophil-related markers are associated with clinical outcome in heart failure patients. *ESC Heart Fail.* 2020;7:1190-1200.
- 639.** Patel VB, Basu R, Oudit GY. ACE2/Ang 1-7 axis: A critical regulator of epicardial adipose tissue inflammation and cardiac dysfunction in obesity. *Adipocyte.* 2016;5:306-311.
- 640.** Morimoto H, Mori J, Nakajima H, et al. Angiotensin 1-7 stimulates brown adipose tissue and reduces diet-induced obesity. *Am J Physiol Endocrinol Metab.* 2018;314:E131-E138.
- 641.** Cao X, Shi TT, Zhang CH, et al. ACE2 pathway regulates thermogenesis and energy metabolism. *Elife.* 2022;11:e72266. <https://doi.org/10.7554/elife.72266>
- 642.** Santos SH, Andrade JM, Fernandes LR, et al. Oral angiotensin-(1-7) prevented obesity and hepatic inflammation by inhibition of resistin/TLR4/MAPK/NF-kappaB in rats fed with high-fat diet. *Peptides.* 2013;46:47-52.
- 643.** Ma C, Shi T, Song L, Liu J, Yuan M. Angiotensin(1-7) attenuates visceral adipose tissue expansion and lipogenesis by suppression of endoplasmic reticulum stress via Mas receptor. *Nutr Metab (Lond).* 2022;19(1):82. <https://doi.org/10.1186/s12986-022-00716-x>
- 644.** Oliveira Andrade JM, Paraíso AF, Garcia ZM, et al. Cross talk between angiotensin-(1-7)/Mas axis and sirtuins in adipose tissue and metabolism of high-fat feed mice. *Peptides.* 2014;55:158-165.
- 645.** Kawabe Y, Mori J, Morimoto H, et al. ACE2 exerts anti-obesity effect via stimulating brown adipose tissue and induction of browning in white adipose tissue. *Am J Physiol Endocrinol Metab.* 2019;317(6):E1140-E1149.
- 646.** Nishida N, Sugimoto S, Miyagaki S, et al. Anti-inflammatory effect of Angiotensin 1-7 in white adipose tissue. *Adipocyte.* 2025;14(1):2449027. <https://doi.org/10.1080/21623945.2024.2449027>
- 647.** Moreira CCL, Lourenço FC, Mario EG, Santos RAS, Botion LM, Chaves VE. Long-term effects of angiotensin-(1-7) on lipid metabolism in the adipose tissue and liver. *Peptides.* 2017;92:16-22.
- 648.** Than A, Leow MK, Chen P. Control of adipogenesis by the autocrine interplays between angiotensin 1-7/Mas receptor and angiotensin II/AT1 receptor signaling pathways. *J Biol Chem.* 2013;288:15520-15531.
- 649.** Santos SH, Fernandes LR, Pereira CS, et al. Increased circulating angiotensin-(1-7) protects white adipose tissue against development of a proinflammatory state stimulated by a high-fat diet. *Regul Pept.* 2012;178:64-70.
- 650.** Shoemaker R, Tannock LR, Su W, et al. Adipocyte deficiency of ACE2 increases systolic blood pressures of obese female C57BL/6 mice. *Biol Sex Differ.* 2019;10(1):45. <https://doi.org/10.1186/s13293-019-0260-8>
- 651.** Schinzari F, Tesauro M, Veneziani A, Mores N, Di Daniele N, Cardillo C. Favorable vascular actions of angiotensin-(1-7) in human obesity. *Hypertension.* 2018;71:185-191.
- 652.** Zhong J, Basu R, Guo D, et al. Angiotensin-converting enzyme 2 suppresses pathological hypertrophy, myocardial fibrosis, and cardiac dysfunction. *Circulation.* 2010;122:717-728.
- 653.** Huentelman MJ, Grobe JL, Vazquez J, et al. Protection from angiotensin II-induced cardiac hypertrophy and fibrosis by systemic lentiviral delivery of ACE2 in rats. *Exp Physiol.* 2005;90:783-790.
- 654.** Gheblawi M, de Oliveira AA, Williams VR, et al. An advanced endothelial murine HFpEF model: eNOS is critical for angiotensin 1-7 rescue of the diabetic phenotype. *J Mol Cell Cardiol.* 2022;169:10-12.
- 655.** Patel VB, Zhong JC, Grant MB, Oudit GY. Role of the ACE2/angiotensin 1-7 axis of the renin-angiotensin system in heart failure. *Circ Res.* 2016;118:1313-1326.
- 656.** Patel VB, Bodiga S, Fan D, et al. Cardioprotective effects mediated by angiotensin II type 1 receptor blockade and enhancing angiotensin 1-7 in experimental heart failure in angiotensin-converting enzyme 2-null mice. *Hypertension.* 2012;59:1195-1203.
- 657.** Alghamri MS, Weir NM, Anstadt MP, Elased KM, Gurley SB, Morris M. Enhanced angiotensin II-induced cardiac and aortic remodeling in ACE2 knockout mice. *J Cardiovasc Pharmacol Ther.* 2013;18:138-151.
- 658.** Santos RA, Ferreira AJ, Nadu AP, et al. Expression of an angiotensin-(1-7)-producing fusion protein produces cardioprotective effects in rats. *Physiol Genomics.* 2004;17:292-299.
- 659.** Gupte M, Boustany-Kari CM, Bharadwaj K, et al. ACE2 is expressed in mouse adipocytes and regulated by a high-fat diet. *Am J Physiol Regul Integr Comp Physiol.* 2008;295:R781-R788.
- 660.** Fernandes FB, Fernandes AB, Febba ACS, et al. Association of Ang-(1-7) and des-Arg(9)BK as new biomarkers of obesity and cardiometabolic risk factors in adolescents. *Hypertens Res.* 2021;44:969-977.
- 661.** Emilsson V, Gudmundsson EF, Aspelund T, et al. Serum levels of ACE2 are higher in patients with obesity and diabetes. *Obes Sci Pract.* 2020;7:239-243.
- 662.** Patel VB, Mori J, McLean BA, et al. ACE2 deficiency worsens epicardial adipose tissue inflammation and cardiac dysfunction in response to diet-induced obesity. *Diabetes.* 2016;65:85-95.
- 663.** Hussain A, Tang O, Sun C, et al. Soluble angiotensin-converting enzyme 2, cardiac biomarkers, structure, and function, and cardiovascular events (from the Atherosclerosis Risk in Communities Study). *Am J Cardiol.* 2021;146:15-21.
- 664.** Yu J, Wu Y, Zhang Y, Zhang L, Ma Q, Luo X. Role of ACE2-Ang (1-7)-Mas receptor axis in heart failure with preserved ejection fraction with hypertension. *Zhong Nan Da Xue Xue Bao Yi Xue Ban.* 2018;43:738-746.
- 665.** Epelman S, Tang WH, Chen SY, Van Lente F, Francis GS, Sen S. Detection of soluble angiotensin-converting enzyme 2 in heart failure: insights into the endogenous counter-regulatory pathway of the renin-angiotensin-aldosterone system. *J Am Coll Cardiol.* 2008;52:750-754.
- 666.** Wang K, Basu R, Poglitsch M, Bakal JA, Oudit GY. Elevated angiotensin 1-7/angiotensin II ratio predicts favorable outcomes in patients With heart failure. *Circ Heart Fail.* 2020;13(7):e006939. <https://doi.org/10.1161/CIRCH-EARTFAILURE.120.006939>
- 667.** Basu R, Poglitsch M, Yogasundaram H, Thomas J, Rowe BH, Oudit GY. Roles of angiotensin peptides and recombinant human ACE2 in heart failure. *J Am Coll Cardiol.* 2017;69:805-819.

- 668.** Moisan A, Lee YK, Zhang JD, et al. White-to-brown metabolic conversion of human adipocytes by JAK inhibition. *Nat Cell Biol.* 2015;17:57-67.
- 669.** Xi Z, Shu L, Xiao L, et al. Macrophage NLRP3 inflamasome mediates the effects of sympathetic nerve on cardiac remodeling in obese rats. *Mol Cell Endocrinol.* 2025;596:112417. <https://doi.org/10.1016/j.mce.2024.112417>
- 670.** Guo X, Yan F, Li J, Zhang C, Su H, Bu P. SIRT3 ablation deteriorates obesity-related cardiac remodeling by modulating ROS-NF-kappaB-MCP-1 signaling pathway. *J Cardiovasc Pharmacol.* 2020;76:296-304.
- 671.** Dhingra S, Sharma AK, Arora RC, Slezak J, Singal PK. IL-10 attenuates TNF-alpha-induced NF kappaB pathway activation and cardiomyocyte apoptosis. *Cardiovasc Res.* 2009;82:59-66.
- 672.** Tuo QH, Xiong GZ, Zeng H, et al. Angiopoietin-1 protects myocardial endothelial cell function blunted by angiopoietin-2 and high glucose condition. *Acta Pharmacol Sin.* 2011;32:45-51.
- 673.** Dallabrida SM, Zurkowski D, Shih SC, et al. Adipose tissue growth and regression are regulated by angiopoietin-1. *Biochem Biophys Res Commun.* 2003;31:563-571.
- 674.** Kim YH, Pyo S. Interleukin-10 suppresses adipogenesis via Wnt5a signaling pathway in 3T3-L1 preadipocytes. *Biochem Biophys Res Commun.* 2019;509:877-885.
- 675.** Son Y, Cox JM, Stevenson JL, Cooper JA, Paton CM. Angiopoietin-1 protects 3T3-L1 preadipocytes from saturated fatty acid-induced cell death. *Nutr Res.* 2020;76:20-28.
- 676.** Nakata M, Yamamoto S, Okada T, et al. IL-10 gene transfer upregulates arcuate POMC and ameliorates hyperphagia, obesity and diabetes by substituting for leptin. *Int J Obes (Lond).* 2016;40:425-433.
- 677.** Calcaterra V, De Amici M, Klersy C, et al. Adiponectin, IL-10 and metabolic syndrome in obese children and adolescents. *Acta Biomed.* 2009;80:117-123.
- 678.** Pasarica M, Sereda OR, Redman LM, et al. Reduced adipose tissue oxygenation in human obesity: evidence for rarefaction, macrophage chemotaxis, and inflammation without an angiogenic response. *Diabetes.* 2009;58:718-725.
- 679.** Acosta JR, Tavira B, Douagi I, et al. Human-specific function of IL-10 in adipose tissue linked to insulin resistance. *J Clin Endocrinol Metab.* 2019;104:4552-4562.
- 680.** Wang Z, Cui M, Sun L, et al. Angiopoietin-1 protects H9c2 cells from H2O2-induced apoptosis through AKT signaling. *Biochem Biophys Res Commun.* 2007;359:685-690.
- 681.** Dallabrida SM, Ismail N, Oberle JR, Himes BE, Rupnick MA. Angiopoietin-1 promotes cardiac and skeletal myocyte survival through integrins. *Circ Res.* 2005;96:e8-e24.
- 682.** Jiang Y, Hong S, Zhu X, et al. IL-10 partly mediates the ability of MSC-derived extracellular vesicles to attenuate myocardial damage in experimental metabolic renovascular hypertension. *Front Immunol.* 2022;13:940093. <https://doi.org/10.3389/fimmu.2022.940093>
- 683.** Tuo QH, Zeng H, Stinnett A, et al. Critical role of angiopoietins/Tie-2 in hyperglycemic exacerbation of myocardial infarction and impaired angiogenesis. *Am J Physiol Heart Circ Physiol.* 2008;294:H2547-H2557.
- 684.** Verma SK, Krishnamurthy P, Barefield D, et al. Interleukin-10 treatment attenuates pressure overload-induced hypertrophic remodeling and improves heart function via signal transducers and activators of transcription 3-dependent inhibition of nuclear factor-kappaB. *Circulation.* 2012;126:418-429.
- 685.** Kondo H, Abe I, Gotoh K, et al. Interleukin 10 treatment ameliorates high-fat diet-induced inflammatory atrial remodeling and fibrillation. *Circ Arrhythm Electrophysiol.* 2018;11(5):e006040. <https://doi.org/10.1161/CIRCEP.117.006040>
- 686.** Singh S, Manson SR, Lee H, et al. Tubular overexpression of angiopoietin-1 attenuates renal fibrosis. *PLoS One.* 2016;11(7):e0158908. <https://doi.org/10.1371/journal.pone.0158908>
- 687.** Dessapt-Baradez C, Woolf AS, White KE, et al. Targeted glomerular angiopoietin-1 therapy for early diabetic kidney disease. *J Am Soc Nephrol.* 2014;25:33-42.
- 688.** Mansour SG, Bhatraju PK, Coca SG, et al. Angiopoietins as prognostic markers for future kidney disease and heart failure events after acute kidney injury. *J Am Soc Nephrol.* 2022;33:613-627.
- 689.** Kosar F, Aksoy Y, Ozguntekin G, Ozerol I, Varol E. Relationship between cytokines and tumour markers in patients with chronic heart failure. *Eur J Heart Fail.* 2006;8:270-274.
- 690.** Aukrust P, Ueland T, Lien E, et al. Cytokine network in congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol.* 1999;83:376-382.
- 691.** Lopnow H, Werdan K, Werner C. The enhanced plasma levels of soluble tumor necrosis factor receptors (sTNF-R1; sTNF-R2) and interleukin-10 (IL-10) in patients suffering from chronic heart failure are reversed in patients treated with beta-adrenoceptor antagonist. *Auton Autacoid Pharmacol.* 2002;22:83-92.
- 692.** Yamaoka M, Yamaguchi S, Okuyama M, Tomoike H. Anti-inflammatory cytokine profile in human heart failure: behavior of interleukin-10 in association with tumor necrosis factor-alpha. *Jpn Circ J.* 1999;63:951-956.
- 693.** Fang L, Ellims AH, Beale AL, Taylor AJ, Murphy A, Dart AM. Systemic inflammation is associated with myocardial fibrosis, diastolic dysfunction, and cardiac hypertrophy in patients with hypertrophic cardiomyopathy. *Am J Transl Res.* 2017;9:5063-5073.
- 694.** Kosmala W, Derzhko R, Przewlocka-Kosmala M, Orda A, Mazurek W. Plasma levels of TNF-alpha, IL-6, and IL-10 and their relationship with left ventricular diastolic function in patients with stable angina pectoris and preserved left ventricular systolic performance. *Coron Artery Dis.* 2008;19:375-382.
- 695.** Vistnes M, Waehre A, Nygård S, et al. Circulating cytokine levels in mice with heart failure are etiology dependent. *J Appl Physiol (1985).* 2010;108:1357-1364.
- 696.** Hamid T, Gu Y, Ortines RV, et al. Divergent tumor necrosis factor receptor-related remodeling responses in heart failure: role of nuclear factor-kappaB and inflammatory activation. *Circulation.* 2009;119:1386-1397.
- 697.** Hou L, Xie M, Cao L, et al. Browning of pig white preadipocytes by co-overexpressing pig PGC-1alpha and mice UCP1. *Cell Physiol Biochem.* 2018;48:556-568.
- 698.** Tseng YH, Kokkotou E, Schulz TJ, et al. New role of bone morphogenetic protein 7 in brown adipogenesis and energy expenditure. *Nature.* 2008;454:1000-1004.
- 699.** Um JH, Park SY, Hur JH, et al. Bone morphogenic protein 9 is a novel thermogenic hepatokine secreted in response to cold exposure. *Metabolism.* 2022;129:155139. <https://doi.org/10.1016/j.metabol.2022.155139>
- 700.** Casana E, Jimenez V, Jambrina C, et al. AAV-mediated BMP7 gene therapy counteracts insulin resistance and obesity. *Mol Ther Methods Clin Dev.* 2022;25:190-204.
- 701.** Kuo MM, Kim S, Tseng CY, Jeon YH, Choe S, Lee DK. BMP-9 as a potent brown adipogenic inducer with anti-obesity capacity. *Biomaterials.* 2014;35:3172-3179.
- 702.** Liu R, Hu W, Li X, et al. Association of circulating BMP9 with coronary heart disease and hypertension in Chinese populations. *BMC Cardiovasc Disord.* 2019;19(1):131. <https://doi.org/10.1186/s12872-019-1095-2>
- 703.** Xu X, Li X, Yang G, et al. Circulating bone morphogenetic protein-9 in relation to metabolic syndrome and insulin resistance. *Sci Rep.* 2017;7(1):17529. <https://doi.org/10.1038/s41598-017-17807-y>
- 704.** Aluganti Narasimhulu C, Singla DK. The role of bone morphogenetic protein 7 (BMP-7) in inflammation in heart diseases. *Cells.* 2020;9(2):280. <https://doi.org/10.3390/cells9020280>
- 705.** Salido-Medina AB, Gil A, Expósito V, et al. BMP7-based peptide agonists of BMPR1A protect the left ventricle against pathological remodeling induced by pressure overload. *Biomed Pharmacother.* 2022;149:112910. <https://doi.org/10.1016/j.bioph.2022.112910>
- 706.** Morine KJ, Qiao X, York S, et al. Bone morphogenetic protein 9 reduces cardiac fibrosis and improves cardiac function in heart failure. *Circulation.* 2018;138:513-526.
- 707.** Tate M, Perera N, Prakoso D, et al. Bone morphogenetic protein 7 gene delivery improves cardiac structure and function in a murine model of diabetic cardiomyopathy. *Front Pharmacol.* 2021;12:719290. <https://doi.org/10.3389/fphar.2021.719290>
- 708.** Townsend KL, Suzuki R, Huang TL, et al. Bone morphogenetic protein 7 (BMP7) reverses obesity and regulates appetite through a central mTOR pathway. *FASEB J.* 2012;26:2187-2196.
- 709.** Long L, Ormiston ML, Yang X, Southwood M, Graf S, Machado RD. Selective

- enhancement of endothelial BMPR-II with BMP9 reverses pulmonary arterial hypertension.** *Nat Med.* 2015;21:777-785.
- 710.** Geng Y, Dong Y, Yu M, et al. Follistatin-like 1 (Fstl1) is bone morphogenetic protein (BMP) 4 signaling antagonist in controlling mouse lung development. *Proc Natl Acad Sci U S A.* 2011;108:7058-7063.
- 711.** Fang D, Shi X, Jia X, et al. Ups and downs: The PPARgamma/p-PPARgamma seesaw of follistatin-like 1 and integrin receptor signaling in adipogenesis. *Mol Metab.* 2022;55:101400. <https://doi.org/10.1016/j.molmet.2021.101400>
- 712.** Fang D, Shi X, Lu T, Ruan H, Gao Y. The glycoprotein follistatin-like 1 promotes brown adipose thermogenesis. *Metabolism.* 2019;98:16-26.
- 713.** El-Armouche A, Ouchi N, Tanaka K. Follistatin-like 1 in chronic systolic heart failure: a marker of left ventricular remodeling. *Circ Heart Fail.* 2011;4:621-627.
- 714.** Tanaka K, Valero-Muñoz M, Wilson RM, et al. Follistatin like 1 regulates hypertrophy in heart failure with preserved ejection fraction. *JACC Basic Transl Sci.* 2016;1:207-221.
- 715.** Fan N, Sun H, Wang Y, et al. Follistatin-like 1: a potential mediator of inflammation in obesity. *Mediators Inflamm.* 2013;2013:752519. <https://doi.org/10.1155/2013/752519>
- 716.** Shimano M, Ouchi N, Nakamura K, et al. Cardiac myocyte follistatin-like 1 functions to attenuate hypertrophy following pressure overload. *Proc Natl Acad Sci U S A.* 2011;108:E899-E906.
- 717.** Zhao Y, Sun J, Zhang W, et al. Follistatin-like 1 protects against doxorubicin-induced cardiomyopathy through upregulation of Nrf2. *Oxid Med Cell Longev.* 2020;2020:3598715. <https://doi.org/10.1155/2020/3598715>
- 718.** Zhang Y, Chua S Jr. Leptin function and regulation. *Compr Physiol.* 2017;8:351-369.
- 719.** Jensen MD, Hensrud D, O'Brien PC, Nielsen S. Collection and interpretation of plasma leptin concentration data in humans. *Obes Res.* 1999;7:241-245.
- 720.** Gruzdeva O, Uchrasova E, Dyleva Y, et al. Relationships between epicardial adipose tissue thickness and adipofibrokin indicator profiles post-myocardial infarction. *Cardiovasc Diabetol.* 2018;17(1):40. <https://doi.org/10.1186/s12933-018-0679-y>
- 721.** Mark AL, Correia ML, Rahmouni K, Haynes WG. Selective leptin resistance: a new concept in leptin physiology with cardiovascular implications. *J Hypertens.* 2002;20:1245-1250.
- 722.** Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity, kidney dysfunction and hypertension: mechanistic links. *Nat Rev Nephrol.* 2019;15:367-385.
- 723.** Hall JE, Mouton AJ, da Silva AA, et al. Obesity, kidney dysfunction, and inflammation: interactions in hypertension. *Cardiovasc Res.* 2021;117:1859-1876.
- 724.** Faulkner JL, Bruder-Nascimento T, Belin de Chantemèle EJ. The regulation of aldosterone secretion by leptin: implications in obesity-related cardiovascular disease. *Curr Opin Nephrol Hypertens.* 2018;27:63-69.
- 725.** Xie D, Bollag WB. Obesity, hypertension and aldosterone: is leptin the link? *J Endocrinol.* 2016;230:F7-F11.
- 726.** Bettowski J. Leptin and the regulation of renal sodium handling and renal Na<sup>+</sup>-transporting ATPases: role in the pathogenesis of arterial hypertension. *Curr Cardiol Rev.* 2010;6:31-40. <https://doi.org/10.2174/157340310790231644>
- 727.** Flores Gomez D, Bekkerling S, Ter Horst R, et al. The effect of leptin on trained innate immunity and on systemic inflammation in subjects with obesity. *J Leukoc Biol.* 2024;115:374-384.
- 728.** Polyakova EA, Mikhaylov EN, Galagudza MM, Shlyakhto EV. Hyperleptinemia results in systemic inflammation and the exacerbation of ischemia-reperfusion myocardial injury. *Heliyon.* 2021;7(1):e08491. <https://doi.org/10.1101/e08491>
- 729.** Abe Y, Ono K, Kawamura T, et al. Leptin induces elongation of cardiac myocytes and causes eccentric left ventricular dilatation with compensation. *Am J Physiol Heart Circ Physiol.* 2007;292:H2387-H2396.
- 730.** Rajapurohitam V, Gan XT, Kirshenbaum LA, Karmazyn M. The obesity-associated peptide leptin induces hypertrophy in neonatal rat ventricular myocytes. *Circ Res.* 2003;93:277-279.
- 731.** Perego L, Pizzocri P, Corradi D, et al. Circulating leptin correlates with left ventricular mass in morbid (grade III) obesity before and after weight loss induced by bariatric surgery: a potential role for leptin in mediating human left ventricular hypertrophy. *J Clin Endocrinol Metab.* 2005;90:4087-4093.
- 732.** Na T, Dai DZ, Tang XY, Dai Y. Upregulation of leptin pathway correlates with abnormal expression of SERCA2a, phospholamban and the endothelin pathway in heart failure and reversal by CPU86017. *Naunyn Schmiedebergs Arch Pharmacol.* 2007;375:39-49.
- 733.** Gogiraju R, Hubert A, Fahrer J, et al. Endothelial leptin receptor deletion promotes cardiac autophagy and angiogenesis following pressure overload by suppressing Akt/mTOR signaling. *Circ Heart Fail.* 2019;12(1):e005622. <https://doi.org/10.1161/CIRCHEARTFAILURE.118.005565>
- 734.** Zibadi S, Cordova F, Slack EH, Watson RR, Larson DF. Leptin's regulation of obesity-induced cardiac extracellular matrix remodeling. *Cardiovasc Toxicol.* 2011;11:325-333.
- 735.** Mellott E, Faulkner JL. Mechanisms of leptin-induced endothelial dysfunction. *Curr Opin Nephrol Hypertens.* 2023;32:118-123.
- 736.** Chen H, Liu L, Li M, Zhu D, Tian G. Epicardial adipose tissue-derived leptin promotes myocardial injury in metabolic syndrome rats through PKC/NADPH Oxidase/ROS pathway. *J Am Heart Assoc.* 2023;12(15):e029415. <https://doi.org/10.1161/JAHA.123.029415>
- 737.** Lieb W, Sullivan LM, Harris TB, et al. Plasma leptin levels and incidence of heart failure, cardiovascular disease, and total mortality in elderly individuals. *Diabetes Care.* 2009;32:612-616. <https://doi.org/10.2337/dc08-1596>
- 738.** Fontes-Carvalho R, Pimenta J, Bettencourt P, Leite-Moreira A, Azevedo A. Association between plasma leptin and adiponectin levels and diastolic function in the general population. *Expert Opin Ther Targets.* 2015;19:1283-1291.
- 739.** Abd El-Aziz TA, Mohamed RH, Mohamed RH, Pasha HF. Leptin, leptin gene and leptin receptor gene polymorphism in heart failure with preserved ejection fraction. *Heart Vessels.* 2012;27:271-279.
- 740.** Wannamethee SG, Shaper AG, Whincup PH, Lennon L, Sattar N. Obesity and risk of incident heart failure in older men with and without pre-existing coronary heart disease: does leptin have a role? *J Am Coll Cardiol.* 2011;58:1870-1877.
- 741.** Wojciechowska C, Jachec W, Romuk E, Nowalany-Kozlinska E, Tomasik A, Siemińska L. The effect of BMI, serum leptin, and adiponectin levels on prognosis in patients with non-ischaemic dilated cardiomyopathy. *Endokrynol Pol.* 2017;68:26-34.
- 742.** Bobbert P, Jenke A, Bobbert T, et al. High leptin and resistin expression in chronic heart failure: adverse outcome in patients with dilated and inflammatory cardiomyopathy. *Eur J Heart Fail.* 2012;14:1265-1275.
- 743.** Polhemus DJ, Trivedi RK, Gao J, et al. Renal sympathetic denervation protects the failing heart via inhibition of neprilysin activity in the kidney. *J Am Coll Cardiol.* 2017;70:2139-2153.
- 744.** Liu Y, Zhong C, Si J, Chen S, Kang L, Xu B. The impact of sacubitril/valsartan on cardiac fibrosis early after myocardial infarction in hypertensive rats. *J Hypertens.* 2022;40:1822-1830.
- 745.** Burke RM, Lighthouse JK, Mickelsen DM, Small EM. Sacubitril/valsartan decreases cardiac fibrosis in left ventricle pressure overload by restoring PKG signaling in cardiac fibroblasts. *Circ Heart Fail.* 2019;12(4):e005565. <https://doi.org/10.1161/CIRCHEARTFAILURE.118.005565>
- 746.** Ong WK, Tan CS, Chan KL, et al. Identification of specific cell-surface markers of adipose-derived stem cells from subcutaneous and visceral fat depots. *Stem Cell Rep.* 2014;2:171-179.
- 747.** Jing F, Mogi M, Horiuchi M. Role of renin-angiotensin-aldosterone system in adipose tissue dysfunction. *Mol Cell Endocrinol.* 2013;378:23-28.
- 748.** Kim J, Han D, Byun SH, et al. Neprilysin facilitates adipogenesis through potentiation of the phosphatidylinositol 3-kinase (PI3K) signaling pathway. *Mol Cell Biochem.* 2017;430:1-9.
- 749.** Lee M, Sorn SR, Lee Y, Kang I. Salt induces adipogenesis/lipogenesis and inflammatory adipocytokines secretion in adipocytes. *Int J Mol Sci.* 2019;20(1):160. <https://doi.org/10.3390/ijms20010160>
- 750.** Caprio M, Antelmi A, Chetrite G, et al. Anti-adipogenic effects of the mineralocorticoid receptor antagonist dospirenone: potential implications for the treatment of metabolic syndrome. *Endocrinology.* 2011;152:113-125.
- 751.** Hegyi B, Mira Hernandez J, Ko CY, et al. Diabetes and excess aldosterone promote heart failure with preserved ejection fraction. *J Am*

- Heart Assoc.* 2022;11(23):e027164. <https://doi.org/10.1161/JAHA.122.027164>
- 752.** Irie D, Kawahito H, Wakana N, et al. Transplantation of periaortic adipose tissue from angiotensin receptor blocker-treated mice markedly ameliorates atherosclerosis development in apoE<sup>-/-</sup> mice. *J Renin Angiotensin Aldosterone Syst.* 2015;16:67-78.
- 753.** Hayashi M, Takeshita K, Uchida Y, et al. Angiotensin II receptor blocker ameliorates stress-induced adipose tissue inflammation and insulin resistance. *PLoS One.* 2014;9(12):e116163. <https://doi.org/10.1371/journal.pone.0116163>
- 754.** Goossens GH, Moors CC, van der Zijl NJ, et al. Valsartan improves adipose tissue function in humans with impaired glucose metabolism: a randomized placebo-controlled double-blind trial. *PLoS One.* 2012;7(6):e39930. <https://doi.org/10.1371/journal.pone.0039930>
- 755.** Blumensatt M, Fahlbusch P, Hilgers R, et al. Secretory products from epicardial adipose tissue from patients with type 2 diabetes impair mitochondrial beta-oxidation in cardiomyocytes via activation of the cardiac renin-angiotensin system and induction of miR-208a. *Basic Res Cardiol.* 2017;112(1):2. <https://doi.org/10.1007/s00395-016-0591-0>
- 756.** Carroll WX, Kalupahana NS, Booker SL, et al. Angiotensinogen gene silencing reduces markers of lipid accumulation and inflammation in cultured adipocytes. *Front Endocrinol (Lausanne).* 2013;4:10. <https://doi.org/10.3389/fendo.2013.00010>
- 757.** Nguyen Dinh Cat A, Antunes TT, Callera GE, et al. Adipocyte-specific mineralocorticoid receptor overexpression in mice is associated with metabolic syndrome and vascular dysfunction: role of redox-sensitive PKG-1 and Rho kinase. *Diabetes.* 2016;65:2392-2403.
- 758.** Changchien EM, Ahmed S, Betti F, et al. B-type natriuretic peptide increases after gastric bypass surgery and correlates with weight loss. *Surg Endosc.* 2011;25:2338-2343.
- 759.** Matsumoto S, Nakazawa G, Ohno Y, et al. Efficacy of exogenous atrial peptide in patients with heart failure with preserved ejection fraction: deficiency of atrial natriuretic peptide and replacement therapy. *ESC Heart Fail.* 2020;7:4172-4181.
- 760.** Miura SI, Suematsu Y, Matsuo Y, et al. The angiotensin II type 1 receptor-neprilisin inhibitor LCZ696 blocked aldosterone synthesis in a human adrenocortical cell line. *Hypertens Res.* 2016;39:758-763.
- 761.** Alex L, Russo I, Holoborodko V, Frangogiannis NG. Characterization of a mouse model of obesity-related fibrotic cardiomyopathy that recapitulates features of human heart failure with preserved ejection fraction. *Am J Physiol Heart Circ Physiol.* 2018;315:H934-H949.
- 762.** Packer M. Do sodium-glucose co-transporter-2 inhibitors prevent heart failure with a preserved ejection fraction by counterbalancing the effects of leptin? A novel hypothesis. *Diabetes Obes Metab.* 2018;20:1361-1366.
- 763.** Tsutsumi C, Okuno M, Tannous L, et al. Retinoids and retinoid-binding protein expression in rat adipocytes. *J Biol Chem.* 1992;267:1805-1810.
- 764.** Lamounier-Zepter V, Look C, Alvarez J, et al. Adipocyte fatty acid-binding protein suppresses cardiomyocyte contraction: a new link between obesity and heart disease. *Circ Res.* 2009;105:326-334.
- 765.** Baxa CA, Sha RS, Buelt MK, et al. Human adipocyte lipid-binding protein: purification of the protein and cloning of its complementary DNA. *Biochemistry.* 1989;28:8683-8690.
- 766.** Yang Q, Graham TE, Mody N, et al. Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. *Nature.* 2005;436:356-362.
- 767.** Kilicarslan M, de Weijer BA, Simonyte Sjödin K, et al. RBP4 increases lipolysis in human adipocytes and is associated with increased lipolysis and hepatic insulin resistance in obese women. *FASEB J.* 2020;34:6099-6110.
- 768.** Inouye KE, Prentice KJ, Lee A, et al. Endothelial-derived FABP4 constitutes the majority of basal circulating hormone and regulates lipolysis-driven insulin secretion. *JCI Insight.* 2023;8(14):e164642. <https://doi.org/10.1172/jci.insight.164642>
- 769.** Ertunc ME, Sikkeland J, Fenaroli F, et al. Secretion of fatty acid binding protein aP2 from adipocytes through a nonclassical pathway in response to adipocyte lipase activity. *J Lipid Res.* 2015;56:423-434.
- 770.** Yan QW, Yang Q, Mody N, et al. The adipokine lipocalin 2 is regulated by obesity and promotes insulin resistance. *Diabetes.* 2007;56:2533-2540.
- 771.** Guo H, Foncea R, O'Byrne SM, et al. Lipocalin 2, a regulator of retinoid homeostasis and retinoid-mediated thermogenic activation in adipose tissue. *J Biol Chem.* 2016;291:11216-11229.
- 772.** Zhang Y, Guo H, Deis JA, et al. Lipocalin 2 regulates brown fat activation via a nonadrenergic activation mechanism. *J Biol Chem.* 2014;289:22063-22077.
- 773.** Sandoval-Bórquez A, Carrión P, Hernández MP, et al. Adipose tissue dysfunction and the role of adipocyte-derived extracellular vesicles in obesity and metabolic syndrome. *J Endocr Soc.* 2024;8(8):bvae126. <https://doi.org/10.1210/jendso/bvae126>
- 774.** Scheja L, Makowski L, Uysal KT, et al. Altered insulin secretion associated with reduced lipolytic efficiency in aP2<sup>-/-</sup> mice. *Diabetes.* 1999;48:1987-1994.
- 775.** Nakamura R, Okura T, Fujioka Y, et al. Serum fatty acid-binding protein 4 (FABP4) concentration is associated with insulin resistance in peripheral tissues, a clinical study. *PLoS One.* 2017;12(6):e0179737. <https://doi.org/10.1371/journal.pone.0179737>
- 776.** Norseen J, Hosooka T, Hammarstedt A, et al. Retinol-binding protein 4 inhibits insulin signalling in adipocytes by inducing proinflammatory cytokines in macrophages through a c-Jun N-terminal kinase- and toll-like receptor 4-dependent and retinol-independent mechanism. *Mol Cell Biol.* 2012;32:2010-2019.
- 777.** Furuhashi M, Fucho R, Görgün CZ, et al. Adipocyte/macrophage fatty acid-binding proteins contribute to metabolic deterioration through actions in both macrophages and adipocytes in mice. *J Clin Invest.* 2008;118:2640-2650.
- 778.** Javaid HMA, Ko E, Joo EJ, et al. TNFalpha-induced NLRP3 inflammasome mediates adipocyte dysfunction and activates macrophages through adipocyte-derived lipocalin 2. *Metabolism.* 2023;142:155527. <https://doi.org/10.1016/j.metabol.2023.155527>
- 779.** Lee SA, Yuen JJ, Jiang H, Kahn BB, Blaner WS. Adipocyte-specific overexpression of retinol-binding protein 4 causes hepatic steatosis in mice. *Hepatology.* 2016;64:1534-1546.
- 780.** Chen MT, Huang JS, Gao DD, Li YX, Wang HY. Combined treatment with FABP4 inhibitor ameliorates rosiglitazone-induced liver steatosis in obese diabetic db/db mice. *Basic Clin Pharmacol Toxicol.* 2021;129:173-182.
- 781.** Chella Krishnan K, Sabir S, Shum M, et al. Sex-specific metabolic functions of adipose Lipocalin-2. *Mol Metab.* 2019;30:30-47.
- 782.** Moraes-Vieira PM, Yore MM, Sontheimer-Phelps A, et al. Retinol binding protein 4 primes the NLRP3 inflammasome by signaling through Toll-like receptors 2 and 4. *Proc Natl Acad Sci U S A.* 2020;117:31309-31318.
- 783.** Wang Y, Lam KS, Kraegen EW, et al. Lipocalin-2 is an inflammatory marker closely associated with obesity, insulin resistance, and hyperglycemia in humans. *Clin Chem.* 2007;53:34-41.
- 784.** Szychowski KA, Skóra B, Kryshchyshyn-Dylevych A, et al. 4-thiazolidinone-based derivatives do not affect differentiation of mouse embryo fibroblasts (3T3-L1 cell line) into adipocytes. *Chem Biol Interact.* 2021;345:109538. <https://doi.org/10.1016/j.cbi.2021.109538>
- 785.** Xu A, Wang Y, Xu JY, et al. Adipocyte fatty acid-binding protein is a plasma biomarker closely associated with obesity and metabolic syndrome. *Clin Chem.* 2006;52:405-413.
- 786.** Yoon MY, Sung JM, Song CS, et al. Enhanced A-FABP expression in visceral fat: potential contributor to the progression of NASH. *Clin Mol Heppatol.* 2012;18:279-286.
- 787.** Won JC, Park CY, Oh SW, Park SW. Increased plasma levels of retinol-binding protein 4 with visceral obesity is associated with cardiovascular risk factors. *J Diabetes Investig.* 2012;3:457-463.
- 788.** Klöting N, Graham TE, Berndt J, et al. Serum retinol-binding protein is more highly expressed in visceral than in subcutaneous adipose tissue and is a marker of intra-abdominal fat mass. *Cell Metab.* 2007;6:79-87.
- 789.** Lee JW, Lee HR, Shim JY, Im JA, Lee DC. Abdominal visceral fat reduction is associated with favorable changes of serum retinol binding protein-4 in nondiabetic subjects. *Endocr J.* 2008;55:811-818.
- 790.** Luo Y, Ma X, Pan X, et al. Serum lipocalin-2 levels are positively associated with not only total body fat but also visceral fat area in Chinese men. *Medicine (Baltimore).* 2016;95(30):e4039.

- <https://doi.org/10.1097/MD.0000000000000004039>
- 791.** Milner KL, van der Poorten D, Xu A, et al. Adipocyte fatty acid binding protein levels relate to inflammation and fibrosis in nonalcoholic fatty liver disease. *Hepatology*. 2009;49:1926-1934.
- 792.** Catalán V, Gómez-Ambrosi J, Rodríguez A, et al. Increased adipose tissue expression of lipocalin-2 in obesity is related to inflammation and matrix metalloproteinase-2 and metalloproteinase-9 activities in humans. *J Mol Med (Berl)*. 2009;87:803-813.
- 793.** Couselo-Seijas M, Vázquez-Abuín X, Gómez-Lázaro M, et al. FABP4 enhances lipidic and fibrotic cardiac structural and Ca(2+) dynamic changes. *Circ Arrhythm Electrophysiol*. 2024;17(9):e012683. <https://doi.org/10.1161/CIRCEP.123.012683>
- 794.** Lamounier-Zepter V, Look C, Alvarez J, et al. Adipocyte fatty acid-binding protein suppresses cardiomyocyte contraction: a new link between obesity and heart disease. *Circ Res*. 2009;105:326-334.
- 795.** Marques FZ, Prestes PR, Byars SG, et al. Experimental and human evidence for lipocalin-2 (neutrophil gelatinase-associated lipocalin [NGAL]) in the development of cardiac hypertrophy and heart failure. *J Am Heart Assoc*. 2017;6(6):e005971. <https://doi.org/10.1161/JAHA.117.005971>
- 796.** Gao W, Wang H, Zhang L, et al. Retinol-binding protein 4 induces cardiomyocyte hypertrophy by activating TLR4/MyD88 pathway. *Endocrinology*. 2016;157:2282-2293.
- 797.** Zhang KZ, Shen XY, Wang M, et al. Retinol-binding protein 4 promotes cardiac injury after myocardial infarction via inducing cardiomyocyte pyroptosis through an interaction with NLRP3. *J Am Heart Assoc*. 2021;10(22):e022011. <https://doi.org/10.1161/JAHA.121.022011>
- 798.** Du L, Wang X, Guo Y, et al. Altered lipid metabolism promoting cardiac fibrosis is mediated by CD34(+) cell-derived FABP4(+) fibroblasts. *Exp Mol Med*. 2024;56:1869-1886.
- 799.** Sun F, Chen G, Yang Y, Lei M. Fatty acid-binding protein 4 silencing protects against lipopolysaccharide-induced cardiomyocyte hypertrophy and apoptosis by inhibiting the Toll-like receptor 4-nuclear factor-kappaB pathway. *J Int Med Res*. 2021;49(3):300060521998233. <https://doi.org/10.1177/0300060521998233>
- 800.** Zhang J, Qiao C, Chang L, et al. Cardiomyocyte overexpression of FABP4 aggravates pressure overload-induced heart hypertrophy. *PLoS One*. 2016;11(6):e0157372. <https://doi.org/10.1371/journal.pone.0157372>
- 801.** Kraus BJ, Sartoretti JL, Polak P, et al. Novel role for retinol-binding protein 4 in the regulation of blood pressure. *FASEB J*. 2015;29:3133-3140.
- 802.** Girona J, Rosales R, Plana N, Saavedra P, Masana L, Vallvé JC. FABP4 induces vascular smooth muscle cell proliferation and migration through a MAPK-dependent pathway. *PLoS One*. 2013;8(11):e81914. <https://doi.org/10.1371/journal.pone.0081914>
- 803.** Aragonès G, Saavedra P, Heras M, Cabré A, Girona J, Masana L. Fatty acid-binding protein 4 impairs the insulin-dependent nitric oxide pathway in vascular endothelial cells. *Cardiovasc Diabetol*. 2012;11:72. <https://doi.org/10.1186/1475-2840-11-72>
- 804.** Chen MC, Hsu BG, Lee CJ, Yang CF, Wang JH. High serum adipocyte fatty acid binding protein level as a potential biomarker of aortic arterial stiffness in hypertensive patients with metabolic syndrome. *Clin Chim Acta*. 2017;473:166-172.
- 805.** Chondrou A, Nigdelis MP, Armeni E, et al. Retinol-binding protein 4 is associated with arterial stiffness in early postmenopausal women. *Menopause*. 2020;27:906-912.
- 806.** Farjo KM, Farjo RA, Halsey S, Moiseyev G, Ma JX. Retinol-binding protein 4 induces inflammation in human endothelial cells by an NADPH oxidase- and nuclear factor kappa B-dependent and retinol-independent mechanism. *Mol Cell Biol*. 2012;32:5103-5115.
- 807.** Park CG, Choi KM. Lipocalin-2, A-FABP and inflammatory markers in relation to flow-mediated vasodilation in patients with essential hypertension. *Clin Exp Hypertens*. 2014;36:478-483.
- 808.** Fuseya T, Furuhashi M, Yuda S, et al. Elevation of circulating fatty acid-binding protein 4 is independently associated with left ventricular diastolic dysfunction in a general population. *Cardiovasc Diabetol*. 2014;13:126. <https://doi.org/10.1186/s12933-014-0126-7>
- 809.** Porcar-Almela M, Codoñer-Franch P, Tuzón M, Navarro-Solera M, Carrasco-Luna J, Ferrando J. Left ventricular diastolic function and cardiometabolic factors in obese normotensive children. *Nutr Metab Cardiovasc Dis*. 2015;25:108-115.
- 810.** von Jeinsen B, Short MI, Xanthakis V, Carneiro H, Cheng S, Mitchell GF, Vasan RS. Association of circulating adipokines with echocardiographic measures of cardiac structure and function in a community-based cohort. *J Am Heart Assoc*. 2018;7(13):e008997. <https://doi.org/10.1161/JAHA.118.008997>
- 811.** Engeli S, Utz W, Haufe S, Lamounier-Zepter V, et al. Fatty acid binding protein 4 predicts left ventricular mass and longitudinal function in overweight and obese women. *Heart*. 2013;99:944-948.
- 812.** Harada T, Sunaga H, Sorimachi H, et al. Pathophysiological role of fatty acid-binding protein 4 in Asian patients with heart failure and preserved ejection fraction. *ESC Heart Fail*. 2020;7:4256-4266.
- 813.** Li XZ, Zhang KZ, Yan JJ, et al. Serum retinol-binding protein 4 as a predictor of cardiovascular events in elderly patients with chronic heart failure. *ESC Heart Fail*. 2020;7:542-550.
- 814.** Liu M, Zhou M, Bao Y, et al. Circulating adipocyte fatty acid-binding protein levels are independently associated with heart failure. *Clin Sci (Lond)*. 2013;124:115-122.
- 815.** Brankovic M, Akkerhuis KM, Mouthaan H, et al. Cardio-metabolic biomarkers and their temporal patterns predict poor outcome in chronic heart failure (Bio-SHIFT Study). *J Clin Endocrinol Metab*. 2018;103:3954-3964.
- 816.** Pronschinske KB, Qiu S, Wu C, et al. Neutrophil gelatinase-associated lipocalin and cystatin C for the prediction of clinical events in patients with advanced heart failure and after ventricular assist device placement. *J Heart Lung Transplant*. 2014;33:1215-1222.
- 817.** Zhou X, Zhang J, Lv W, et al. The pleiotropic roles of adipocyte secretome in remodeling breast cancer. *J Exp Clin Cancer Res*. 2022;41(1):203. <https://doi.org/10.1186/s13046-022-02408-z>
- 818.** Sun WY, Bai B, Luo C, et al. Lipocalin-2 derived from adipose tissue mediates aldosterone-induced renal injury. *JCI Insight*. 2018;3(17):e120196. <https://doi.org/10.1172/jci.insight.120196>
- 819.** Tarjus A, Martínez-Martínez E, Amador C, et al. Neutrophil gelatinase-associated lipocalin, a novel mineralocorticoid biotarget, mediates vascular profibrotic effects of mineralocorticoids. *Hypertension*. 2015;66:158-166.
- 820.** Martínez-Martínez E, Buonafine M, Boukhalfa I, et al. Aldosterone target NGAL (neutrophil gelatinase-associated lipocalin) is involved in cardiac remodeling after myocardial infarction through NFκappaB pathway. *Hypertension*. 2017;70:1148-1156.
- 821.** Chavarria NI, Kato TS, Khan R, et al. Increased levels of retinol binding protein 4 in patients with advanced heart failure correct after hemodynamic improvement through ventricular assist device placement. *Circ J*. 2012;76:2148-2152.
- 822.** Tsantilas P, Lao S, Wu Z, et al. Chitinase 3 like 1 is a regulator of smooth muscle cell physiology and atherosclerotic lesion stability. *Cardiovasc Res*. 2021;117:2767-2780.
- 823.** Kyrgios I, Galli-Tsinopoulou A, Stylianou C, et al. Elevated circulating levels of the serum acute-phase protein YKL-40 (chitinase 3-like protein 1) are a marker of obesity and insulin resistance in prepubertal children. *Metabolism*. 2012;61:562-568.
- 824.** Iwata T, Kuwajima M, Sukeno A, et al. YKL-40 secreted from adipose tissue inhibits degradation of type I collagen. *Biochem Biophys Res Commun*. 2009;388:511-516.
- 825.** Wang Q, Shen H, Min J, et al. YKL-40 is highly expressed in the epicardial adipose tissue of patients with atrial fibrillation and associated with atrial fibrosis. *J Transl Med*. 2018;16(1):229. <https://doi.org/10.1186/s12967-018-1598-0>
- 826.** Hempen M, Kopp HP, Elenicky M, et al. YKL-40 is elevated in morbidly obese patients and declines after weight loss. *Obes Surg*. 2009;19:1557-1563.
- 827.** Stephan JK, Knerr T, Gu Z, et al. Neutrophil-secreted CHI3L1 exacerbates cardiac dysfunction and inflammation after myocardial infarction. *FASEB J*. 2025;39(5):e70422. <https://doi.org/10.1096/fj.202401654R>
- 828.** Huusonen C, Hämäläinen M, Kivikangas N, Paavonen T, Molanen E, Mennander AA. Early reversibility of histological changes after experimental acute cardiac volume-overload. *Am J Cardiovasc Dis*. 2022;12:205-211.

- 829.** Henry A, Gordillo-Marañón M, Finan C, et al. Therapeutic targets for heart failure identified using proteomics and Mendelian randomization. *Circulation*. 2022;145:1205-1217.
- 830.** Tang Y, Du M, Qian W, et al. The diagnostic value of serum YKL-40 for myocardial involvement in idiopathic inflammatory myopathy. *Clin Chim Acta*. 2022;537:167-172.
- 831.** Bouwens E, van den Berg VJ, Akkerhuis KM, et al. Circulating biomarkers of cell adhesion predict clinical outcome in patients with chronic heart failure. *J Clin Med*. 2020;9(1):195. <https://doi.org/10.3390/jcm9010195>
- 832.** Bilim O, Takeishi Y, Kitahara T, et al. Serum YKL-40 predicts adverse clinical outcomes in patients with chronic heart failure. *J Card Fail*. 2010;16:873-879.
- 833.** Rathcke CN, Kistorp C, Raymond I, et al. Plasma YKL-40 levels are elevated in patients with chronic heart failure. *Scand Cardiovasc J*. 2010;44:92-99.
- 834.** Henkens MTHM, van Ommen AM, Remmelzwaal S, et al. The HFA-PEFF score identifies 'early-HFpEF' phenogroups associated with distinct biomarker profiles. *ESC Heart Fail*. 2022;9:2032-2036.
- 835.** Arain F, Abraityte A, Bogdanova M, et al. YKL-40 (chitinase-3-like protein 1) serum levels in aortic stenosis. *Circ Heart Fail*. 2020;13(10):e006643. <https://doi.org/10.1161/CIRCHARTFAILURE.119.006643>
- 836.** Chirinos JA, Orlenko A, Zhao L, et al. Multiple plasma biomarkers for risk stratification in patients with heart failure and preserved ejection fraction. *J Am Coll Cardiol*. 2020;75:1281-1295.
- 837.** Hage C, Michaëlsson E, Linde C, et al. Inflammatory biomarkers predict heart failure severity and prognosis in patients with heart failure with preserved ejection fraction: a holistic proteomic approach. *Circ Cardiovasc Genet*. 2017;10(1):e001633. <https://doi.org/10.1161/CIRCGENETICS.116.001633>
- 838.** Bolla GB, Fedele A, Faggiano A, Sala C, Santangelo G, Carugo S. Effects of sacubitril/valsartan on biomarkers of fibrosis and inflammation in patients with heart failure with reduced ejection fraction. *BMC Cardiovasc Disord*. 2022;22(1):217. <https://doi.org/10.1186/s12872-022-02647-0>
- 839.** Wilson JM, Lin Y, Luo MJ, et al. The dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist tirzepatide improves cardiovascular risk biomarkers in patients with type 2 diabetes: a post hoc analysis. *Diabetes Obes Metab*. 2022;24:148-153.
- 840.** Bozoglu K, Bolton K, McMillan J, et al. Chemerin is a novel adipokine associated with obesity and metabolic syndrome. *Endocrinology*. 2007;148:4687-4694.
- 841.** Goralski KB, McCarthy TC, Hanniman EA, et al. Chemerin, a novel adipokine that regulates adipogenesis and adipocyte metabolism. *J Biol Chem*. 2007;282:28175-28188.
- 842.** Roh SG, Song SH, Choi KC, et al. Chemerin—a new adipokine that modulates adipogenesis via its own receptor. *Biochem Biophys Res Commun*. 2007;362(4):1013-1018.
- 843.** Muruganandan S, Parlee SD, Rourke JL, Ernst MC, Goralski KB, Sinal CJ. Chemerin, a novel peroxisome proliferator-activated receptor gamma (PPARgamma) target gene that promotes mesenchymal stem cell adipogenesis. *J Biol Chem*. 2011;286:23982-23995.
- 844.** Ernst MC, Issa M, Goralski KB, Sinal CJ. Chemerin exacerbates glucose intolerance in mouse models of obesity and diabetes. *Endocrinology*. 2010;151:1998-2007.
- 845.** Rourke JL, Muruganandan S, Dranse HJ, McMullen NM, Sinal CJ. Gpr1 is an active chemerin receptor influencing glucose homeostasis in obese mice. *J Endocrinol*. 2014;222:201-215.
- 846.** Stelmanska E, Sledzinski T, Turyn J, Presler M, Korczynska J, Swierczynski J. Chemerin gene expression is regulated by food restriction and food restriction-refeeding in rat adipose tissue but not in liver. *Regul Pept*. 2013;181:22-29.
- 847.** Ferland DJ, Garver H, Contreras GA, Fink GD, Watts SW. Chemerin contributes to in vivo adipogenesis in a location-specific manner. *PLoS One*. 2020;15(2):e0229251. <https://doi.org/10.1371/journal.pone.0229251>
- 848.** Hart R, Greaves DR. Chemerin contributes to inflammation by promoting macrophage adhesion to VCAM-1 and fibronectin through clustering of VLA-4 and VLA-5. *J Immunol*. 2010;185:3728-3739.
- 849.** Dimitriadis GK, Kaur J, Adya R, et al. Chemerin induces endothelial cell inflammation: activation of nuclear factor-kappa beta and monocyte-endothelial adhesion. *Oncotarget*. 2018;9:16678-16690.
- 850.** Chakaroun R, Raschpichler M, Klöting N, et al. Effects of weight loss and exercise on chemerin serum concentrations and adipose tissue expression in human obesity. *Metabolism*. 2012;61:706-714.
- 851.** Cheon DY, Kang JG, Lee SJ, et al. Serum chemerin levels are associated with visceral adiposity, independent of waist circumference, in newly diagnosed type 2 diabetic subjects. *Yonsei Med J*. 2017;58:319-325.
- 852.** Chang SS, Eisenberg D, Zhao L, et al. Chemerin activation in human obesity. *Obesity (Silver Spring)*. 2016;24:1522-1529.
- 853.** Kunimoto H, Kazama K, Takai M, Oda M, Okada M, Yamawaki H. Chemerin promotes the proliferation and migration of vascular smooth muscle and increases mouse blood pressure. *Am J Physiol Heart Circ Physiol*. 2015;309:H1017-H1028.
- 854.** Kennedy AJ, Yang P, Read C, et al. Chemerin elicits potent constrictor actions via chemokine-like receptor 1 (CMKLR1), not G-protein-coupled receptor 1 (GPR1), in human and rat vasculature. *J Am Heart Assoc*. 2016;5(10):e004421. <https://doi.org/10.1161/JAHA.116.004421>
- 855.** Wabel EA, Krieger-Burke T, Watts SW. Vascular chemerin from PVAT contributes to norepinephrine and serotonin-induced vasoconstriction and vascular stiffness in a sex-dependent manner. *Am J Physiol Heart Circ Physiol*. 2024;327:H1577-H1589.
- 856.** Xie Y, Huang Y, Ling X, Qin H, Wang M, Luo B. Chemerin/CMKLR1 axis promotes inflammation and pyroptosis by activating NLRP3 inflammasome in diabetic cardiomyopathy rat. *Front Physiol*. 2020;11:381. <https://doi.org/10.3389/fphys.2020.00381>
- 857.** Rodríguez-Pénas D, Feijóo-Bandín S, García-Rúa V, et al. The adipokine chemerin induces apoptosis in cardiomyocytes. *Cell Physiol Biochem*. 2015;37:176-192.
- 858.** Yamamoto A, Sagara A, Otani K, Okada M, Yamawaki H. Chemerin-9 stimulates migration in rat cardiac fibroblasts in vitro. *Eur J Pharmacol*. 2021;912:174566. <https://doi.org/10.1016/j.ejphar.2021.174566>
- 859.** Gao X, Mi S, Zhang F, et al. Association of chemerin mRNA expression in human epicardial adipose tissue with coronary atherosclerosis. *Cardiovasc Diabetol*. 2011;10:87. <https://doi.org/10.1186/1475-2840-10-87>
- 860.** Goñi-Olóriz M, Garaikoetxea Zubillaga M, San Ildefonso-García S, et al. Chemerin is a new sex-specific target in aortic stenosis concomitant with diabetes regulated by the aldosterone/mineralocorticoid receptor axis. *Am J Physiol Heart Circ Physiol*. 2025;328(3):H639-H647. <https://doi.org/10.1152/ajpheart.00763.2024>
- 861.** Omori A, Goshima M, Kakuda C, et al. Chemerin-9-induced contraction was enhanced through the upregulation of smooth muscle chemokine-like receptor 1 in isolated pulmonary artery of pulmonary arterial hypertensive rats. *Pflugers Arch*. 2020;472:335-342.
- 862.** Neves KB, Nguyen Dinh, Cat A, Lopes RA, et al. Chemerin regulates crosstalk between adipocytes and vascular cells through Nox. *Hypertension*. 2015;66:657-666.
- 863.** Menzel J, di Giuseppe R, Biemann R, et al. Association between chemerin, omentin-1 and risk of heart failure in the population-based EPIC-Potsdam study. *Sci Rep*. 2017;7(1):14171. <https://doi.org/10.1038/s41598-017-14518-2>
- 864.** Aksu F, Caliskan M, Keles N, et al. Chemerin as a marker of subclinical cardiac involvement in psoriatic patients. *Cardiol J*. 2017;24:276-283.
- 865.** Oguntola BO, Oguntola SO, Ojo OE, Ukpabio PA, Omoaghe AO, Olaniyi KS. Left ventricular hypertrophy in young hypertensives: the possible crosstalk of mTOR and angiotensin-II -a case-control study. *BMC Cardiovasc Disord*. 2025;25(1):9. <https://doi.org/10.1186/s12872-025-04470-9>
- 866.** Michaëlsson E, Lund LH, Hage C, et al. Myeloperoxidase inhibition reverses biomarker profiles associated with clinical outcomes in HFpEF. *JACC Heart Fail*. 2023;11:775-787.
- 867.** Zhang O, Ji Q, Lin Y, et al. Circulating chemerin levels elevated in dilated cardiomyopathy patients with overt heart failure. *Clin Chim Acta*. 2015;448:27-32.
- 868.** Chen D, Wang J, Fu J. Serum chemerin predicts the prognosis of patients with dilated cardiomyopathy. *Heart Surg Forum*. 2020;23:E276-E280.

- 869.** Zhou X, Tao Y, Chen Y, Xu W, Qian Z, Lu X. Serum chemerin as a novel prognostic indicator in chronic heart failure. *J Am Heart Assoc.* 2019;8(15):e012091. <https://doi.org/10.1161/JAHA.119.012091>
- 870.** Aragón-Herrera A, Feijóo-Bandín S, Otero Santiago M, et al. Empagliflozin reduces the levels of CD36 and cardiotoxic lipids while improving autophagy in the hearts of Zucker diabetic fatty rats. *Biochem Pharmacol.* 2019;170:113677.
- 871.** Aragón-Herrera A, Otero-Santiago M, Anido-Varela L, et al. The treatment With the SGLT2 inhibitor empagliflozin modifies the hepatic metabolome of male Zucker diabetic fatty rats towards a protective profile. *Front Pharmacol.* 2022;13:827033. <https://doi.org/10.3389/fphar.2022.827033>
- 872.** Neves KB, Montezano AC, Alves-Lopes R, et al. Upregulation of Nrf2 and decreased redox signaling contribute to renoprotective effects of chemerin receptor blockade in diabetic mice. *Int J Mol Sci.* 2018;19(8):2454. <https://doi.org/10.3390/ijms19082454>
- 873.** Neves KB, Nguyen Dinh, Cat A, Alves-Lopes R, et al. Chemerin receptor blockade improves vascular function in diabetic obese mice via redox-sensitive and Akt-dependent pathways. *Am J Physiol Heart Circ Physiol.* 2018;315:H1851-H1860.
- 874.** Ye ZW, Wu XM, Jiang JG. Expression changes of angiotensin II pathways and bioactive mediators during human preadipocytes-visceral differentiation. *Metabolism.* 2009;58:1288-1296.
- 875.** Janke J, Engeli S, Gorzelniak K, Luft FC, Sharma AM. Resistin gene expression in human adipocytes is not related to insulin resistance. *Obes Res.* 2002;10:1-5.
- 876.** Nagaev I, Bokarewa M, Tarkowski A, Smith U. Human resistin is a systemic immune-derived proinflammatory cytokine targeting both leukocytes and adipocytes. *PLoS One.* 2006;1(1):e31. <https://doi.org/10.1371/journal.pone.0000031>
- 877.** Qatanani M, Szweigold NR, Greaves DR, Ahima RS, Lazar MA. Macrophage-derived human resistin exacerbates adipose tissue inflammation and insulin resistance in mice. *J Clin Invest.* 2009;119:531-539.
- 878.** Rajala MW, Obici S, Scherer PE, Rossetti L. Adipose-derived resistin and gut-derived resistin-like molecule-beta selectively impair insulin action on glucose production. *J Clin Invest.* 2003;111:225-230.
- 879.** Satoh H, Nguyen MT, Miles PD, Imamura T, Usui I, Olefsky JM. Adenovirus-mediated chronic "hyper-resistinemia" leads to in vivo insulin resistance in normal rats. *J Clin Invest.* 2004;114:224-231.
- 880.** Stepan CM, Bailey ST, Bhat S, et al. The hormone resistin links obesity to diabetes. *Nature.* 2001;409:307-312.
- 881.** Rajala MW, Qi Y, Patel HR, Takahashi N, et al. Regulation of resistin expression and circulating levels in obesity, diabetes, and fasting. *Diabetes.* 2004;53:1671-1679.
- 882.** McTernan CL, McTernan PG, Harte AL, Levick PL, Barnett AH, Kumar S. Resistin, central obesity, and type 2 diabetes. *Lancet.* 2002;359:46-47.
- 883.** Cai X, Allison MA, Ambale-Venkatesh B, et al. Resistin and risks of incident heart failure subtypes and cardiac fibrosis: the Multi-Ethnic Study of Atherosclerosis. *ESC Heart Fail.* 2022;9:3452-3460.
- 884.** Frankel DS, Vasan RS, D'Agostino RB Sr, et al. Resistin, adiponectin, and risk of heart failure the Framingham offspring study. *J Am Coll Cardiol.* 2009;53(9):754-762.
- 885.** Butler J, Kalogeropoulos A, Georgiopoulou V, et al. Serum resistin concentrations and risk of new onset heart failure in older persons: the health, aging, and body composition (Health ABC) study. *Arterioscler Thromb Vasc Biol.* 2009;29:1144-1149.
- 886.** Zhang MH, Na B, Schiller NB, Whaley MA. Association of resistin with heart failure and mortality in patients with stable coronary heart disease: data from the Heart and Soul Study. *J Card Fail.* 2011;17:24-30.
- 887.** Norman G, Norton GR, Peterson V, et al. Associations between circulating resistin concentrations and left ventricular mass are not accounted for by effects on aortic stiffness or renal dysfunction. *BMC Cardiovasc Disord.* 2020;20(1):35. <https://doi.org/10.1186/s12872-019-01319-w>
- 888.** Toczyłowski K, Hirnle T, Harasiuk D, et al. Plasma concentration and expression of adipokines in epicardial and subcutaneous adipose tissue are associated with impaired left ventricular filling pattern. *J Transl Med.* 2019;17(1):310. <https://doi.org/10.1186/s12967-019-2060-7>
- 889.** Norman G, Norton GR, Libhaber CD, et al. Independent associations between resistin and left ventricular mass and myocardial dysfunction in a community sample with prevalent obesity. *Int J Cardiol.* 2015;196:81-87.
- 890.** Cheng JM, Akkerhuis KM, Batté LC, et al. Biomarkers of heart failure with normal ejection fraction: a systematic review. *Eur J Heart Fail.* 2013;15:1350-1362.
- 891.** Takeishi Y, Niizeki T, Arimoto T, et al. Serum resistin is associated with high risk in patients with congestive heart failure-a novel link between metabolic signals and heart failure. *Circ J.* 2007;71:460-464.
- 892.** Wu XM, Lin YH, Chen A, et al. Prognostic significance of adipocytokines in systolic heart failure patients. *Eur J Clin Invest.* 2012;42:1079-1086.
- 893.** Verma S, Li SH, Wang CH, et al. Resistin promotes endothelial cell activation: further evidence of adipokine-endothelial interaction. *Circulation.* 2003;108:736-740.
- 894.** Chen C, Jiang J, Lü JM, et al. Resistin decreases expression of endothelial nitric oxide synthase through oxidative stress in human coronary artery endothelial cells. *Am J Physiol Heart Circ Physiol.* 2010;299:H193-H201.
- 895.** Pirvulescu M, Manduteanu I, Gan AM, et al. A novel pro-inflammatory mechanism of action of resistin in human endothelial cells: up-regulation of SOCS3 expression through STAT3 activation. *Biochem Biophys Res Commun.* 2012;422:321-326.
- 896.** Rothwell SE, Richards AM, Pemberton CJ. Resistin worsens cardiac ischaemia-reperfusion injury. *Biochem Biophys Res Commun.* 2006;349:400-407.
- 897.** Kim M, Oh JK, Sakata S, et al. Role of resistin in cardiac contractility and hypertrophy. *J Mol Cell Cardiol.* 2008;45:270-280.
- 898.** Kang S, Chemaly ER, Hajjar RJ, Lebeche D. Resistin promotes cardiac hypertrophy via the AMP-activated protein kinase/mammalian target of rapamycin (AMPK/mTOR) and c-Jun N-terminal kinase/insulin receptor substrate 1 (JNK/IRS1) pathways. *J Biol Chem.* 2011;286:18465-18473.
- 899.** Singh R, Kaundal RK, Zhao B, Bouchareb R, Lebeche D. Resistin induces cardiac fibroblast-myofibroblast differentiation through JAK/STAT3 and JNK/c-Jun signaling. *Pharmacol Res.* 2021;167:105414. <https://doi.org/10.1016/j.phrs.2020.105414>
- 900.** Chemaly ER, Hadri L, Zhang S, et al. Long-term in vivo resistin overexpression induces myocardial dysfunction and remodeling in rats. *J Mol Cell Cardiol.* 2011;51:144-155.
- 901.** Zhao B, Bouchareb R, Lebeche D. Resistin deletion protects against heart failure injury by targeting DNA damage response. *Cardiovasc Res.* 2022;118:1947-1963.
- 902.** Qin K, Yu M, Fan J, et al. Canonical and noncanonical Wnt signaling: Multilayered mediators, signaling mechanisms and major signaling crosstalk. *Genes Dis.* 2023;11:103-134.
- 903.** Cohen ED, Tian Y, Morrisey EE. Wnt signaling: an essential regulator of cardiovascular differentiation, morphogenesis and progenitor self-renewal. *Development.* 2008;135:789-798.
- 904.** Mazzotta S, Neves C, Bonner RJ, Bernardo AS, Docherty K, Hoppler S. Distinctive roles of canonical and noncanonical Wnt signaling in human embryonic cardiomyocyte development. *Stem Cell Rep.* 2016;7:764-776.
- 905.** Catalán V, Gómez-Ambrosi J, Rodríguez A, et al. Activation of noncanonical Wnt signaling through WNT5A in visceral adipose tissue of obese subjects is related to inflammation. *J Clin Endocrinol Metab.* 2014;99:E1407-E1417.
- 906.** Schulte DM, Müller N, Neumann K, et al. Pro-inflammatory wnt5a and anti-inflammatory sFRP5 are differentially regulated by nutritional factors in obese human subjects. *PLoS One.* 2012;7(2):e32437. <https://doi.org/10.1371/journal.pone.0032437>
- 907.** Bilkovski R, Schulte DM, Oberhauser F, et al. Role of WNT-5a in the determination of human mesenchymal stem cells into preadipocytes. *J Biol Chem.* 2010;285:6170-6178.
- 908.** Yiew NKH, Chatterjee TK, Tang YL, et al. A novel role for the Wnt inhibitor APCDD1 in adipocyte differentiation: Implications for diet-induced obesity. *J Biol Chem.* 2017;292:6312-6324.
- 909.** Nishizuka M, Koyanagi A, Osada S, Imagawa M. Wnt4 and Wnt5a promote adipocyte differentiation. *FEBS Lett.* 2008;582:3201-3205.

- 910.** Fuster JJ, Zuriaga MA, Ngo DT, et al. Non-canonical Wnt signaling promotes obesity-induced adipose tissue inflammation and metabolic dysfunction independent of adipose tissue expansion. *Diabetes*. 2015;64:1235-1248.
- 911.** Lee GJ, Kim YJ, Park B, et al. YAP-dependent Wnt5a induction in hypertrophic adipocytes restrains adiposity. *Cell Death Dis*. 2022;13(4):407. <https://doi.org/10.1038/s41419-022-04847-0>
- 912.** Farb MG, Karki S, Park SY, et al. WNT5A-JNK regulation of vascular insulin resistance in human obesity. *Vasc Med*. 2016;21:489-496.
- 913.** Zuriaga MA, Fuster JJ, Farb MG, et al. Activation of non-canonical WNT signaling in human visceral adipose tissue contributes to local and systemic inflammation. *Sci Rep*. 2017;7(1):17326. <https://doi.org/10.1038/s41598-017-17509-5>
- 914.** Akoumianakis I, Sanna F, Margaritis M, et al. Adipose tissue-derived WNT5A regulates vascular redox signaling in obesity via USP17/RAC1-mediated activation of NADPH oxidases. *Sci Transl Med*. 2019;11(510):eaav5055. <https://doi.org/10.1126/scitranslmed.aav5055>
- 915.** Tong S, Du Y, Ji Q, Dong R, et al. Expression of Sfrp5/Wnt5a in human epicardial adipose tissue and their relationship with coronary artery disease. *Life Sci*. 2020;245:117338. <https://doi.org/10.1016/j.lfs.2020.117338>
- 916.** Duan DY, Tang J, Tian HT, Shi YY, Jia J. Adipocyte-secreted microvesicle-derived miR-148a regulates adipogenic and osteogenic differentiation by targeting Wnt5a/Ror2 pathway. *Life Sci*. 2021;278:119548. <https://doi.org/10.1016/j.lfs.2021.119548>
- 917.** Dzialo E, Rudnik M, Koning RI, et al. WNT3a and WNT5a transported by exosomes activate WNT signaling pathways in human cardiac fibroblasts. *Int J Mol Sci*. 2019;20(6):1436. <https://doi.org/10.3390/ijms20061436>
- 918.** Zou Y, Pan L, Shen Y, et al. Cardiac Wnt5a and Wnt11 promote fibrosis by the crosstalk of FZD5 and EGFR signaling under pressure overload. *Cell Death Dis*. 2021;12(10):877. <https://doi.org/10.1038/s41419-021-04152-2>
- 919.** Wang Y, Sano S, Oshima K, et al. Wnt5a-mediated neutrophil recruitment has an obligatory role in pressure overload-induced cardiac dysfunction. *Circulation*. 2019;140:487-499.
- 920.** Hagenmueller M, Riffel JH, Bernhold E, Fan J, Katus HA, Hardt SE. Dapper-1 is essential for Wnt5a induced cardiomyocyte hypertrophy by regulating the Wnt/PCP pathway. *FEBS Lett*. 2014;588:2230-2237.
- 921.** Kishimoto H, Iwasaki M, Wada K, et al. Wnt5a-YAP signaling axis mediates mechano-transduction in cardiac myocytes and contributes to contractile dysfunction induced by pressure overload. *iScience*. 2023;26(7):107146. <https://doi.org/10.1016/j.isci.2023.107146>
- 922.** Hong P, Wang L, Wang H, Shi M, Guo B. Effect of secreted frizzled-related protein 5 in mice with heart failure. *Evid Based Complement Alternat Med*. 2022;2022:1606212.
- 923.** Wu H, Tang LX, Wang XM, et al. Porcupine inhibitor CGX1321 alleviates heart failure with preserved ejection fraction in mice by blocking WNT signaling. *Acta Pharmacol Sin*. 2023;44:1149-1160.
- 924.** Chong A, Joshua J, Raheb S, et al. Evaluation of potential novel biomarkers for feline hypertrophic cardiomyopathy. *Res Vet Sci*. 2024;180:105430. <https://doi.org/10.1016/j.rvsc.2024.105430>
- 925.** Abraityte A, Vinge LE, Askevold ET, et al. Wnt5a is elevated in heart failure and affects cardiac fibroblast function. *J Mol Med (Berl)*. 2017;95:767-777.
- 926.** Ueland T, Abraityte A, Norum H, et al. Circulating regulators of the wingless pathway in precapillary pulmonary hypertension. *Respirology*. 2021;26:574-581.
- 927.** Abraityte A, Lunde IG, Askevold ET, et al. Wnt5a is associated with right ventricular dysfunction and adverse outcome in dilated cardiomyopathy. *Sci Rep*. 2017;7(1):3490. <https://doi.org/10.1038/s41598-017-03625-9>
- 928.** Laeremans H, Hackeng TM, van Zandvoort MA, et al. Blocking of Frizzled signaling with a homologous peptide fragment of Wnt3a/Wnt5a reduces infarct expansion and prevents the development of heart failure after myocardial infarction. *Circulation*. 2011;124:1626-1635.
- 929.** Yang D, Fu W, Li L, et al. Therapeutic effect of a novel Wnt pathway inhibitor on cardiac regeneration after myocardial infarction. *Clin Sci (Lond)*. 2017;131:2919-2932.
- 930.** Ferry G, Tellier E, Try A, et al. Autotaxin is released from adipocytes, catalyzes lysophosphatidic acid synthesis, and activates pre-adipocyte proliferation. Up-regulated expression with adipocyte differentiation and obesity. *J Biol Chem*. 2003;278:18162-18169.
- 931.** Simon MF, Daviaud D, Pradère JP, et al. Lysophosphatidic acid inhibits adipocyte differentiation via lysophosphatidic acid 1 receptor-dependent down-regulation of peroxisome proliferator-activated receptor gamma2. *J Biol Chem*. 2005;280:14656-14662.
- 932.** Dusaulcy R, Rancoule C, Grès S, et al. Adipose-specific disruption of autotaxin enhances nutritional fattening and reduces plasma lysophosphatidic acid. *J Lipid Res*. 2011;52:1247-1255.
- 933.** Brown A, Hossain I, Perez LJ, et al. Lysophosphatidic acid receptor mRNA levels in heart and white adipose tissue are associated with obesity in mice and humans. *PLoS One*. 2017;12(12):e0189402. <https://doi.org/10.1371/journal.pone.0189402>
- 934.** Rancoule C, Dusaulcy R, Tréguer K, et al. Depot-specific regulation of autotaxin with obesity in human adipose tissue. *J Physiol Biochem*. 2012;68:635-644.
- 935.** Reeves VL, Trybula JS, Wills RC, et al. Serum autotaxin/ENPP2 correlates with insulin resistance in older humans with obesity. *Obesity (Silver Spring)*. 2015;23:2371-2376.
- 936.** Michalczuk A, Budkowska M, Dotęgowska B, Chlubek D, Safranow K. Lysophosphatidic acid plasma concentrations in healthy subjects: circadian rhythm and associations with demographic, anthropometric and biochemical parameters. *Lipids Health Dis*. 2017;16(1):140. <https://doi.org/10.1186/s12944-017-0536-0>
- 937.** Rachakonda VP, Reeves VL, Aljammal J, et al. Serum autotaxin is independently associated with hepatic steatosis in women with severe obesity. *Obesity (Silver Spring)*. 2015;23:965-972.
- 938.** Weng J, Jiang S, Ding L, Xu Y, Zhu X, Jin P. Autotaxin/lysophosphatidic acid signaling mediates obesity-related cardiomyopathy in mice and human subjects. *J Cell Mol Med*. 2019;23:1050-1058.
- 939.** Fayyaz S, Japtok L, Schumacher F, et al. Lysophosphatidic acid inhibits insulin signaling in primary rat hepatocytes via the LPA3 receptor subtype and is increased in obesity. *Cell Physiol Biochem*. 2017;43:445-456.
- 940.** Nishimura S, Nagasaki M, Okudaira S, et al. ENPP2 contributes to adipose tissue expansion and insulin resistance in diet-induced obesity. *Diabetes*. 2014;63:4154-4164.
- 941.** Brandon JA, Kraemer M, Vandria J, et al. Adipose-derived autotaxin regulates inflammation and steatosis associated with diet-induced obesity. *PLoS One*. 2019;14(2):e0208099. <https://doi.org/10.1371/journal.pone.0208099>
- 942.** Yang J, Xu J, Han X, et al. Lysophosphatidic acid is associated with cardiac dysfunction and hypertrophy by suppressing autophagy via the LPA3/AKT/mTOR pathway. *Front Physiol*. 2018;9:1315. <https://doi.org/10.3389/fphys.2018.01315>
- 943.** Xu Y, Wang Y, Liu J, et al. Adipose tissue-derived autotaxin causes cardiomyopathy in obese mice. *J Mol Endocrinol*. 2019;63:113-121.
- 944.** Tripathi H, Al-Darraji A, Abo-Aly M, et al. Autotaxin inhibition reduces cardiac inflammation and mitigates adverse cardiac remodeling after myocardial infarction. *J Mol Cell Cardiol*. 2020;149:95-114.
- 945.** Araki T, Okumura T, Hiraiwa H, et al. Serum autotaxin as a novel prognostic marker in patients with non-ischaemic dilated cardiomyopathy. *ESC Heart Fail*. 2022;9:1304-1313.
- 946.** Axelsson Raja A, Wakimoto H, DeLaughter DM, et al. Ablation of lysophosphatidic acid receptor 1 attenuates hypertrophic cardiomyopathy in a mouse model. *Proc Natl Acad Sci U S A*. 2022;119(28):e2204174119. <https://doi.org/10.1073/pnas.2204174119>
- 947.** Chandra M, Escalante-Alcalde D, Bhuiyan MS, et al. Cardiac-specific inactivation of LPP3 in mice leads to myocardial dysfunction and heart failure. *Redox Biol*. 2018;14:261-271.
- 948.** Maher TM, Ford P, Brown KK, et al. Zirbitzestat, a novel autotaxin inhibitor, and lung function in idiopathic pulmonary fibrosis: the ISABELA 1 and 2 randomized clinical trials. *JAMA*. 2023;329:1567-1578.
- 949.** Summers KM, Bush SJ, Davis MR, et al. Fibillin-1 and asprosin, novel players in metabolic syndrome. *Mol Genet Metab*. 2023;138(1):106979. <https://doi.org/10.1016/j.ymgme.2022.106979>
- 950.** Romere C, Duerrschmid C, Bournat J, et al. Asprosin, a fasting-induced glucogenic protein hormone. *Cell*. 2016;165:566-579.

- 951.** Chen S, Yuan W, Huang Q, et al. Asprosin contributes to pathogenesis of obesity by adipocyte mitophagy induction to inhibit white adipose browning in mice. *Int J Obes (Lond)*. 2024;48:913-922.
- 952.** Jung TW, Kim HC, Kim HU, et al. Asprosin attenuates insulin signaling pathway through PKCdelta-activated ER stress and inflammation in skeletal muscle. *J Cell Physiol*. 2019;234:20888-20899.
- 953.** Miao Y, Qin H, Zhong Y, Huang K, Rao C. Novel adipokine asprosin modulates browning and adipogenesis in white adipose tissue. *J Endocrinol*. 2021;249:83-93.
- 954.** Mazur-Bialy AI. Asprosin enhances cytokine production by a co-culture of fully differentiated mature adipocytes and macrophages leading to the exacerbation of the condition typical of obesity-related inflammation. *Int J Mol Sci*. 2023;24(6):5745. <https://doi.org/10.3390/ijms24065745>
- 955.** Wang M, Yin C, Wang L, et al. Serum asprosin concentrations are increased and associated with insulin resistance in children with obesity. *Ann Nutr Metab*. 2019;75:205-212.
- 956.** Lv D, Wang Z, Meng C, Li Y, Ji S. A study of the relationship between serum asprosin levels and MAFLD in a population undergoing physical examination. *Sci Rep*. 2024;14(1):11170. <https://doi.org/10.1038/s41598-024-62124-w>
- 957.** Cantay H, Binnetoglu K, Gul HF, Bingol SA. Investigation of serum and adipose tissue levels of asprosin in patients with severe obesity undergoing sleeve gastrectomy. *Obesity (Silver Spring)*. 2022;30:1639-1646.
- 958.** Wang C, Zeng W, Wang L, et al. Asprosin aggravates nonalcoholic fatty liver disease via inflammation and lipid metabolic disturbance mediated by reactive oxygen species. *Drug Dev Res*. 2024;85(4):e22213. <https://doi.org/10.1002/ddr.22213>
- 959.** Hong T, Li JY, Wang YD, et al. High serum asprosin levels are associated with presence of metabolic syndrome. *Int J Endocrinol*. 2021;2021:662129. <https://doi.org/10.1155/2021/662129>
- 960.** Dai C, Zhu W. Effects of GLP-1 receptor agonists on asprosin levels in normal weight or overweight/obesity patients with type 2 diabetes mellitus. *Medicine (Baltimore)*. 2022;101(43):e31334. <https://doi.org/10.1097/MD.00000000000031334>
- 961.** Wang CY, Lin TA, Liu KH, et al. Serum asprosin levels and bariatric surgery outcomes in obese adults. *Int J Obes (Lond)*. 2019;43:1019-1025.
- 962.** Yin T, Chen S, Zeng G, et al. Angiogenesis-browning interplay mediated by asprosin-knockout contributes to weight loss in mice with obesity. *Int J Mol Sci*. 2022;23(24):16166. <https://doi.org/10.3390/ijms232416166>
- 963.** Mishra I, Duerrscheid C, Ku Z, et al. Asprosin-neutralizing antibodies as a treatment for metabolic syndrome. *Elife*. 2021;10:e63784. <https://doi.org/10.7554/elife.63784>
- 964.** Shabir K, Brown JE, Afzal I, et al. Asprosin, a novel pleiotropic adipokine implicated in fasting and obesity-related cardio-metabolic disease: Comprehensive review of preclinical and clinical evidence. *Cytokine Growth Factor Rev*. 2021;60:120-132.
- 965.** Lu Y, Yuan W, Xiong X, et al. Asprosin aggravates vascular endothelial dysfunction via disturbing mitochondrial dynamics in obesity models. *Obesity (Silver Spring)*. 2023;31:732-743.
- 966.** Ge R, Chen JL, Zheng F, et al. Asprosin promotes vascular inflammation via TLR4-NFκB-mediated NLRP3 inflammasome activation in hypertension. *Heliyon*. 2024;10(11):e31659. <https://doi.org/10.1016/j.heliyon.2024.e31659>
- 967.** You M, Liu Y, Wang B, et al. Asprosin induces vascular endothelial-to-mesenchymal transition in diabetic lower extremity peripheral artery disease. *Cardiovasc Diabetol*. 2022;21(1):25. <https://doi.org/10.1186/s12933-022-01457-0>
- 968.** Xu ZQ, Li XZ, Zhu R, et al. Asprosin contributes to vascular remodeling in hypertensive rats via superoxide signaling. *J Hypertens*. 2024;42:1427-1439.
- 969.** Zheng F, Ye C, Lei JZ, et al. Intervention of asprosin attenuates oxidative stress and neointima formation in vascular injury. *Antioxid Redox Signal*. 2024;41:488-504.
- 970.** Wen MS, Wang CY, Yeh JK, et al. The role of Asprosin in patients with dilated cardiomyopathy. *BMC Cardiovasc Disord*. 2020;20(1):402. <https://doi.org/10.1186/s12872-020-01680-1>
- 971.** Wang G, Fan C, Chai Y, et al. Association of serum Asprosin concentrations with heart failure. *BMC Cardiovasc Disord*. 2023;23(1):617. <https://doi.org/10.1186/s12872-023-03668-z>
- 972.** Liang D, Shi G, Xu M, et al. The correlation between serum asprosin and left ventricular diastolic dysfunction in elderly patients with type 2 diabetes mellitus in the community. *J Diabetes Investig*. 2024;15:608-613.
- 973.** Haider N, Larose L. Harnessing adipogenesis to prevent obesity. *Adipocyte*. 2019;8:98-104.
- 974.** Lee YH, Petkova AP, Mottillo EP, Granneman JG. In vivo identification of bipotential adipocyte progenitors recruited by β3-adrenoceptor activation and high-fat feeding. *Cell Metab*. 2012;15:480-491.
- 975.** Gallini R, Lindblom P, Bondjers C, Betsholtz C, Andrae J. PDGF-A and PDGF-B induces cardiac fibrosis in transgenic mice. *Exp Cell Res*. 2016;349:282-290.
- 976.** Gao Z, Daquinag AC, Su F, Snyder B, Kolonin MG. PDGFRα/PDGFRβ signaling balance modulates progenitor cell differentiation into white and beige adipocytes. *Development*. 2018;145(1):dev155861. <https://doi.org/10.1242/dev.155861>
- 977.** Marcellin G, Ferreira A, Liu Y, et al. A PDGFRα-mediated switch toward CD9high adipocyte progenitors controls obesity-induced adipose tissue fibrosis. *Cell Metab*. 2017;25(3):673-685.
- 978.** Sun C, Berry WL, Olson LE. PDGFRα controls the balance of stromal and adipogenic cells during adipose tissue organogenesis. *Development*. 2017;144:83-94.
- 979.** Iwayama T, Steele C, Yao L, et al. PDGFRα signaling drives adipose tissue fibrosis by targeting progenitor cell plasticity. *Genes Dev*. 2015;29:1106-1119.
- 980.** Hepler C, Shan B, Zhang Q, et al. Identification of functionally distinct fibro-inflammatory and adipogenic stromal subpopulations in visceral adipose tissue of adult mice. *Elife*. 2018;7:e39636. <https://doi.org/10.7554/elife.39636>
- 981.** Onogi Y, Wada T, Kamiya C, et al. PDGFRβ regulates adipose tissue expansion and glucose metabolism via vascular remodeling in diet-induced obesity. *Diabetes*. 2017;66:1008-1021.
- 982.** Watanabe E, Wada T, Okekawa A, et al. Stromal cell-derived factor 1 (SDF1) attenuates platelet-derived growth factor-B (PDGF-B)-induced vascular remodeling for adipose tissue expansion in obesity. *Angiogenesis*. 2020;23:667-684.
- 983.** Benvie AM, Berry DC. Reversing Pdgfrβ signaling restores metabolically active beige adipocytes by alleviating ILC2 suppression in aged and obese mice. *Mol Metab*. 2024;89:102028. <https://doi.org/10.1016/j.molmet.2024.102028>
- 984.** Cheng YW, Zhang ZB, Lan BD, et al. PDGF-D activation by macrophage-derived uPA promotes AngII-induced cardiac remodeling in obese mice. *J Exp Med*. 2021;218(9):e20210252. <https://doi.org/10.1084/jem.20210252>
- 985.** Zhao W, Zhao T, Huang V, Chen Y, Ahokas RA, Sun Y. Platelet-derived growth factor involvement in myocardial remodeling following infarction. *J Mol Cell Cardiol*. 2011;51:830-838.
- 986.** Hamid T, Xu Y, Ismail MA, et al. Cardiac mesenchymal stem cells promote fibrosis and remodeling in heart failure: role of PDGF signaling. *JACC Basic Transl Sci*. 2022;7:465-483.
- 987.** Pontén A, Folestad EB, Pietras K, Eriksson U. Platelet-derived growth factor D induces cardiac fibrosis and proliferation of vascular smooth muscle cells in heart-specific transgenic mice. *Circ Res*. 2005;97:1036-1045.
- 988.** Zhao T, Zhao W, Chen Y, Li VS, Meng W, Sun Y. Platelet-derived growth factor-D promotes fibrogenesis of cardiac fibroblasts. *Am J Physiol Heart Circ Physiol*. 2013;304:H1719-H1726.
- 989.** Liu J, Bai H, Xing DQ, Sun YP, Wu LL. Role of platelet-derived growth factor receptor-mediated signal transduction in myocardial hypertrophy of spontaneously hypertensive rats. *Sheng Li Xue Bao*. 2002;54:159-164.
- 990.** Kazama K, Okada M, Yamawaki H. A novel adipocytokine, omentin, inhibits platelet-derived growth factor-BB-induced vascular smooth muscle cell migration through antioxidative mechanism. *Am J Physiol Heart Circ Physiol*. 2014;306:H1714-H1719.
- 991.** Abed HS, Samuel CS, Lau DH, et al. Obesity results in progressive atrial structural and electrical remodeling: implications for atrial fibrillation. *Heart Rhythm*. 2013;10:90-100.
- 992.** Valero-Muñoz M, Oh A, Faudoa E, et al. Endothelial-mesenchymal transition in heart failure with a preserved ejection fraction: insights into the cardiorenal syndrome. *Circ Heart Fail*.

- 2021;14(9):e008372. <https://doi.org/10.1161/CIRCHEARTFAILURE.121.008372>
- 993.** Chuang HH, Huang CG, Chuang LP, et al. Relationships among and predictive values of obesity, inflammation markers, and disease severity in pediatric patients with obstructive sleep apnea before and after adenotonsillectomy. *J Clin Med.* 2020;9(2):579. <https://doi.org/10.3390/jcm9020579>
- 994.** Rivera P, Martos-Moreno GÁ, Barrios V, et al. A novel approach to childhood obesity: circulating chemokines and growth factors as biomarkers of insulin resistance. *Pediatr Obes.* 2019;14(3):e12473. <https://doi.org/10.1111/ijpo.12473>
- 995.** Onogi Y, Wada T, Okekawa A, et al. Pro-inflammatory macrophages coupled with glycolysis remodel adipose vasculature by producing platelet-derived growth factor-B in obesity. *Sci Rep.* 2020;10(1):670. <https://doi.org/10.1038/s41598-019-57368-w>
- 996.** Zheng Q, Zhou F, Cui X, et al. Novel serum biomarkers detected by protein array in polycystic ovary syndrome with low progesterone level. *Cell Physiol Biochem.* 2018;46:2297-2310.
- 997.** Eizidzadeh A, Schnelle M, Leha A, et al. Biomarker profiles in heart failure with preserved vs. reduced ejection fraction: results from the DIAST-CHF study. *ESC Heart Fail.* 2023;10(1):200-210.
- 998.** Arita Y, Kihara S, Ouchi N, et al. Adipocyte-derived plasma protein adiponectin acts as a platelet-derived growth factor-BB-binding protein and regulates growth factor-induced common postreceptor signal in vascular smooth muscle cell. *Circulation.* 2002;105:2893-2898.
- 999.** Hooper MM, Barst RJ, Bourge RC, et al. Imatinib mesylate as add-on therapy for pulmonary arterial hypertension: results of the randomized IMPRES study. *Circulation.* 2013;127:1128-1138.
- 1000.** Jang SW, Ihm SH, Choo EH, et al. Imatinib mesylate attenuates myocardial remodeling through inhibition of platelet-derived growth factor and transforming growth factor activation in a rat model of hypertension. *Hypertension.* 2014;63:1228-1234.
- 1001.** Khalil H, Kanisicak O, Prasad V, et al. Fibroblast-specific TGF-beta-Smad2/3 signaling underlies cardiac fibrosis. *J Clin Invest.* 2017;127:3770-3783.
- 1002.** Zaragosi LE, Wdziekonski B, Villageois P, et al. Activin plays a critical role in proliferation and differentiation of human adipose progenitors. *Diabetes.* 2010;59:2513-2521.
- 1003.** Hong SK, Choo EH, Ihm SH, Chang K, Seung KB. Dipeptidyl peptidase 4 inhibitor attenuates obesity-induced myocardial fibrosis by inhibiting transforming growth factor-beta and Smad2/3 pathways in high-fat diet-induced obesity rat model. *Metabolism.* 2017;76:42-55.
- 1004.** Lin Y, Nakachi K, Ito Y, et al. Variations in serum transforming growth factor-beta1 levels with gender, age and lifestyle factors of healthy Japanese adults. *Dis Markers.* 2009;27:23-28.
- 1005.** Bu Y, Okunishi K, Yogosawa S, et al. Insulin regulates lipolysis and fat mass by upregulating growth/differentiation factor 3 in adipose tissue macrophages. *Diabetes.* 2018;67:1761-1772.
- 1006.** Carlsson LM, Jacobson P, Walley A, et al. ALK7 expression is specific for adipose tissue, reduced in obesity and correlates to factors implicated in metabolic disease. *Biochem Biophys Res Commun.* 2009;382:309-314.
- 1007.** Murakami M, Shirai M, Ooishi R, et al. Expression of activin receptor-like kinase 7 in adipose tissues. *Biochem Genet.* 2013;51:202-210.
- 1008.** Kogame M, Matsuo S, Nakatani M, et al. ALK7 is a novel marker for adipocyte differentiation. *J Med Invest.* 2006;53:238-245.
- 1009.** Wang W, Yang Y, Meng Y, Shi Y. GDF-3 is an adipogenic cytokine under high fat dietary condition. *Biochem Biophys Res Commun.* 2004;321:1024-1031.
- 1010.** Chen X, Zhao C, Xu Y, et al. Adipose-specific BMP and activin membrane-bound inhibitor (BAMBI) deletion promotes adipogenesis by accelerating ROS production. *J Biol Chem.* 2021;296:100037. <https://doi.org/10.1074/jbc.RA120.014793>
- 1011.** Koncarevic A, Kajimura S, Cornwall-Brady M, et al. A novel therapeutic approach to treating obesity through modulation of TGFβ signaling. *Endocrinology.* 2012;153:3133-3146.
- 1012.** Zhao M, Okunishi K, Bu Y, et al. Targeting activin receptor-like kinase 7 ameliorates adiposity and associated metabolic disorders. *JCI Insight.* 2023;8(4):e161229. <https://doi.org/10.1172/jci.insight.161229>
- 1013.** Shen JJ, Huang L, Li L, Jorgez C, Matzuk MM, Brown CW. Deficiency of growth differentiation factor 3 protects against diet-induced obesity by selectively acting on white adipose. *Mol Endocrinol.* 2009;23:113-123.
- 1014.** Andersson O, Korach-Andre M, Reissmann E, Ibáñez CF, Bertolino P. Growth/differentiation factor 3 signals through ALK7 and regulates accumulation of adipose tissue and diet-induced obesity. *Proc Natl Acad Sci U S A.* 2008;105:7252-7256.
- 1015.** Hall JA, Ramachandran D, Roh HC, et al. Obesity-linked PPARgamma S273 phosphorylation promotes insulin resistance through growth differentiation factor 3. *Cell Metab.* 2020;32:665-675.
- 1016.** Camell CD, Sander J, Spadaro O, et al. Inflammasome-driven catecholamine catabolism in macrophages blunts lipolysis during ageing. *Nature.* 2017;550:119-123.
- 1017.** Emdin CA, Khera AV, Aragam K, et al. DNA sequence variation in ACVR1C encoding the activin receptor-like kinase 7 influences body fat distribution and protects against type 2 diabetes. *Diabetes.* 2019;68:226-234.
- 1018.** Tangseefa P, Jin H, Zhang H, Xie M, Ibáñez CF. Human ACVR1C missense variants that correlate with altered body fat distribution produce metabolic alterations of graded severity in knock-in mutant mice. *Mol Metab.* 2024;81:101890. <https://doi.org/10.1016/j.molmet.2024.101890>
- 1019.** Niepsuj J, Piwowar A, Franik G, Bizoń A. The concentration of follistatin and Activin A in serum and selected biochemical parameters in women with polycystic ovary syndrome: stratification by tobacco smoke exposure, insulin resistance, and overweight/obesity. *J Clin Med.* 2024;13(17):5316. <https://doi.org/10.3390/jcm13175316>
- 1020.** Kostopoulou E, Kalavritioti D, Davoulou P, et al. Monocyte chemoattractant protein-1 (MCP-1), activin-A and clusterin in children and adolescents with obesity or type-1 diabetes mellitus. *Diagnostics (Basel).* 2024;14(4):450. <https://doi.org/10.3390/diagnostics14040450>
- 1021.** Pham TCP, Bojsen-Møller KN, Madsbad S, Wojtaszewski JFP, Richter EA, Sylow L. Effects of Roux-en-Y gastric bypass on circulating follistatin, activin A, and peripheral ActRIIB signaling in humans with obesity and type 2 diabetes. *Int J Obes (Lond).* 2021;45:316-325.
- 1022.** Perakakis N, Kokkinos A, Peradze N, et al. Metabolic regulation of activins in healthy individuals and in obese patients undergoing bariatric surgery. *Diabetes Metab Res Rev.* 2020;36(5):e3297. <https://doi.org/10.1002/dmrr.3297>
- 1023.** Greulich S, Maxhera B, Vandenplas G, et al. Secretory products from epicardial adipose tissue of patients with type 2 diabetes mellitus induce cardiomyocyte dysfunction. *Circulation.* 2012;126:2324-2334.
- 1024.** Masurkar N, Bouvet M, Logeart D, et al. Novel cardiokine GDF3 predicts adverse fibrotic remodeling after myocardial infarction. *Circulation.* 2023;147:498-511.
- 1025.** Hu J, Wang X, Wei SM, Tang YH, Zhou Q, Huang CX. Activin A stimulates the proliferation and differentiation of cardiac fibroblasts via the ERK1/2 and p38-MAPK pathways. *Eur J Pharmacol.* 2016;789:319-327.
- 1026.** Swan J, Szabó Z, Peters J, et al. Inhibition of activin receptor 2 signalling ameliorates metabolic dysfunction-associated steatotic liver disease in western diet/L-NNAME induced cardiometabolic disease. *Biomed Pharmacother.* 2024;175:116683. <https://doi.org/10.1016/j.biopharma.2024.116683>
- 1027.** Liu L, Ding WY, Zhao J, et al. Activin receptor-like kinase 7 mediates high glucose-induced H9c2 cardiomyoblast apoptosis through activation of Smad2/3. *Int J Biochem Cell Biol.* 2013;45:2027-2035.
- 1028.** Liu L, Zhou X, Zhang Q, et al. Activin receptor-like kinase 7 silencing alleviates cardiomyocyte apoptosis, cardiac fibrosis, and dysfunction in diabetic rats. *Exp Biol Med (Maywood).* 2022;247:1397-1409.
- 1029.** Cao S, Yuan Q, Dong Q, et al. Activin receptor-like kinase 7 promotes apoptosis of vascular smooth muscle cells via activating Smad2/3 signaling in diabetic atherosclerosis. *Front Pharmacol.* 2022;13:926433. <https://doi.org/10.3389/fphar.2022.926433>
- 1030.** Gong FH, Cheng WL, Zhang Q, et al. ALK7 promotes vascular smooth muscle cells phenotypic modulation by negative regulating PPAR-gamma expression. *J Cardiovasc Pharmacol.* 2020;76:237-245.

- 1031.** Joshi SR, Atabay EK, Liu J, et al. Sotatercept analog improves cardiopulmonary remodeling and pulmonary hypertension in experimental left heart failure. *Front Cardiovasc Med.* 2023;10:1064290. <https://doi.org/10.3389/fcmv.2023.1064290>
- 1032.** Lin JF, Hsu SY, Teng MS, et al. Activin A predicts left ventricular remodeling and mortality in patients with ST-elevation myocardial infarction. *Acta Cardiol Sin.* 2016;32:420-427.
- 1033.** Chen WJ, Greulich S, van der Meer RW, et al. Activin A is associated with impaired myocardial glucose metabolism and left ventricular remodeling in patients with uncomplicated type 2 diabetes. *Cardiovasc Diabetol.* 2013;12:150. <https://doi.org/10.1186/1475-2840-12-150>
- 1034.** Guignabert C, Savale L, Boucly A, et al. Serum and pulmonary expression profiles of the activin signaling system in pulmonary arterial hypertension. *Circulation.* 2023;147:1809-1822.
- 1035.** Zhang W, Wang H, Zhang W, et al. ALK7 gene polymorphism is associated with metabolic syndrome risk and cardiovascular remodeling. *Arq Bras Cardiol.* 2013;101:134-140.
- 1036.** Zeller J, Krüger C, Lamounier-Zepter V, et al. The adipofibrokine activin A is associated with metabolic abnormalities and left ventricular diastolic dysfunction in obese patients. *ESC Heart Fail.* 2019;6:362-370.
- 1037.** Tsai YL, Chou RH, Kuo CS, et al. Circulating activin A is a surrogate for the incidence of diastolic dysfunction and heart failure in patients with preserved ejection fraction. *Circ J.* 2019;25;(83):1514-1519.
- 1038.** Hooper MM, Badesch DB, Ghofrani HA, et al. Phase 3 trial of sotatercept for treatment of pulmonary arterial hypertension. *N Engl J Med.* 2023;388:1478-1490.
- 1039.** Kaur M, Misra S. Bimagrumab: an investigational human monoclonal antibody against activin type II receptors for treating obesity. *J Basic Clin Physiol Pharmacol.* 2024;35:325-334.
- 1040.** Klöting N, Koch L, Wunderlich T, et al. Autocrine IGF-1 action in adipocytes controls systemic IGF-1 concentrations and growth. *Diabetes.* 2008;57:2074-2082.
- 1041.** Smith PJ, Wise LS, Berkowitz R, Wan C, Rubin CS. Insulin-like growth factor-I is an essential regulator of the differentiation of 3T3-L1 adipocytes. *J Biol Chem.* 1988;263:9402-9408.
- 1042.** Scavo LM, Karas M, Murray M, Leroith D. Insulin-like growth factor-I stimulates both cell growth and lipogenesis during differentiation of human mesenchymal stem cells into adipocytes. *J Clin Endocrinol Metab.* 2004;89:3543-3553.
- 1043.** Ricco RC, Ricco RG, Queluz MC, et al. IGF-1R mRNA expression is increased in obese children. *Growth Horm IGF Res.* 2018;39:1-5.
- 1044.** Imrie H, Viswambharan H, Haywood NJ, et al. Cixutumumab reveals a critical role for IGF-1 in adipose and hepatic tissue remodelling during the development of diet-induced obesity. *Adipocyte.* 2022;11:366-378.
- 1045.** Luk C, Bridge KI, Warmke N, et al. Paracrine role of endothelial IGF-1 receptor in depot-specific adipose tissue adaptation in male mice. *Nat Commun.* 2025;16(1):170. <https://doi.org/10.1038/s41467-024-54669-1>
- 1046.** Siddals KW, Westwood M, Gibson JM, White A. IGF-binding protein-1 inhibits IGF effects on adipocyte function: implications for insulin-like actions at the adipocyte. *J Endocrinol.* 2002;174:289-297.
- 1047.** Rahman A, Hammad MM, Al Khairi I, et al. Profiling of insulin-like growth factor binding proteins (IGFBPs) in obesity and their association with ox-LDL and hs-CRP in adolescents. *Front Endocrinol (Lausanne).* 2021;12:727004. <https://doi.org/10.3389/fendo.2021.727004>
- 1048.** Alderete TL, Byrd-Williams CE, Toledo-Corral CM, Conti DV, Weigensberg MJ, Goran MI. Relationships between IGF-1 and IGFBP-1 and adiposity in obese African-American and Latino adolescents. *Obesity (Silver Spring).* 2011;19:933-938.
- 1049.** Gancheva S, Kahl S, Herder C, et al. Metabolic surgery-induced changes of the growth hormone system relate to improved adipose tissue function. *Int J Obes (Lond).* 2023;47:505-511.
- 1050.** Pires KM, Buffalo M, Schaaf C, et al. Activation of IGF-1 receptors and Akt signaling by systemic hyperinsulinemia contributes to cardiac hypertrophy but does not regulate cardiac autophagy in obese diabetic mice. *J Mol Cell Cardiol.* 2017;113:39-50.
- 1051.** Zhu J, Li Q, Sun Y, et al. Insulin-like growth factor 1 receptor deficiency alleviates angiotensin II-induced cardiac fibrosis through the protein kinase B/extracellular signal-regulated kinase/nuclear factor-kB pathway. *J Am Heart Assoc.* 2023;12(18):e029631. <https://doi.org/10.1161/JAHA.123.029631>
- 1052.** Lee WS, Kim J. Insulin-like growth factor-1 signaling in cardiac aging. *Biochim Biophys Acta Mol Basis Dis.* 2018;1864:1931-1938.
- 1053.** D'Assante R, Arcopinto M, Rengo G, et al. Myocardial expression of somatotropic axis, adrenergic signalling, and calcium handling genes in heart failure with preserved ejection fraction and heart failure with reduced ejection fraction. *ESC Heart Fail.* 2021;8:1681-1686.
- 1054.** Abdellatif M, Trummer-Herbst V, Heberle AM, et al. Fine-tuning cardiac insulin-like growth factor 1 receptor signaling to promote health and longevity. *Circulation.* 2022;145:1853-1866.
- 1055.** Oh Y, Nagalla SR, Yamanaka Y, Kim HS, Wilson E, Rosenfeld RG. Synthesis and characterization of insulin-like growth factor-binding protein (IGFBP)-7. Recombinant human mac25 protein specifically binds IGF-I and -II. *J Biol Chem.* 1996;271:30322-30325.
- 1056.** Wu PL, Zhu JW, Zeng C, Li X, Xue Q, Yang HX. IGFBP7 enhances trophoblast invasion via IGF-1R/c-Jun signaling in unexplained recurrent spontaneous abortion. *Reproduction.* 2022;164:231-241.
- 1057.** Artico LL, Laranjeira ABA, Campos LW, et al. Physiologic IGFBP7 levels prolong IGFIR activation in acute lymphoblastic leukemia. *Blood Adv.* 2021;5:3633-3646.
- 1058.** Wang HB, Li H, Wang QG, Zhang XY, Wang SZ, Wang YX, Wang XP. Profiling of chicken adipose tissue gene expression by genome array. *BMC Genomics.* 2007;8:193. <https://doi.org/10.1186/1471-2164-8-193>
- 1059.** Liu Y, Wu M, Ling J, Cai L, et al. Serum IGFBP7 levels associate with insulin resistance and the risk of metabolic syndrome in a Chinese population. *Sci Rep.* 2015;5:10227. <https://doi.org/10.1038/srep10227>
- 1060.** Guzmán C, Bautista-Ubaldo MG, Campos-Espinosa A, Romero-Bello II, Santana-Vargas ÁD, Gutierrez-Reyes G. Insulin-like growth factor binding proteins and cellular senescence are involved in the progression of non-alcoholic fatty liver disease and fibrosis in a mouse model. *Medicina (Kaunas).* 2024;60(3):429. <https://doi.org/10.3390/medicina60030429>
- 1061.** Zhang L, Smyth D, Al-Khalaf M, et al. Insulin-like growth factor-binding protein-7 (IGFBP7) links senescence to heart failure. *Nat Cardiovasc Res.* 2022;1:1195-1214.
- 1062.** Ko T, Nomura S, Yamada S, et al. Cardiac fibroblasts regulate the development of heart failure via HtrA3-TGF-beta-IGFBP7 axis. *Nat Commun.* 2022;13(1):3275. <https://doi.org/10.1038/s41467-022-30630-y>
- 1063.** Katoh M, Nomura S, Yamada S, et al. Vaccine therapy for heart failure targeting the inflammatory cytokine IGFBP7. *Circulation.* 2024;150:374-389.
- 1064.** Siraj Y, Aprile D, Alessio N, et al. IGFBP7 is a key component of the senescence-associated secretory phenotype (SASP) that induces senescence in healthy cells by modulating the insulin, IGF, and activin A pathways. *Cell Commun Signal.* 2024;22(1):540. <https://doi.org/10.1186/s12964-024-01921-2>
- 1065.** Hage C, Bjerre M, Frystyk J, et al. Comparison of prognostic usefulness of serum insulin-like growth factor-binding protein 7 in patients with heart failure and preserved versus reduced left ventricular ejection fraction. *Am J Cardiol.* 2018;121:1558-1566.
- 1066.** Gandhi PU, Gaggin HK, Redfield MM, et al. Insulin-like growth factor-binding protein-7 as a biomarker of diastolic dysfunction and functional capacity in heart failure with preserved ejection fraction: results from the RELAX trial. *JACC Heart Fail.* 2016;4:860-869.
- 1067.** Barroso MC, Kramer F, Greene SJ, et al. Serum insulin-like growth factor-1 and its binding protein-7: potential novel biomarkers for heart failure with preserved ejection fraction. *BMC Cardiovasc Disord.* 2016;16(1):199. <https://doi.org/10.1186/s12872-016-0376-2>
- 1068.** Gandhi PU, Chow SL, Rector TS, et al. Prognostic value of insulin-like growth factor-binding protein 7 in patients with heart failure and preserved ejection fraction. *J Card Fail.* 2017;23:20-28.
- 1069.** Sanders-van Wijk S, Tromp J, Beussink Nelson L, et al. Proteomic evaluation of the comorbidity-inflammation paradigm in heart failure with preserved ejection fraction: results from the PROMIS-HFpEF Study. *Circulation.* 2020;142:2029-2044.

- 1070.** Januzzi JL Jr, Packer M, Claggett B, et al. IGFBP7 (insulin-like growth factor-binding protein-7) and neprilysin inhibition in patients with heart failure. *Circ Heart Fail.* 2018;11(10):e005133. <https://doi.org/10.1161/CIRCHERTFAILURE.118.005133>
- 1071.** Tan ESJ, Chan SP, Choi YC, et al. Regional handling and prognostic performance of circulating insulin-like growth factor binding protein-7 in heart failure. *JACC Heart Fail.* 2023;11:662-674.
- 1072.** D'Assante R, Napoli R, Salzano A, et al. Human heart shifts from IGF-1 production to utilization with chronic heart failure. *Endocrine.* 2019;65:714-716.
- 1073.** Murphy-Ullrich JE, Sage EH. Revisiting the matricellular concept. *Matrix Biol.* 2014;37:1-14.
- 1074.** Arif S, Moulin VJ. Extracellular vesicles on the move: Traversing the complex matrix of tissues. *Eur J Cell Biol.* 2023;102(4):151372. <https://doi.org/10.1016/j.ejcb.2023.151372>
- 1075.** Buras ED, Woo MS, Kaul Verma R, et al. Thrombospondin-1 promotes fibro-adipogenic stromal expansion and contractile dysfunction of the diaphragm in obesity. *JCI Insight.* 2024;9(16):e175047. <https://doi.org/10.1172/jci.insight.175047>
- 1076.** Kong P, Gonzalez-Quesada C, Li N, Cavalera M, Lee DW, Frangogiannis NG. Thrombospondin-1 regulates adiposity and metabolic dysfunction in diet-induced obesity enhancing adipose inflammation and stimulating adipocyte proliferation. *Am J Physiol Endocrinol Metab.* 2013;305:E439-E450.
- 1077.** Li Y, Tong X, Rumala C, Clemons K, Wang S. Thrombospondin1 deficiency reduces obesity-associated inflammation and improves insulin sensitivity in a diet-induced obese mouse model. *PLoS One.* 2011;6(10):e26656. <https://doi.org/10.1371/journal.pone.0026656>
- 1078.** Varma V, Yao-Borengasser A, Bodles AM, et al. Thrombospondin-1 is an adipokine associated with obesity, adipose inflammation, and insulin resistance. *Diabetes.* 2008;57:432-439.
- 1079.** Ruiz-Ojeda FJ, Méndez-Gutiérrez A, Aguilera CM, Plaza-Díaz J. Extracellular matrix remodeling of adipose tissue in obesity and metabolic diseases. *Int J Mol Sci.* 2019;20(19):4888. <https://doi.org/10.3390/ijms20194888>
- 1080.** Ramis JM, Franssen-van Hal NL, Kramer E, et al. Carboxypeptidase E and thrombospondin-1 are differently expressed in subcutaneous and visceral fat of obese subjects. *Cell Mol Life Sci.* 2002;59:1960-1971.
- 1081.** Hida K, Wada J, Zhang H, et al. Identification of genes specifically expressed in the accumulated visceral adipose tissue of OLETF rats. *J Lipid Res.* 2000;41:1615-1622.
- 1082.** Camino T, Lago-Baameiro N, Bravo SB, et al. Human obese white adipose tissue sheds depot-specific extracellular vesicles and reveals candidate biomarkers for monitoring obesity and its comorbidities. *Transl Res.* 2022;239:85-102.
- 1083.** Inoue M, Jiang Y, Barnes RH 2nd, et al. Thrombospondin 1 mediates high-fat diet-induced muscle fibrosis and insulin resistance in male mice. *Endocrinology.* 2013;154:4548-4559.
- 1084.** Maimaitiyiming H, Norman H, Zhou Q, Wang S. CD47 deficiency protects mice from diet-induced obesity and improves whole body glucose tolerance and insulin sensitivity. *Sci Rep.* 2015;5:8846. <https://doi.org/10.1038/srep08846>
- 1085.** Matsuo Y, Tanaka M, Yamakage H, et al. Thrombospondin 1 as a novel biological marker of obesity and metabolic syndrome. *Metabolism.* 2015;64:1490-1499.
- 1086.** Gutierrez LS, Gutierrez J. Thrombospondin 1 in metabolic diseases. *Front Endocrinol (Lausanne).* 2021;12:638536. <https://doi.org/10.3389/fendo.2021.638536>
- 1087.** Sharifi-Sanjani M, Shoushtari AH, Quiroz M, et al. Cardiac CD47 drives left ventricular heart failure through Ca<sup>2+</sup>-CaMKII-regulated induction of HDAC3. *J Am Heart Assoc.* 2014;3(3):e000670. <https://doi.org/10.1161/JAHA.113.000670>
- 1088.** Wang HB, Yang J, Ding JW, et al. RNAi-mediated down-regulation of CD47 protects against ischemia/reperfusion-induced myocardial damage via activation of eNOS in a rat model. *Cell Physiol Biochem.* 2016;40:e1163-1174.
- 1089.** Hao Y, Chen L, Jiang Z. CD47 antibody protects mice from doxorubicin-induced myocardial damage by suppressing cardiomyocyte apoptosis. *Exp Ther Med.* 2022;23(5):350. <https://doi.org/10.3892/etm.2022.11277>
- 1090.** Li Y, Zhao K, Zong P, et al. CD47 deficiency protects cardiomyocytes against hypoxia/reoxygenation injury by rescuing autophagic clearance. *Mol Med Rep.* 2019;19:5453-5463.
- 1091.** Li Y, Chen X, Li P, Xiao Q, Hou D, Kong X. CD47 antibody suppresses isoproterenol-induced cardiac hypertrophy through activation of autophagy. *Am J Transl Res.* 2020;12:5908-5923.
- 1092.** Zhou Y, Ng DYE, Richards AM, Wang P. microRNA-221 inhibits latent TGF-beta1 activation through targeting thrombospondin-1 to attenuate kidney failure-induced cardiac fibrosis. *Mol Ther Nucleic Acids.* 2020;22:803-814.
- 1093.** Xu L, Zhang Y, Chen J, Xu Y. Thrombospondin-1: a key protein that induces fibrosis in diabetic complications. *J Diabetes Res.* 2020;2020:8043135. <https://doi.org/10.1155/2020/8043135>
- 1094.** Tang M, Zhou F, Zhang W, et al. The role of thrombospondin-1-mediated TGF-beta1 on collagen type III synthesis induced by high glucose. *Mol Cell Biochem.* 2011;346:49-56.
- 1095.** Barallobre-Barreiro J, Radovits T, Fava M, et al. Extracellular matrix in heart failure: role of ADAMTS5 in proteoglycan remodeling. *Circulation.* 2021;144:2021-2034.
- 1096.** Isenberg JS, Qin Y, Maxhimer JB, et al. Thrombospondin-1 and CD47 regulate blood pressure and cardiac responses to vasoactive stress. *Matrix Biol.* 2009;28:110-119.
- 1097.** Rogers NM, Ghimire K, Calzada MJ, Isenberg JS. Matricellular protein thrombospondin-1 in pulmonary hypertension: multiple pathways to disease. *Cardiovasc Res.* 2017;113:858-868.
- 1098.** Gonzalez-Quesada C, Cavalera M, Biernacka A, et al. Thrombospondin-1 induction in the diabetic myocardium stabilizes the cardiac matrix in addition to promoting vascular rarefaction through angiopoietin-2 upregulation. *Circ Res.* 2013;113:1331-1344.
- 1099.** Masuda T, Muto S, Fujisawa G, et al. Heart angiotensin II-induced cardiomyocyte hypertrophy suppresses coronary angiogenesis and progresses diabetic cardiomyopathy. *Am J Physiol Heart Circ Physiol.* 2012;302(9):H1871-H1883.
- 1100.** Belmadani S, Bernal J, Wei CC, et al. A thrombospondin-1 antagonist of transforming growth factor-beta activation blocks cardiomyopathy in rats with diabetes and elevated angiotensin II. *Am J Pathol.* 2007;171:777-789.
- 1101.** Captur G, Doykov I, Chung SC, et al. Novel multiplexed plasma biomarker panel has diagnostic and prognostic potential in children with hypertrophic cardiomyopathy. *Circ Genom Precis Med.* 2024;17(3):e004448. <https://doi.org/10.1161/CRCGEN.123.004448>
- 1102.** Rogers NM, Sharifi-Sanjani M, Yao M, et al. TSP1-CD47 signaling is upregulated in clinical pulmonary hypertension and contributes to pulmonary arterial vasculopathy and dysfunction. *Cardiovasc Res.* 2017;113:15-29.
- 1103.** Martínez-Sales V, Sánchez-Lázaro I, Vila V, Almenar L, Contreras T, Reganon E. Circulating endothelial cells in patients with heart failure and left ventricular dysfunction. *Dis Markers.* 2011;31:75-82.
- 1104.** Xiang Y, Zhang Z, Xie C, et al. Serum Cat S, TSP-1, IL-11, BNP and sST2 diagnostic and prognostic value in chronic heart failure. *Altern Ther Health Med.* 2022;28:55-59.
- 1105.** Battle M, Pérez-Villa F, Lázaro A, et al. Decreased expression of thrombospondin-1 in failing hearts may favor ventricular remodeling. *Transplant Proc.* 2009;41:2231-2233.
- 1106.** Kos K, Wilding JP. SPARC: a key player in the pathologies associated with obesity and diabetes. *Nat Rev Endocrinol.* 2010;6:225-235.
- 1107.** Kos K, Wong S, Tan B, et al. Regulation of the fibrosis and angiogenesis promoter SPARC/osteonectin in human adipose tissue by weight change, leptin, insulin, and glucose. *Diabetes.* 2009;58:1780-1788.
- 1108.** Chavey C, Boucher J, Monthouél-Kartmann MN, et al. Regulation of secreted protein acidic and rich in cysteine during adipose conversion and adipose tissue hyperplasia. *Obesity (Silver Spring).* 2006;14:1890-1897.
- 1109.** Tartare-Deckert S, Chavey C, Monthouél MN, Gautier N, Van Obberghen E. The matricellular protein SPARC/osteonectin as a newly identified factor up-regulated in obesity. *J Biol Chem.* 2001;276:22231-22237.
- 1110.** Lee SH, Lee JA, Park HS, et al. Associations among SPARC mRNA expression in adipose tissue, serum SPARC concentration and metabolic parameters in Korean women. *Obesity (Silver Spring).* 2013;21:2296-2302.
- 1111.** Lee YJ, Heo YS, Park HS, Lee SH, Lee SK, Jang YJ. Serum SPARC and matrix metalloproteinase-2 and metalloproteinase-9

- concentrations after bariatric surgery in obese adults. *Obes Surg.* 2014;24:604-610.
- 1112.** Puolakkainen P, Bradshaw AD, Kyriakides TR, et al. Compromised production of extracellular matrix in mice lacking secreted protein, acidic and rich in cysteine (SPARC) leads to a reduced foreign body reaction to implanted biomaterials. *Am J Pathol.* 2003;162:627-635.
- 1113.** Ryu S, Spadaro O, Sidorov S, et al. Reduction of SPARC protects mice against NLRP3 inflammasome activation and obesity. *J Clin Invest.* 2023;133(19):e169173. <https://doi.org/10.1172/JCI169173>
- 1114.** Kelly KA, Allport JR, Yu AM, et al. SPARC is a VCAM-1 counter-ligand that mediates leukocyte transmigration. *J Leukoc Biol.* 2007;81:748-756.
- 1115.** Socha MJ, Manhiani M, Said N, Imig JD, Motamed K. Secreted protein acidic and rich in cysteine deficiency ameliorates renal inflammation and fibrosis in angiotensin hypertension. *Am J Pathol.* 2007;171:1104-1112.
- 1116.** Atorrasagasti C, Peixoto E, Aquino JB, et al. Lack of the matricellular protein SPARC (secreted protein, acidic and rich in cysteine) attenuates liver fibrogenesis in mice. *PLoS One.* 2013;8(2):e54962. <https://doi.org/10.1371/journal.pone.0054962>
- 1117.** Harris BS, Zhang Y, Card L, Rivera LB, Brekke RA, Bradshaw AD. SPARC regulates collagen interaction with cardiac fibroblast cell surfaces. *Am J Physiol Heart Circ Physiol.* 2011;301:H841-H847.
- 1118.** Bradshaw AD, Baicu CF, Rentz TJ, Van Laer AO, Bonnema DD, Zile MR. Age-dependent alterations in fibrillar collagen content and myocardial diastolic function: role of SPARC in post-synthetic procollagen processing. *Am J Physiol Heart Circ Physiol.* 2010;298:H614-H622.
- 1119.** Bradshaw AD, Baicu CF, Rentz TJ, et al. Pressure overload-induced alterations in fibrillar collagen content and myocardial diastolic function: role of secreted protein acidic and rich in cysteine (SPARC) in post-synthetic procollagen processing. *Circulation.* 2009;119:269-280.
- 1120.** Toba H, de Castro Brás LE, Baicu CF, Zile MR, Lindsey ML, Bradshaw AD. Secreted protein acidic and rich in cysteine facilitates age-related cardiac inflammation and macrophage M1 polarization. *Am J Physiol Cell Physiol.* 2015;308:C972-C982.
- 1121.** Bradshaw AD, Baicu CF, Rentz TJ, Van Laer AO, Bonnema DD, Zile MR. Age-dependent alterations in fibrillar collagen content and myocardial diastolic function: role of SPARC in post-synthetic procollagen processing. *Am J Physiol Heart Circ Physiol.* 2010;298(2):H614-H622.
- 1122.** Fan D, Takawale A, Basu R, Patel V, Lee J, Kandalam V, Wang X, Oudit GY, Kassiri Z. Differential role of TIMP2 and TIMP3 in cardiac hypertrophy, fibrosis, and diastolic dysfunction. *Cardiovasc Res.* 2014;103:268-280.
- 1123.** Li X, Zhao W, Li X, et al. The association of SPARC with hypertension and its function in endothelial-dependent relaxation. *Atherosclerosis.* 2024;388:117390. <https://doi.org/10.1016/j.atherosclerosis.2023>
- 1124.** Veith C, Vartürk-Özcan I, Wujak M, et al. SPARC, a novel regulator of vascular cell function in pulmonary hypertension. *Circulation.* 2022;145:916-933.
- 1125.** Chen X, Guo H, Li X, et al. Elevated serum extracellular vesicle-packaged SPARC in hypertension: a cross-sectional study in a middle-aged and elderly population. *J Clin Hypertens (Greenwich).* 2025;27(1):e14954. <https://doi.org/10.1111/jch.14954>
- 1126.** Ahmad F, Karim A, Khan J, Qaisar R. Circulating osteonectin predicts postural imbalance and cardiac dysfunction in heart failure. *Vasc Pharmacol.* 2025;158:107468. <https://doi.org/10.1016/j.vph.2025.107468>
- 1127.** Berezin AE, Kremzer AA. Predictive value of circulating osteonectin in patients with ischemic symptomatic chronic heart failure. *Biomed J.* 2015;38:523-530.
- 1128.** Riley HJ, Kelly RR, Van Laer AO, et al. SPARC production by bone marrow-derived cells contributes to myocardial fibrosis in pressure overload. *Am J Physiol Heart Circ Physiol.* 2021;320:H604-H612.
- 1129.** Nabi IR, Shankar J, Dennis JW. The galectin lattice at a glance. *J Cell Sci.* 2015;128:2213-2219.
- 1130.** Rienks M, Papageorgiou AP. Novel regulators of cardiac inflammation: Matricellular proteins expand their repertoire. *J Mol Cell Cardiol.* 2016;91:172-178.
- 1131.** Baek JH, Kim SJ, Kang HG, et al. Galectin-3 activates PPARgamma and supports white adipose tissue formation and high-fat diet-induced obesity. *Endocrinology.* 2015;156:147-156.
- 1132.** Krautbauer S, Eisinger K, Hader Y, Buechler C. Free fatty acids and IL-6 induce adipocyte galectin-3 which is increased in white and brown adipose tissues of obese mice. *Cytokine.* 2014;69:263-271.
- 1133.** Kiwaki K, Novak CM, Hsu DK, Liu FT, Levine JA. Galectin-3 stimulates preadipocyte proliferation and is up-regulated in growing adipose tissue. *Obesity (Silver Spring).* 2007;15:32-39.
- 1134.** Martínez-Martínez E, Calvier L, Rossignol P, et al. Galectin-3 inhibition prevents adipose tissue remodelling in obesity. *Int J Obes (Lond).* 2016;40:1034-1038.
- 1135.** Comeglio P, Guarneri G, Filippi S, et al. The galectin-3 inhibitor selvagaltin reduces liver inflammation and fibrosis in a high fat diet rabbit model of metabolic-associated steatohepatitis. *Front Pharmacol.* 2024;15:1430109. <https://doi.org/10.3389/fphar.2024.1430109>
- 1136.** Du W, Piek A, Schouten EM, et al. Plasma levels of heart failure biomarkers are primarily a reflection of extracardiac production. *Theranostics.* 2018;8:4155-4169.
- 1137.** Jiménez-González S, Delgado-Valero B, Islas F, et al. The detrimental role of galectin-3 and endoplasmic reticulum stress in the cardiac consequences of myocardial ischemia in the context of obesity. *FASEB J.* 2024;38(14):e23818. <https://doi.org/10.1096/fj.202400747R>
- 1138.** Fischer J, Völzke H, Kassubek J, et al. Associations of a panel of adipokines with fat deposits and metabolic phenotypes in a general population. *Obesity (Silver Spring).* 2020;28:1550-1559.
- 1139.** Dencker M, Arvidsson D, Karlsson MK, Wollmer P, Andersen LB, Thorsson O. Galectin-3 levels relate in children to total body fat, abdominal fat, body fat distribution, and cardiac size. *Eur J Pediatr.* 2018;177:461-467.
- 1140.** Pang J, Nguyen VT, Rhodes DH, Sullivan ME, Braunschweig C, Fantuzzi G. Relationship of galectin-3 with obesity, IL-6, and CRP in women. *J Endocrinol Invest.* 2016;39:1435-1443.
- 1141.** Weigert J, Neumeier M, Wanninger J, et al. Serum galectin-3 is elevated in obesity and negatively correlates with glycosylated hemoglobin in type 2 diabetes. *J Clin Endocrinol Metab.* 2010;95:1404-1411.
- 1142.** Naylor M, Wang N, Larson MG, Vasan RS, Levy D, Ho JE. Circulating galectin-3 is associated with cardiometabolic disease in the community. *J Am Heart Assoc.* 2015;5(1):e002347. <https://doi.org/10.1161/JAHA.115.002347>
- 1143.** Florido R, Kwak L, Echouffo-Tcheugui JB, et al. Obesity, galectin-3, and incident heart failure: the ARIC study. *J Am Heart Assoc.* 2022;11(9):e023238. <https://doi.org/10.1161/JAHA.121.023238>
- 1144.** Padgett CA, Bátori RK, Speese AC, et al. Galectin-3 mediates vascular dysfunction in obesity by regulating NADPH oxidase 1. *Arterioscler Thromb Vasc Biol.* 2023;43:e381-e395.
- 1145.** Marín-Royo G, Gallardo I, Martínez-Martínez E, et al. Inhibition of galectin-3 ameliorates the consequences of cardiac lipotoxicity in a rat model of diet-induced obesity. *Dis Model Mech.* 2018;11(2):dmm032086.
- 1146.** Gonçalves N, Silva AF, Rodrigues PG, et al. Early cardiac changes induced by a hypercaloric Western-type diet in "subclinical" obesity. *Am J Physiol Heart Circ Physiol.* 2016;310:H655-H666.
- 1147.** Martínez-Martínez E, Jurado-López R, Valero-Muñoz M, et al. Leptin induces cardiac fibrosis through galectin-3, mTOR and oxidative stress: potential role in obesity. *J Hypertens.* 2014;32:1104-1114.
- 1148.** Sharma UC, Pokharel S, van Brakel TJ, et al. Galectin-3 marks activated macrophages in failure-prone hypertrophied hearts and contributes to cardiac dysfunction. *Circulation.* 2004;110:3121-3128.
- 1149.** Vergaro G, Prud'homme M, Fazal L, et al. Inhibition of galectin-3 pathway prevents isoproterenol-induced left ventricular dysfunction and fibrosis in mice. *Hypertension.* 2016;67:606-612.
- 1150.** Ho JE, Liu C, Lyass A, et al. Galectin-3, a marker of cardiac fibrosis, predicts incident heart failure in the community. *J Am Coll Cardiol.* 2012;60:1249-1256.
- 1151.** Lebedev DA, Lyasnikova EA, Vasilyeva EY, Likhonosov NP, Sitnikova MY, Babenko AY. Association between markers of fibrosis and heart failure incidence in patients with type 2 diabetes mellitus. *J Diabetes Res.* 2021;2021:9589185. <https://doi.org/10.1155/2021/9589185>

- 1152.** Gopal DM, Ayalon N, Wang YC, et al. Galectin-3 is associated with stage B metabolic heart disease and pulmonary hypertension in young obese patients. *J Am Heart Assoc.* 2019;8(7):e011100. <https://doi.org/10.1161/JAHA.118.011100>
- 1153.** Redondo A, Paradela-Dobarro B, Moscoso I, et al. Galectin-3 and soluble RAGE as new biomarkers of post-infarction cardiac remodeling. *J Mol Med (Berl).* 2021;99:943-953.
- 1154.** Lok DJ, Lok SI, Bruggink-André de la Porte PW, et al. Galectin-3 is an independent marker for ventricular remodeling and mortality in patients with chronic heart failure. *Clin Res Cardiol.* 2013;102:103-110.
- 1155.** Lok DJ, Van Der Meer P, de la Porte PW, et al. Prognostic value of galectin-3, a novel marker of fibrosis, in patients with chronic heart failure: data from the DEAL-HF study. *Clin Res Cardiol.* 2010;99:323-328.
- 1156.** Shi Y, Dong G, Liu J, et al. Clinical implications of plasma galectin-3 in heart failure with preserved ejection fraction: a meta-analysis. *Front Cardiovasc Med.* 2022;9:854501. <https://doi.org/10.3389/fcvm.2022.854501>
- 1157.** Jiang J, Yang B, Sun Y, Jin J, Zhao Z, Chen S. Diagnostic value of serum concentration of galectin-3 in patients with heart failure with preserved ejection fraction. *Front Cardiovasc Med.* 2022;8:829151. <https://doi.org/10.3389/fcvm.2021.829151>
- 1158.** de Boer RA, Lok DJ, Jaarsma T, et al. Predictive value of plasma galectin-3 levels in heart failure with reduced and preserved ejection fraction. *Ann Med.* 2011;43:60-68.
- 1159.** Li P, Wang L, Yang F, Yu H, Xiao FK. Association of ST2, galectin-3, and NT- proBNP in elderly hypertensive patients and heart failure with a preserved ejection fraction. *Curr Vasc Pharmacol.* Published online January 24, 2025. <https://doi.org/10.2174/0115701611315697241230075727>
- 1160.** Lepojärvi ES, Piira OP, Pääkkö E, et al. Serum PINP, PIIINP, galectin-3, and ST2 as surrogates of myocardial fibrosis and echocardiographic left ventricular diastolic filling properties. *Front Physiol.* 2015;6:200. <https://doi.org/10.3389/fphys.2015.00200>
- 1161.** Vergaro G, Del Franco A, Giannoni A, et al. Galectin-3 and myocardial fibrosis in nonischemic dilated cardiomyopathy. *Int J Cardiol.* 2015;184:96-100.
- 1162.** Milting H, Ellinghaus P, Seewald M, et al. Plasma biomarkers of myocardial fibrosis and remodeling in terminal heart failure patients supported by mechanical circulatory support devices. *J Heart Lung Transplant.* 2008;27:589-596.
- 1163.** Grupper A, Nativi-Nicolau J, Maleszewski JJ, et al. Circulating galectin-3 levels are persistently elevated after heart transplantation and are associated with renal dysfunction. *JACC Heart Fail.* 2016;4:847-856.
- 1164.** Murahovschi V, Pivovarova O, Ilkavets I, et al. WISPI is a novel adipokine linked to inflammation in obesity. *Diabetes.* 2015;64:856-866.
- 1165.** Hörbelt T, Tacke C, Markova M, et al. The novel adipokine WISPI associates with insulin resistance and impairs insulin action in human myotubes and mouse hepatocytes. *Diabetologia.* 2018;61:2054-2065.
- 1166.** Lancha A, Rodríguez A, Catalán V, et al. Osteopontin deletion prevents the development of obesity and hepatic steatosis via impaired adipose tissue matrix remodeling and reduced inflammation and fibrosis in adipose tissue and liver in mice. *PLoS One.* 2014;9(5):e98398. <https://doi.org/10.1371/journal.pone.0098398>
- 1167.** Catalán V, Gómez-Ambrosi J, Rodríguez A, et al. Increased tenascin C and Toll-like receptor 4 levels in visceral adipose tissue as a link between inflammation and extracellular matrix remodeling in obesity. *J Clin Endocrinol Metab.* 2012;97:E1880-E1889.
- 1168.** Zeyda M, Gollinger K, Todoric J, et al. Osteopontin is an activator of human adipose tissue macrophages and directly affects adipocyte function. *Endocrinology.* 2011;152:2219-2227.
- 1169.** Ferrand N, Béreziat V, Moldes M, Zaoui M, Larsen AK, Sabbah M. WISPI/CCN4 inhibits adipocyte differentiation through repression of PPARgamma activity. *Sci Rep.* 2017;7(1):1749. <https://doi.org/10.1038/s41598-017-01866-2>
- 1170.** Leitner L, Schuch K, Jürets A, et al. Immunological blockade of adipocyte inflammation caused by increased matrix metalloproteinase-cleaved osteopontin in obesity. *Obesity (Silver Spring).* 2015;23:779-785.
- 1171.** Fukusada S, Shimura T, Natsume M, et al. Osteopontin secreted from obese adipocytes enhances angiogenesis and promotes progression of pancreatic ductal adenocarcinoma in obesity. *Cell Oncol (Dordr).* 2024;47:229-244.
- 1172.** Klimontov VV, Bulumbavaeva DM, Fazullina ON, et al. Circulating Wnt1-inducible signaling pathway protein-1 (WISP1/CCN4) is a novel biomarker of adiposity in subjects with type 2 diabetes. *J Cell Commun Signal.* 2020;14:101-109.
- 1173.** Lorenzo PM, Izquierdo AG, Sajoux I, et al. Obesity-related osteopontin protein and methylation blood levels are differentially modulated by a very low-calorie ketogenic diet or bariatric surgery. *Clin Nutr.* 2025;47:40-49.
- 1174.** Wang C, He M, Peng J, et al. Increased plasma osteopontin levels are associated with nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus. *Cytokine.* 2020;125:154837. <https://doi.org/10.1016/j.cyto.2019.154837>
- 1175.** Sato K, Hikita H, Shigekawa M, et al. The serum tenascin C level is a marker of metabolic disorder-related inflammation affecting pancreatic cancer prognosis. *Sci Rep.* 2024;14(1):12028. <https://doi.org/10.1038/s41598-024-62498-x>
- 1176.** Li Z, Williams H, Jackson ML, Johnson JL, George SJ. WISPI regulates cardiac fibrosis by promoting cardiac fibroblasts' activation and collagen processing. *Cells.* 2024;13(11):989. <https://doi.org/10.3390/cells13110989>
- 1177.** Colston JT, de la Rosa SD, Koehler M, et al. Wnt-induced secreted protein-1 is a prohypertrophic and profibrotic growth factor. *Am J Physiol Heart Circ Physiol.* 2007;293:H1839-H1846.
- 1178.** Lin R, Wu S, Zhu D, Qin M, Liu X. Osteopontin induces atrial fibrosis by activating Akt/GSK-3beta/beta-catenin pathway and suppressing autophagy. *Life Sci.* 2020;245:117328. <https://doi.org/10.1016/j.lfs.2020.117328>
- 1179.** Imanaka-Yoshida K, Tawara I, Yoshida T. Tenascin-C in cardiac disease: a sophisticated controller of inflammation, repair, and fibrosis. *Am J Physiol Cell Physiol.* 2020;319:C781-C796.
- 1180.** Shimojo N, Hashizume R, Kanayama K, et al. Tenascin-C may accelerate cardiac fibrosis by activating macrophages via the integrin alphaV-beta3/nuclear factor-kappaB/interleukin-6 axis. *Hypertension.* 2015;66:757-766.
- 1181.** Podesser BK, Kreibich M, Dzilic E, et al. Tenascin-C promotes chronic pressure overload-induced cardiac dysfunction, hypertrophy and myocardial fibrosis. *J Hypertens.* 2018;36:847-856.
- 1182.** Renault MA, Robbesyn F, Réant P, et al. Osteopontin expression in cardiomyocytes induces dilated cardiomyopathy. *Circ Heart Fail.* 2010;3:431-439.
- 1183.** Luna-Luna M, Criales-Vera S, Medina-Leyte D, et al. Bone morphogenetic protein-2 and osteopontin gene expression in epicardial adipose tissue from patients with coronary artery disease is associated with the presence of calcified atherosclerotic plaques. *Diabetes Metab Syndr Obes.* 2020;13:1943-1951.
- 1184.** Terasaki F, Okamoto H, Onishi K, et al. Higher serum tenascin-C levels reflect the severity of heart failure, left ventricular dysfunction and remodeling in patients with dilated cardiomyopathy. *Circ J.* 2007;71:327-330.
- 1185.** Aso N, Tamura A, Nasu M. Circulating tenascin-C levels in patients with idiopathic dilated cardiomyopathy. *Am J Cardiol.* 2004;94:1468-1470.
- 1186.** Kanagala P, Arnold JR, Khan JN, et al. Plasma Tenascin-C: a prognostic biomarker in heart failure with preserved ejection fraction. *Biomarkers.* 2020;25:556-565.
- 1187.** Kitaoka H, Kubo T, Baba Y, et al. Serum tenascin-C levels as a prognostic biomarker of heart failure events in patients with hypertrophic cardiomyopathy. *J Cardiol.* 2012;59:209-214.
- 1188.** Sato A, Aonuma K, Imanaka-Yoshida K, et al. Serum tenascin-C might be a novel predictor of left ventricular remodeling and prognosis after acute myocardial infarction. *J Am Coll Cardiol.* 2006;47:2319-2325.
- 1189.** Kanagala P, Arnold JR, Singh A, et al. Characterizing heart failure with preserved and reduced ejection fraction: An imaging and plasma biomarker approach. *PLoS One.* 2020;15(4):e0232280. <https://doi.org/10.1371/journal.pone.0232280>
- 1190.** Krebber MM, van Dijk CGM, Vernooy RWM, et al. Matrix metalloproteinases and tissue inhibitors of metalloproteinases in extracellular matrix remodeling during left ventricular diastolic dysfunction and heart failure with preserved ejection fraction: a systematic review and meta-

- analysis. *Int J Mol Sci.* 2020;21(18):6742. <https://doi.org/10.3390/ijms21186742>
- 1191.** Molière S, Jaulin A, Tomasetto CL, Dali-Youcef N. Roles of matrix metalloproteinases and their natural inhibitors in metabolism: insights into health and disease. *Int J Mol Sci.* 2023;24(13):10649. <https://doi.org/10.3390/ijms241310649>
- 1192.** Jung KK, Liu XW, Chirco R, Friedman R, Kim HR. Identification of CD63 as a tissue inhibitor of metalloproteinase-1 interacting cell surface protein. *EMBO J.* 2006;25:3934-3942.
- 1193.** Maquoi E, Munaut C, Colige A, Collen D, Lijnen HR. Modulation of adipose tissue expression of murine matrix metalloproteinases and their tissue inhibitors with obesity. *Diabetes.* 2002;51:1093-1101.
- 1194.** Chavey C, Mari B, Monthouel MN, et al. Matrix metalloproteinases are differentially expressed in adipose tissue during obesity and modulate adipocyte differentiation. *J Biol Chem.* 2003;278:11888-11896.
- 1195.** Lijnen HR, Demeulemeester D, Van Hoef B, Collen D, Maquoi E. Deficiency of tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) impairs nutritionally induced obesity in mice. *Thromb Haemost.* 2003;89:249-255.
- 1196.** Fjære E, Andersen C, Myrmeal LS, et al. Tissue inhibitor of matrix metalloproteinase-1 is required for high-fat diet-induced glucose intolerance and hepatic steatosis in mice. *PLoS One.* 2015;10(7):e0132910. <https://doi.org/10.1371/journal.pone.0132910>
- 1197.** Meissburger B, Stachorski L, Röder E, Rudofsky G, Wolfrum C. Tissue inhibitor of matrix metalloproteinase 1 (TIMP1) controls adipogenesis in obesity in mice and in humans. *Diaabetologia.* 2011;54:1468-1479.
- 1198.** Heymans S, Schroen B, Vermeersch P, et al. Increased cardiac expression of tissue inhibitor of metalloproteinase-1 and tissue inhibitor of metalloproteinase-2 is related to cardiac fibrosis and dysfunction in the chronic pressure-overloaded human heart. *Circulation.* 2005;112:1136-1144.
- 1199.** Takawale A, Zhang P, Patel VB, Wang X, Oudit G, Kassiri Z. Tissue inhibitor of matrix metalloproteinase-1 promotes myocardial fibrosis by mediating CD63-ontegrin beta1 interaction. *Hypertension.* 2017;69:1092-1103.
- 1200.** Neff LS, Zhang Y, Van Laer AO, et al. Mechanisms that limit regression of myocardial fibrosis following removal of left ventricular pressure overload. *Am J Physiol Heart Circ Physiol.* 2022;323:H165-H175.
- 1201.** Kremastiatis G, Handa I, Jackson C, George S, Johnson J. Disparate effects of MMP and TIMP modulation on coronary atherosclerosis and associated myocardial fibrosis. *Sci Rep.* 2021;11(1):23081. <https://doi.org/10.1038/s41598-021-02508-4>
- 1202.** Creemers EE, Davis JN, Parkhurst AM, et al. Deficiency of TIMP-1 exacerbates LV remodeling after myocardial infarction in mice. *Am J Physiol Heart Circ Physiol.* 2003;284:H364-H371.
- 1203.** Mukherjee R, Parkhurst AM, Mingoia JT, et al. Myocardial remodeling after discrete radiofrequency injury: effects of tissue inhibitor of matrix metalloproteinase-1 gene deletion. *Am J Physiol Heart Circ Physiol.* 2004;286:H1242-H1247.
- 1204.** Ikonomidou JS, Hendrick JW, Parkhurst AM, et al. Accelerated LV remodeling after myocardial infarction in TIMP-1-deficient mice: effects of exogenous MMP inhibition. *Am J Physiol Heart Circ Physiol.* 2005;288:H149-H158.
- 1205.** Hung CS, Chou CH, Liao CW, et al. Aldosterone induces tissue inhibitor of metalloproteinases-1 expression and further contributes to collagen accumulation: from clinical to bench studies. *Hypertension.* 2016;67:1309-1320.
- 1206.** Ranta J, Havulinna AS, Tervahartiala T, et al. Serum MMP-8 and TIMP-1 concentrations in a population-based cohort: effects of age, gender, and health status. *Front Dent Med.* 2024;5:1315596. <https://doi.org/10.3389/fdmed.2024.1315596>
- 1207.** Erman H, Gelisgen R, Cengiz M, Tabak O, Erdenen F, Uzun H. The association of vascular endothelial growth factor, metalloproteinases and their tissue inhibitors with cardiovascular risk factors in the metabolic syndrome. *Eur Rev Med Pharmacol Sci.* 2016;20:1015-1022.
- 1208.** Abdelaziz R, Elbasel M, Esmat S, Essam K, Abdelaaty S. Tissue inhibitors of metalloproteinase-1 and 2 and obesity related non-alcoholic fatty liver disease: is there a relationship. *Digestion.* 2015;92:130-137.
- 1209.** Karason K, Girerd N, Andersson-Assansson J, et al. Heart failure in obesity: insights from proteomics in patients treated with or without weight-loss surgery. *Int J Obes (Lond).* 2022;46:2088-2094.
- 1210.** Kostov K, Blazhev A. Changes in serum levels of matrix metalloproteinase-1 and tissue inhibitor of metalloproteinases-1 in patients with essential hypertension. *Bioengineering (Basel).* 2022;9(3):119. <https://doi.org/10.3390/bioengineering9030119>
- 1211.** Hansson J, Lind L, Hultre J, Sundström J. Relations of serum MMP-9 and TIMP-1 levels to left ventricular measures and cardiovascular risk factors: a population-based study. *Eur J Cardiovasc Prev Rehabil.* 2009;16:297-303.
- 1212.** Bäz L, Dannberg G, Grün K, et al. Serum biomarkers of cardiovascular remodelling reflect extra-valvular cardiac damage in patients with severe aortic stenosis. *Int J Mol Sci.* 2020;21(11):4174. <https://doi.org/10.3390/ijms21114174>
- 1213.** Lindsay MM, Maxwell P, Dunn FG. TIMP-1: a marker of left ventricular diastolic dysfunction and fibrosis in hypertension. *Hypertension.* 2002;40:136-141.
- 1214.** Zile MR, Desantis SM, Baicu CF, et al. Plasma biomarkers that reflect determinants of matrix composition identify the presence of left ventricular hypertrophy and diastolic heart failure. *Circ Heart Fail.* 2011;4:246-256.
- 1215.** Patel-Murray NL, Zhang L, Claggett BL, et al. Aptamer proteomics for biomarker discovery in heart failure with preserved ejection fraction: the PARAGON-HF Proteomic Substudy. *J Am Heart Assoc.* 2024;13(13):e033544. <https://doi.org/10.1161/JAHA.123.033544>
- 1216.** Mathivanan S, Ji H, Simpson RJ. Exosomes: extracellular organelles important in intercellular communication. *J Proteomics.* 2010;73:1907-1920.
- 1217.** Rao VS, Gu Q, Tschentke S, Lin K, et al. Extravesicular TIMP-1 is a non-invasive independent prognostic marker and potential therapeutic target in colorectal liver metastases. *Oncogene.* 2022;41:1809-1820.
- 1218.** Koeck ES, Iordanskia T, Sevilla S, et al. Adipocyte exosomes induce transforming growth factor beta pathway dysregulation in hepatocytes: a novel paradigm for obesity-related liver disease. *J Surg Res.* 2014;192:268-275.
- 1219.** Zheng J, Zhuang H, Zhang T, et al. Cathepsin S inhibitor reduces high-fat-induced adipogenesis, inflammatory infiltration, and hepatic lipid accumulation in obese mice. *Ann Transl Med.* 2022;10(21):1172. <https://doi.org/10.21037/atm-22-5145>
- 1220.** Taleb S, Cancello R, Clément K, Lacasa D. Cathepsin S promotes human preadipocyte differentiation: possible involvement of fibronectin degradation. *Endocrinology.* 2006;147:4950-4959.
- 1221.** Naour N, Rouault C, Fellahi S, et al. Cathepsins in human obesity: changes in energy balance predominantly affect cathepsin S in adipose tissue and in circulation. *J Clin Endocrinol Metab.* 2010;95:1861-1868.
- 1222.** Taleb S, Lacasa D, Bastard JP, et al. Cathepsin S, a novel biomarker of adiposity: relevance to atherogenesis. *FASEB J.* 2005;19:1540-1542.
- 1223.** Chen L, Lu B, Yang Y, et al. Elevated circulating cathepsin S levels are associated with metabolic syndrome in overweight and obese individuals. *Diabetes Metab Res Rev.* 2019;35(3):e3117. <https://doi.org/10.1002/dmrr.3117>
- 1224.** Taleb S, Cancello R, Poitou C, et al. Weight loss reduces adipose tissue cathepsin S and its circulating levels in morbidly obese women. *J Clin Endocrinol Metab.* 2006;91:1042-1047.
- 1225.** Reynolds TH, Ives SJ. Life without proteinase activated receptor 2 (PAR2) alters body composition and glucose tolerance in mice. *Nutrients.* 2022;14(19):4096. <https://doi.org/10.3390/nu14194096>
- 1226.** Lim J, Iyer A, Liu L, et al. Diet-induced obesity, adipose inflammation, and metabolic dysfunction correlating with PAR2 expression are attenuated by PAR2 antagonism. *FASEB J.* 2013;27:4757-4767.
- 1227.** Li M, Yang X, Zhang Y, et al. Activation of protease-activated receptor-2 is associated with increased expression of inflammatory factors in the adipose tissues of obese mice. *Mol Med Rep.* 2015;12:6227-6234.
- 1228.** Park YJ, Lee B, Kim DH, et al. PAR2 deficiency induces mitochondrial ROS generation and dysfunctions, leading to the inhibition of adipocyte differentiation. *Oxid Med Cell Longev.* 2021;2021:6683033. <https://doi.org/10.1155/2021/6683033>

- 1229.** Cheng XW, Obata K, Kuzuya M, et al. Elastolytic cathepsin induction/activation system exists in myocardium and is upregulated in hypertensive heart failure. *Hypertension*. 2006;48:979-987.
- 1230.** Samouillan V, Revuelta-López E, Durand J, et al. Cardiomyocyte intracellular cholesteryl ester accumulation promotes tropoelastin physical alteration and degradation: Role of LRP1 and cathepsin S. *Int J Biochem Cell Biol*. 2014;55:209-219.
- 1231.** Pan L, Li Y, Jia L, et al. Cathepsin S deficiency results in abnormal accumulation of autophagosomes in macrophages and enhances Ang II-induced cardiac inflammation. *PLoS One*. 2012;7(4):e35315. <https://doi.org/10.1371/journal.pone.0035315>
- 1232.** Sayed S, Faruq O, Preya UH, Kim JT. Cathepsin S knockdown suppresses endothelial inflammation, angiogenesis, and complement protein activity under hyperglycemic conditions in vitro by inhibiting NF- $\kappa$ B signaling. *Int J Mol Sci*. 2023;24(6):5428. <https://doi.org/10.3390/ijms24065428>
- 1233.** Antoniak S, Sparkenbaugh EM, Tencati M, Rojas M, Mackman N, Pawlinski R. Protease activated receptor-2 contributes to heart failure. *PLoS One*. 2013;8(11):e81733. <https://doi.org/10.1371/journal.pone.0081733>
- 1234.** Meyer Zu Schwabedissen A, Vergara-Juarez S, et al. Protease-activated receptor 2 deficient mice develop less angiotensin II induced left ventricular hypertrophy but more cardiac fibrosis. *PLoS One*. 2024;19(12):e0310095. <https://doi.org/10.1371/journal.pone.0310095>
- 1235.** Wang M, Ma Y, Zhang T, Gao L, Zhang S, Chen Q. Proteinase-activated receptor 2 deficiency is a protective factor against cardiomyocyte apoptosis during myocardial ischemia/reperfusion injury. *Mol Med Rep*. 2019;20:3764-3772.
- 1236.** Narita M, Hanada K, Kawamura Y, et al. Rivaroxaban attenuates cardiac hypertrophy by inhibiting protease-activated receptor-2 signaling in renin-overexpressing hypertensive mice. *Hypertens Res*. 2021;44:1261-1273.
- 1237.** Fernlund E, Gyllenhammar T, Jablonowski R, et al. Serum biomarkers of myocardial remodeling and coronary dysfunction in early stages of hypertrophic cardiomyopathy in the young. *Pediatr Cardiol*. 2017;38:853-863.
- 1238.** Russell-Hallinan A, Glezeva N, McDonald I, et al. Elevated levels of cathepsin S are associated with inflammation and pathological remodelling in heart failure with preserved ejection fraction. *Heart*. 2019;105(Suppl 7):A53. <https://doi.org/10.1136/heartjnl-2019-ICS.65>
- 1239.** Liu S, Iskandar R, Chen W, et al. Soluble glycoprotein 130 and heat shock protein 27 as novel candidate biomarkers of chronic heart failure with preserved ejection fraction. *Heart Lung Circ*. 2016;25:1000-1006.
- 1240.** Friebel J, Weithauer A, Witkowski M, et al. Protease-activated receptor 2 deficiency mediates cardiac fibrosis and diastolic dysfunction. *Eur Heart J*. 2019;40:3318-3332.
- 1241.** Lee HS, Park JH, Kang JH, Kawada T, Yu R, Han IS. Chemokine and chemokine receptor gene expression in the mesenteric adipose tissue of KKAY mice. *Cytokine*. 2009;46:160-165.
- 1242.** Dahlman I, Kaaman M, Olsson T, et al. A unique role of monocyte chemoattractant protein 1 among chemokines in adipose tissue of obese subjects. *J Clin Endocrinol Metab*. 2005;90:5834-5840.
- 1243.** Chan PC, Hung LM, Huang JP, et al. Augmented CCL5/CCR5 signaling in brown adipose tissue inhibits adaptive thermogenesis and worsens insulin resistance in obesity. *Clin Sci (Lond)*. 2022;136:121-137.
- 1244.** Chan PC, Liao MT, Lu CH, Tian YF, Hsieh PS. Targeting inhibition of CCR5 on improving obesity-associated insulin resistance and impairment of pancreatic insulin secretion in high fat-fed rodent models. *Eur J Pharmacol*. 2021;891:173703. <https://doi.org/10.1016/j.ejphar.2020.173703>
- 1245.** Lee SJ, Kang JS, Kim HM, et al. CCR2 knockout ameliorates obesity-induced kidney injury through inhibiting oxidative stress and ER stress. *PLoS One*. 2019;14(9):e0222352. <https://doi.org/10.1371/journal.pone.0222352>
- 1246.** Li X, Su Y, Xu Y, et al. Adipocyte-specific Hnrnpal knockout aggravates obesity-induced metabolic dysfunction via upregulation of CCL2. *Diabetes*. 2024;73:713-727.
- 1247.** Ferrari-Cestari M, Okano S, Patel PJ, et al. Serum CC-chemokine ligand 2 is associated with visceral adiposity but not fibrosis in patients with non-alcoholic fatty liver disease. *Dig Dis*. 2023;41:439-446.
- 1248.** Dommel S, Blüher M. Does C-C motif chemokine ligand 2 (CCL2) link obesity to a pro-inflammatory state? *Int J Mol Sci*. 2021;22(3):1500. <https://doi.org/10.3390/ijms22031500>
- 1249.** Fu CP, Sheu WH, Lee IT, et al. Weight loss reduces serum monocyte chemoattractant protein-1 concentrations in association with improvements in renal injury in obese men with metabolic syndrome. *Clin Chem Lab Med*. 2015;53:623-629.
- 1250.** Tamura Y, Sugimoto M, Murayama T, et al. C-C chemokine receptor 2 inhibitor improves diet-induced development of insulin resistance and hepatic steatosis in mice. *J Atheroscler Thromb*. 2010;17:219-228.
- 1251.** Huh JH, Kim HM, Lee ES, et al. Dual CCR2/5 antagonist attenuates obesity-induced insulin resistance by regulating macrophage recruitment and M1/M2 status. *Obesity (Silver Spring)*. 2018;26:378-386.
- 1252.** O'Brien PD, Hinder LM, Parlee SD, et al. Dual CCR2/CCR5 antagonist treatment attenuates adipose inflammation, but not microvascular complications in ob/ob mice. *Diabetes Obes Metab*. 2017;19:1468-1472.
- 1253.** Madani R, Karastergiou K, Ogston NC, et al. RANTES release by human adipose tissue in vivo and evidence for depot-specific differences. *Am J Physiol Endocrinol Metab*. 2009;296:E1262-E1268.
- 1254.** Malavazos AE, Ermetici F, Coman C, Corsi MM, Morricone L, Ambrosi B. Influence of epicardial adipose tissue and adipocytokine levels on cardiac abnormalities in visceral obesity. *Int J Cardiol*. 2007;121:132-134.
- 1255.** Mazurek T, Zhang L, Zalewski A, et al. Human epicardial adipose tissue is a source of inflammatory mediators. *Circulation*. 2003;108:2460-2466.
- 1256.** Niu J, Azfer A, Kolattukudy PE. Monocyte-specific Bcl-2 expression attenuates inflammation and heart failure in monocyte chemoattractant protein-1 (MCP-1)-induced cardiomyopathy. *Cardiovasc Res*. 2006;71:139-148.
- 1257.** Younce CW, Niu J, Ayala J, et al. Exendin-4 improves cardiac function in mice overexpressing monocyte chemoattractant protein-1 in cardiomyocytes. *J Mol Cell Cardiol*. 2014;76:172-176.
- 1258.** Wang X, Li W, Yue Q, et al. C-C chemokine receptor 5 signaling contributes to cardiac remodeling and dysfunction under pressure overload. *Mol Med Rep*. 2021;23(1):49. <https://doi.org/10.3892/mmr.2020.11687>
- 1259.** Damås JK, Eiken HG, Oie E, et al. Myocardial expression of CC- and CXC-chemokines and their receptors in human end-stage heart failure. *Cardiovasc Res*. 2000;47:778-787.
- 1260.** Boyle AJ, Yeghiazarians Y, Shih H, et al. Myocardial production and release of MCP-1 and SDF-1 following myocardial infarction: differences between mice and man. *J Transl Med*. 2011;9:150. <https://doi.org/10.1186/1479-5876-9-150>
- 1261.** Collier P, Watson CJ, Voon V, et al. Can emerging biomarkers of myocardial remodelling identify asymptomatic hypertensive patients at risk for diastolic dysfunction and diastolic heart failure? *Eur J Heart Fail*. 2011;13:1087-1095.
- 1262.** Aukrust P, Ueland T, Müller F, et al. Elevated circulating levels of C-C chemokines in patients with congestive heart failure. *Circulation*. 1998;97:1136-1143.
- 1263.** Höhnsinner PJ, Rychli K, Zorn G, et al. Macrophage-modulating cytokines predict adverse outcome in heart failure. *Thromb Haemost*. 2010;103:435-441.
- 1264.** Behr TM, Wang X, Aiyar N, et al. Monocyte chemoattractant protein-1 is upregulated in rats with volume-overload congestive heart failure. *Circulation*. 2000;102:1315-1322.
- 1265.** Xu S, Zhang G, Tan X, et al. Plasma Olink proteomics reveals novel biomarkers for prediction and diagnosis in dilated cardiomyopathy with heart failure. *J Proteome Res*. 2024;23:4139-4150.
- 1266.** Sundaram S, Yan L. Adipose-specific monocyte chemotactic protein-1 deficiency reduces pulmonary metastasis of Lewis lung carcinoma in mice. *Anticancer Res*. 2019;39:1729-1738.
- 1267.** Zhang W, Chen Z, Qiao S, et al. The effects of extracellular vesicles derived from Kruppel-Like Factor 2 overexpressing endothelial cells on the regulation of cardiac inflammation in the dilated cardiomyopathy. *J Nanobiotechnology*. 2022;20(1):76. <https://doi.org/10.1186/s12951-022-01284-1>

- 1268.** Kuwahara F, Kai H, Tokuda K, et al. Hypertensive myocardial fibrosis and diastolic dysfunction: another model of inflammation? *Hypertension*. 2004;43:739-745.
- 1269.** Costa RM, Cerqueira DM, Bruder-Nascimento A, et al. Role of the CCL5 and its receptor, CCR5, in the genesis of aldosterone-induced hypertension, vascular dysfunction, and end-organ damage. *Hypertension*. 2024;81:776-786.
- 1270.** Singh S, Bruder-Nascimento A, Belin de Chantemele EJ, Bruder-Nascimento T. CCR5 antagonist treatment inhibits vascular injury by regulating NADPH oxidase 1. *Biochem Pharmacol*. 2022;195:114859. <https://doi.org/10.1016/j.bcp.2021.114859>
- 1271.** Amsellem V, Lipskaia L, Abid S, et al. CCR5 as a treatment target in pulmonary arterial hypertension. *Circulation*. 2014;130:880-891.
- 1272.** Montecucco F, Braunerreuther V, Lenglet S, et al. CC chemokine CCL5 plays a central role impacting infarct size and post-infarction heart failure in mice. *Eur Heart J*. 2012;33:1964-1974.
- 1273.** Wang J, Seo MJ, Deci MB, Weil BR, Canty JM, Nguyen J. Effect of CCR2 inhibitor-loaded lipid micelles on inflammatory cell migration and cardiac function after myocardial infarction. *Int J Nanomedicine*. 2018;13:6441-6451.
- 1274.** Cambier S, Gouwy M, Proost P. The chemokines CXCL8 and CXCL12: molecular and functional properties, role in disease and efforts towards pharmacological intervention. *Cell Mol Immunol*. 2023;20:217-251.
- 1275.** Wen J, Wang L. Identification of key genes and their association with immune infiltration in adipose tissue of obese patients: a bioinformatic analysis. *Adipocyte*. 2022;11:401-412.
- 1276.** Kim D, Kim J, Yoon JH, et al. CXCL12 secreted from adipose tissue recruits macrophages and induces insulin resistance in mice. *Diabetologia*. 2014;57:1456-1465.
- 1277.** de Assis-Ferreira A, Saldanha-Gama R, de Brito NM, et al. Obesity enhances the recruitment of mesenchymal stem cells to visceral adipose tissue. *J Mol Endocrinol*. 2021;67:15-26.
- 1278.** Fenton JL, Nuñez NP, Yakar S, Perkins SN, Hord NG, Hursting SD. Diet-induced adiposity alters the serum profile of inflammation in C57BL/6N mice as measured by antibody array. *Diabetes Obes Metab*. 2009;11:343-354.
- 1279.** Shin J, Fukuhara A, Onodera T, et al. SDF-1 is an autocrine insulin-desensitizing factor in adipocytes. *Diabetes*. 2018;67:1068-1078.
- 1280.** Skurnik T, Alberti-Huber C, Herder C, Hauner H. Relationship between adipocyte size and adipokine expression and secretion. *J Clin Endocrinol Metab*. 2007;92:1023-1033.
- 1281.** Fain JN, Madan AK, Hiler ML, Cheema P, Bahouth SW. Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissues of obese humans. *Endocrinology*. 2004;145:2273-2282.
- 1282.** Bruun JM, Lihn AS, Madan AK, et al. Higher production of IL-8 in visceral vs. subcutaneous adipose tissue. Implication of nonadipose cells in adipose tissue. *Am J Physiol Endocrinol Metab*. 2004;286:E8-E13.
- 1283.** Cui S, Qiao L, Yu S, et al. The antagonist of CXCR1 and CXCR2 protects db/db mice from metabolic diseases through modulating inflammation. *Am J Physiol Endocrinol Metab*. 2019;317:E1205-E1217.
- 1284.** Castelli V, Brandolini L, d'Angelo M, et al. CXCR1/2 inhibitor ladarixin ameliorates the insulin resistance of 3T3-L1 adipocytes by inhibiting inflammation and improving insulin signaling. *Cells*. 2021;10(9):2324. <https://doi.org/10.3390/cells10092324>
- 1285.** Straczkowski M, Kowalska I, Nikolajuk A, Dzienis-Straczkowska S, Szalachowska M, Kinalska I. Plasma interleukin 8 concentrations in obese subjects with impaired glucose tolerance. *Cardiovasc Diabetol*. 2003;2:5. <https://doi.org/10.1186/1475-2840-2-5>
- 1286.** Straczkowski M, Dzienis-Straczkowska S, Stępień A, Kowalska I, Szalachowska M, Kinalska I. Plasma interleukin-8 concentrations are increased in obese subjects and related to fat mass and tumor necrosis factor-alpha system. *J Clin Endocrinol Metab*. 2002;87:4602-4606.
- 1287.** Wolf RM, Jaffe AE, Steele KE, et al. Cytokine, chemokine, and cytokine receptor changes are associated with metabolic improvements after bariatric surgery. *J Clin Endocrinol Metab*. 2019;104:947-956.
- 1288.** Liu Y, Hao L, Wang L, Lu M, Yin C, Xiao Y. Serum stromal cell-derived factor-1 concentrations are increased and associated with nonalcoholic fatty liver disease in children with obesity. *BMC Endocr Disord*. 2024;24(1):67. <https://doi.org/10.1186/s12902-024-01597-2>
- 1289.** Kurita K, Ishikawa K, Takeda K, et al. CXCL12-CXCR4 pathway activates brown adipocytes and induces insulin resistance in CXCR4-deficient mice under high-fat diet. *Sci Rep*. 2019;9(1):6165. <https://doi.org/10.1038/s41598-019-42127-8>
- 1290.** Uematsu M, Yoshizaki T, Shimizu T, et al. Sustained myocardial production of stromal cell-derived factor-1alpha was associated with left ventricular adverse remodeling in patients with myocardial infarction. *Am J Physiol Heart Circ Physiol*. 2015;309:H1764-H1771.
- 1291.** Chu PY, Joshi MS, Horlock D, Kiriazis H, Kaye DM. CXCR4 antagonism reduces cardiac fibrosis and improves cardiac performance in dilated cardiomyopathy. *Front Pharmacol*. 2019;10:117. <https://doi.org/10.3389/fphar.2019.00117>
- 1292.** Chu PY, Walder K, Horlock D, et al. CXCR4 antagonism attenuates the development of diabetic cardiac fibrosis. *PLoS One*. 2015;10(7):e0133616. <https://doi.org/10.1371/journal.pone.0133616>
- 1293.** Zhang YL, Geng C, Yang J, et al. Chronic inhibition of chemokine receptor CXCR2 attenuates cardiac remodeling and dysfunction in spontaneously hypertensive rats. *Biochim Biophys Acta Mol Basis Dis*. 2019;1865(12):165551. <https://doi.org/10.1016/j.bbadi.2019.165551>
- 1294.** Chu PY, Zatta A, Kiriazis H, et al. CXCR4 antagonism attenuates the cardiorenal consequences of mineralocorticoid excess. *Circ Heart Fail*. 2011;4:651-658.
- 1295.** Wang L, Zhang YL, Lin QY, et al. CXCL1-CXCR2 axis mediates angiotensin II-induced cardiac hypertrophy and remodelling through regulation of monocyte infiltration. *Eur Heart J*. 2018;39:1818-1831.
- 1296.** Baerts L, Waumans Y, Brandt I, et al. Circulating stromal cell-derived factor 1 $\alpha$  levels in heart failure: a matter of proper sampling. *PLoS One*. 2015;10(11):e0141408. <https://doi.org/10.1371/journal.pone.0141408>
- 1297.** Shin MJ, Lee KH, Chung JH, et al. Circulating IL-8 levels in heart failure patients with and without metabolic syndrome. *Clin Chim Acta*. 2009;405:139-142.
- 1298.** Subramanian S, Liu C, Aviv A, et al. Stromal cell-derived factor 1 as a biomarker of heart failure and mortality risk. *Arterioscler Thromb Vasc Biol*. 2014;34:2100-2105.
- 1299.** Nymo SH, Hulthe J, Ueland T, et al. Inflammatory cytokines in chronic heart failure: interleukin-8 is associated with adverse outcome. Results from CORONA. *Eur J Heart Fail*. 2014;16:68-75.
- 1300.** Ferreira JP, Verdonschot JA, Girerd N, et al. Influence of ejection fraction on biomarker expression and response to spironolactone in people at risk of heart failure: findings from the HOMAGE trial. *Eur J Heart Fail*. 2022;24:771-778.
- 1301.** Chaar D, Dumont BL, Vulesevic B, et al. Neutrophils and circulating inflammatory biomarkers in diabetes mellitus and heart failure with preserved ejection fraction. *Am J Cardiol*. 2022;178:80-88.
- 1302.** Abbott JD, Huang Y, Liu D, Hickey R, Krause DS, Giordano FJ. Stromal cell-derived factor-1alpha plays a critical role in stem cell recruitment to the heart after myocardial infarction but is not sufficient to induce homing in the absence of injury. *Circulation*. 2004;110:3300-3305.
- 1303.** Cheng M, Huang K, Zhou J, et al. A critical role of Src family kinase in SDF-1/CXCR4-mediated bone-marrow progenitor cell recruitment to the ischemic heart. *J Mol Cell Cardiol*. 2015;81:49-53.
- 1304.** Wang ER, Jarrah AA, Benard L, et al. Deletion of CXCR4 in cardiomyocytes exacerbates cardiac dysfunction following isoproterenol administration. *Gene Ther*. 2014;21:496-506.
- 1305.** Larocca TJ, Jeong D, Kohlbrenner E, et al. CXCR4 gene transfer prevents pressure overload induced heart failure. *J Mol Cell Cardiol*. 2012;53:223-232.
- 1306.** Szaraz P, Gratch YS, Iqbal F, Librach CL. In vitro differentiation of human mesenchymal stem cells into functional cardiomyocyte-like cells. *J Vis Exp*. 2017;126:55757. <https://doi.org/10.3791/55757>
- 1307.** Mathiasen AB, Qayyum AA, Jørgensen E, et al. Bone marrow-derived mesenchymal stromal cell treatment in patients with severe ischaemic heart failure: a randomized placebo-controlled

- trial (MSC-HF trial).** *Eur Heart J.* 2015;14;(36):1744–1753.
- 1308.** Chung ES, Miller L, Patel AN, et al. Changes in ventricular remodelling and clinical status during the year following a single administration of stromal cell-derived factor-1 non-viral gene therapy in chronic ischaemic heart failure patients: the STOP-HF randomized Phase II trial. *Eur Heart J.* 2015;36:2228–2238.
- 1309.** Packer M. The alchemist's nightmare: might mesenchymal stem cells that are recruited to repair the injured heart be transformed into fibroblasts rather than cardiomyocytes? *Circulation.* 2018;137:2068–2073.
- 1310.** Anderluh M, Kocic G, Tomovic K, Kocic R, Deljanin-Ilic M, Smicerovic A. Cross-talk between the dipeptidyl peptidase-4 and stromal cell-derived factor-1 in stem cell homing and myocardial repair: Potential impact of dipeptidyl peptidase-4 inhibitors. *Pharmacol Ther.* 2016;167:100–107.
- 1311.** Mulvihill EE, Varin EM, Ussher JR, et al. Inhibition of dipeptidyl peptidase-4 impairs ventricular function and promotes cardiac fibrosis in high fat-fed diabetic mice. *Diabetes.* 2016;65:742–754.
- 1312.** Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med.* 2013;369:1317–1326.
- 1313.** Green JB, Bethel MA, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2015;373:232–242.
- 1314.** Bae H, Hong KY, Lee CK, et al. Angiopoietin-2-integrin alpha5beta1 signaling enhances vascular fatty acid transport and prevents ectopic lipid-induced insulin resistance. *Nat Commun.* 2020;11(1):2980. <https://doi.org/10.1038/s41467-020-16795-4>
- 1315.** Ni B, Chen S, Ryan KA, et al. Selective adipocyte loss of angiopoietin-2 prompts female-specific obesity and metabolic syndrome. *Mol Metab.* 2022;65:101588. <https://doi.org/10.1016/j.molmet.2022.101588>
- 1316.** An YA, Sun K, Joffin N, et al. Angiopoietin-2 in white adipose tissue improves metabolic homeostasis through enhanced angiogenesis. *Elife.* 2017;6:e24071. <https://doi.org/10.7554/elife.24071>
- 1317.** Verseijden F, Jahr H, Posthumus-van Slujs SJ, et al. Angiogenic capacity of human adipose-derived stromal cells during adipogenic differentiation: an *in vitro* study. *Tissue Eng Part A.* 2009;15(2):445–452.
- 1318.** Xue Y, Cao R, Nilsson D, et al. FOXC2 controls Ang-2 expression and modulates angiogenesis, vascular patterning, remodeling, and functions in adipose tissue. *Proc Natl Acad Sci U S A.* 2008;105:10167–10172.
- 1319.** Yi X, Ling J, Tang Y, Cai J, Zhu S, Zhu L. Endothelial Angpt2 promotes adipocyte progenitor cells maturation to increase visceral adipose tissue accumulation. *Diabetes Metab Res Rev.* 2025;41(1):e70012. <https://doi.org/10.1002/dmrr.70012>
- 1320.** Nicolini G, Forini F, Kusmic C, Iervasi G, Balzan S. Angiopoietin 2 signal complexity in cardiovascular disease and cancer. *Life Sci.* 2019;239:117080. <https://doi.org/10.1016/j.lfs.2019.117080>
- 1321.** Ziegler T, Horstkotte J, Schwab C, et al. Angiopoietin 2 mediates microvascular and hemodynamic alterations in sepsis. *J Clin Invest.* 2013;123:3436–3445.
- 1322.** Mirando AC, Shen J, Silva RLE, et al. A collagen IV-derived peptide disrupts  $\alpha$ 5 $\beta$ 1 integrin and potentiates Ang2/Tie2 signaling. *JCI Insight.* 2019;4(4):e122043. <https://doi.org/10.1172/jci.insight.122043>
- 1323.** Mandriota SJ, Pepper MS. Regulation of angiopoietin-2 mRNA levels in bovine microvascular endothelial cells by cytokines and hypoxia. *Circ Res.* 1998;83:852–859.
- 1324.** Kamiyama M, Augustin HG. Alternatively spliced form of angiopoietin-2 as a new vascular rheostat. *Cancer Res.* 2021;81:35–37.
- 1325.** Kim M, Allen B, Korhonen EA, et al. Opposing actions of angiopoietin-2 on Tie2 signaling and FOXO1 activation. *J Clin Invest.* 2016;126:3511–3525.
- 1326.** Chen JX, Zeng H, Reese J, Aschner JL, Meyrick B. Overexpression of angiopoietin-2 impairs myocardial angiogenesis and exacerbates cardiac fibrosis in the diabetic db/db mouse model. *Am J Physiol Heart Circ Physiol.* 2012;302:H1003–H1012.
- 1327.** Cohen B, Barkan D, Levy Y, et al. Leptin induces angiopoietin-2 expression in adipose tissues. *J Biol Chem.* 2001;276:7697–7700.
- 1328.** Chang FC, Liu CH, Luo AJ, et al. Angiopoietin-2 inhibition attenuates kidney fibrosis by hindering chemokine C-C motif ligand 2 expression and apoptosis of endothelial cells. *Kidney Int.* 2022;102:780–797.
- 1329.** Lee SJ, Lee CK, Kang S, et al. Angiopoietin-2 exacerbates cardiac hypoxia and inflammation after myocardial infarction. *J Clin Invest.* 2018;128:5018–5033.
- 1330.** Kümpers P, David S, Haubitz M, et al. The Tie2 receptor antagonist angiopoietin 2 facilitates vascular inflammation in systemic lupus erythematosus. *Ann Rheum Dis.* 2009;68:1638–1643.
- 1331.** Silha JV, Krsek M, Sucharda P, Murphy LJ. Angiogenic factors are elevated in overweight and obese individuals. *Int J Obes (Lond).* 2005;29:1308–1314.
- 1332.** Gozal D, Khalyfa A, Qiao Z, et al. Angiopoietin-2 and soluble Tie-2 receptor plasma levels in children with obstructive sleep apnea and obesity. *Obesity (Silver Spring).* 2017;25:1083–1090.
- 1333.** Yoo KH, Yim HE, Bae ES, Hong YS. Capillary rarefaction and altered renal development: the imbalance between pro- and anti-angiogenic factors in response to angiotensin II inhibition in the developing rat kidney. *J Mol Histol.* 2018;49:219–228.
- 1334.** Lefere S, Van de Velde F, Hoorens A, et al. Angiopoietin-2 promotes pathological angiogenesis and is a therapeutic target in murine nonalcoholic fatty liver disease. *Hepatology.* 2019;69:1087–1104.
- 1335.** David S, Kümpers P, Lukasz A, Kielstein JT, Haller H, Fliser D. Circulating angiopoietin-2 in essential hypertension: relation to atherosclerosis, vascular inflammation, and treatment with olmesartan/pravastatin. *J Hypertens.* 2009;27:1641–1647.
- 1336.** Lorbeer R, Baumeister SE, Dörr M, et al. Angiopoietin-2, its soluble receptor Tie-2, and metabolic syndrome components in a population-based sample. *Obesity (Silver Spring).* 2016;24:2038–2041.
- 1337.** Lieb W, Zachariah JP, Xanthakis V, et al. Clinical and genetic correlates of circulating angiopoietin-2 and soluble Tie-2 in the community. *Circ Cardiovasc Genet.* 2010;3:300–306.
- 1338.** Peplinski BS, Houston BA, Bluemke DA, et al. Associations of angiopoietins with heart failure incidence and severity. *J Card Fail.* 2021;27:786–795.
- 1339.** Benz AP, Hijazi Z, Lindbäck J, et al. Plasma angiopoietin-2 and its association with heart failure in patients with atrial fibrillation. *Europace.* 2023;25(7):euad200. <https://doi.org/10.1093/europace/euad200>
- 1340.** Harrington J, Nixon AB, Daubert MA, et al. Circulating angiokines are associated with reverse remodeling and outcomes in chronic heart failure. *J Card Fail.* 2023;29:896–906.
- 1341.** Eleuteri E, Di Stefano A, Giordano A, et al. Prognostic value of angiopoietin-2 in patients with chronic heart failure. *Int J Cardiol.* 2016;212:364–368.
- 1342.** Eleuteri E, Di Stefano A, Tarro Genta F, et al. Stepwise increase of angiopoietin-2 serum levels is related to haemodynamic and functional impairment in stable chronic heart failure. *Eur J Cardiovasc Prev Rehabil.* 2011;18:607–614.
- 1343.** de Oliveira AAA, de Oliveira TA, de Oliveira LA, et al. Association between angiopoietin-2 and functional cardiac remodeling in hemodialysis patients with normal left ventricular ejection. *J Clin Hypertens (Greenwich).* 2022;24:502–512.
- 1344.** Kim J, Lee SK, Jang YJ, et al. Enhanced ANGPTL2 expression in adipose tissues and its association with insulin resistance in obese women. *Sci Rep.* 2018;8(1):13976. <https://doi.org/10.1038/s41598-018-32419-w>
- 1345.** Wu Z, Liu J, Chen G, et al. CD146 is a novel ANGPTL8 receptor that promotes obesity by manipulating lipid metabolism and energy expenditure. *Adv Sci (Weinh).* 2021;8(6):2004032. <https://doi.org/10.1002/advs.202004032>
- 1346.** Ling M, Qian H, Guo H. Knockdown of ANGPTL4 inhibits adipogenesis of preadipocyte via autophagy. *Vitro Cell Dev Biol Anim.* 2024;60:258–265.
- 1347.** Ghosh A, Leung YH, Yu J, et al. Silencing ANGPTL8 reduces mouse preadipocyte differentiation and insulin signaling. *Biochim Biophys Acta Mol Cell Biol Lipids.* 2024;1869(3):159461. <https://doi.org/10.1016/j.bbala.2024.159461>

- 1348.** Mysore R, Liebsch G, Zhou Y, Olkkonen VM, Nidhina Haridas PA. Angiopoietin-like 8 (Angptl8) controls adipocyte lipolysis and phospholipid composition. *Chem Phys Lipids*. 2017;207:246-252.
- 1349.** Tang J, Ma S, Gao Y, et al. ANGPTL8 promotes adipogenic differentiation of mesenchymal stem cells: potential role in ectopic lipid deposition. *Front Endocrinol (Lausanne)*. 2022;13:927763. <https://doi.org/10.3389/fendo>
- 1350.** Wei X, Han S, Wang S, et al. ANGPTL8 regulates adipocytes differentiation and adipogenesis in bovine. *Gene*. 2019 Jul 30;707:93-99.
- 1351.** Chen YQ, Pottanat TG, Siegel RW, et al. Angiopoietin-like protein 8 differentially regulates ANGPTL3 and ANGPTL4 during postprandial partitioning of fatty acids. *J Lipid Res*. 2020;61:1203-1220.
- 1352.** Ruppert PMM, Michielsen CCJR, Hazebroek EJ, et al. Fasting induces ANGPTL4 and reduces LPL activity in human adipose tissue. *Mol Metab*. 2020;40:101033. <https://doi.org/10.1016/j.molmet.2020.101033>
- 1353.** Kitazawa M, Nagano M, Masumoto KH, Shigeyoshi Y, Natsume T, Hashimoto S. Angiopoietin-like 2, a circadian gene, improves type 2 diabetes through potentiation of insulin sensitivity in mice adipocytes. *Endocrinology*. 2011;152:2558-2567.
- 1354.** Tabata M, Kadomatsu T, Fukuhara S, et al. Angiopoietin-like protein 2 promotes chronic adipose tissue inflammation and obesity-related systemic insulin resistance. *Cell Metab*. 2009;10:178-188.
- 1355.** Barchetta I, Chiappetta C, Ceccarelli V, et al. Angiopoietin-like protein 4 overexpression in visceral adipose tissue from obese subjects with impaired glucose metabolism and relationship with lipoprotein lipase. *Int J Mol Sci*. 2020;21(19):7197. <https://doi.org/10.3390/ijms21197197>
- 1356.** Izumi R, Kusakabe T, Noguchi M, et al. CRISPR/Cas9-mediated Angptl8 knockout suppresses plasma triglyceride concentrations and adiposity in rats. *J Lipid Res*. 2018;59:1575-1585.
- 1357.** Ghosh A, Chénier I, Leung YH, et al. Adipocyte Angptl8 deletion improves glucose and energy metabolism and obesity associated inflammation in mice. *iScience*. 2024;27(12):111292. <https://doi.org/10.1016/j.isci.2024.111292>
- 1358.** Aryal B, Singh AK, Zhang X, et al. Absence of ANGPTL4 in adipose tissue improves glucose tolerance and attenuates atherosclerosis. *JCI Insight*. 2018;3(6):e97918. <https://doi.org/10.1172/jci.insight.97918>
- 1359.** Ye J, Qin Y, Wang D, Yang L, Yuan G. The relationship between circulating ANGPTL8/beta-trophin concentrations and adult obesity: a meta-analysis. *Dis Markers*. 2019;2019:5096860. <https://doi.org/10.1155/2019/5096860>
- 1360.** Arab Sadeghabadi Z, Nourbakhsh M, Alaee M, et al. Angiopoietin-like proteins 2 and 3 in children and adolescents with obesity and their relationship with hypertension and metabolic syndrome. *Int J Hypertens*. 2021;2021:6748515. <https://doi.org/10.1155/2021/6748515>
- 1361.** Dikker O, Çetin Dağ N, Şahin M, Türkkan E, Dağ H. The association of angiopoietin-like peptide 4 levels with obesity and hepatosteatosis in adolescents. *Cytokine*. 2020;125:154802. <https://doi.org/10.1016/j.cyto.2019.154802>
- 1362.** Muramoto A, Tsuchita K, Kato A, et al. Angiopoietin-like protein 2 sensitively responds to weight reduction induced by lifestyle intervention on overweight Japanese men. *Nutr Diabetes*. 2011;1(11):e20. <https://doi.org/10.1038/nutd.2011.16>
- 1363.** Katanasaka Y, Saito A, Sunagawa Y, et al. ANGPTL4 expression is increased in epicardial adipose tissue of patients with coronary artery disease. *J Clin Med*. 2022;11(9):2449. <https://doi.org/10.3390/jcm11092449>
- 1364.** Fan W, Si Y, Xing E, et al. Human epicardial adipose tissue inflammation correlates with coronary artery disease. *Cytokine*. 2023;162:156119. <https://doi.org/10.1016/j.cyto.2022.156119>
- 1365.** Kira S, Abe I, Ishii Y, et al. Role of angiopoietin-like protein 2 in atrial fibrosis induced by human epicardial adipose tissue: analysis using an organo-culture system. *Heart Rhythm*. 2020;17:1591-1601.
- 1366.** Li J, Wan T, Liu C, Liu H, Ke D, Li L. ANGPTL2 aggravates LPS-induced septic cardiomyopathy via NLRP3-mediated inflammasome in a DUSP1-dependent pathway. *Int Immunopharmacol*. 2023;123:110701. <https://doi.org/10.1016/j.intimp.2023.110701>
- 1367.** Dijk W, Beigneux AP, Larsson M, Bensadoun A, Young SG, Kersten S. Angiopoietin-like 4 promotes intracellular degradation of lipoprotein lipase in adipocytes. *J Lipid Res*. 2016;57:1670-1683.
- 1368.** Kolb R, Kluz P, Tan ZW, et al. Obesity-associated inflammation promotes angiogenesis and breast cancer via angiopoietin-like 4. *Oncogene*. 2019;38:2351-2363.
- 1369.** Yu C, Luo X, Duquette N, Thorin-Trescases N, Thorin E. Knockdown of angiopoietin-like-2 protects against angiotensin II-induced cerebral endothelial dysfunction in mice. *Am J Physiol Heart Circ Physiol*. 2015;308:H386-H397.
- 1370.** Horio E, Kadomatsu T, Miyata K, et al. Role of endothelial cell-derived ANGPTL2 in vascular inflammation leading to endothelial dysfunction and atherosclerosis progression. *Arterioscler Thromb Vasc Biol*. 2014;34:790-800.
- 1371.** Yu C, Luo X, Farhat N, et al. Lack of angiopoietin-like-2 expression limits the metabolic stress induced by a high-fat diet and maintains endothelial function in mice. *J Am Heart Assoc*. 2014;3(4):e001024. <https://doi.org/10.1161/JAHA.114.001024>
- 1372.** Liu C, Chen Q, Liu H. ANGPTL2 aggravates doxorubicin-induced cardiotoxicity via inhibiting DUSP1 pathway. *Biosci Biotechnol Biochem*. 2022;86:1631-1640.
- 1373.** Tian Z, Miyata K, Kadomatsu T, et al. ANGPTL2 activity in cardiac pathologies accelerates heart failure by perturbing cardiac function and energy metabolism. *Nat Commun*. 2016;7:13016. <https://doi.org/10.1038/ncomms13016>
- 1374.** Li G, Zhao H, Cheng Z, Liu J, Li G, Guo Y. Single-cell transcriptomic profiling of heart reveals ANGPTL4 linking fibroblasts and angiogenesis in heart failure with preserved ejection fraction. *J Adv Res*. 2025;68:215-230.
- 1375.** Tanaka C, Kurose S, Morinaga J, et al. Serum angiopoietin-like protein 2 and NT-Pro BNP levels and their associated factors in patients with chronic heart failure participating in a phase III cardiac rehabilitation program. *Int Heart J*. 2021;62:980-987.
- 1376.** Tian Z, Miyata K, Morinaga J, et al. Circulating ANGPTL2 levels increase in humans and mice exhibiting cardiac dysfunction. *Circ J*. 2018;82:437-447.
- 1377.** Huang CL, Wu YW, Wu CC, Hwang JJ, Yang WS. Serum angiopoietin-like protein 2 concentrations are independently associated with heart failure. *PLoS One*. 2015;10(9):e0138678. <https://doi.org/10.1371/journal.pone.0138678>
- 1378.** Liu BH, Li YG, Liu JX, et al. Assessing inflammation in Chinese subjects with subtypes of heart failure: an observational study of the Chinese PLA Hospital Heart Failure Registry. *J Geriatr Cardiol*. 2019;16:313-319.
- 1379.** Carland C, Zhao L, Salman O, et al. Urinary proteomics and outcomes in heart failure with preserved ejection fraction. *J Am Heart Assoc*. 2024;13(9):e033410. <https://doi.org/10.1161/JAHA.123.033410>
- 1380.** Mars WM, Jo M, Gonias SL. Activation of hepatocyte growth factor by urokinase-type plasminogen activator is ionic strength-dependent. *Biochem J*. 2005;390:311-315.
- 1381.** Brodsky S, Chen J, Lee A, Akassoglou K, Norman J, Goligorsky MS. Plasmin-dependent and -independent effects of plasminogen activators and inhibitor-1 on ex vivo angiogenesis. *Am J Physiol Heart Circ Physiol*. 2001;281:H1784-H1792.
- 1382.** Kaji H. Adipose tissue-derived plasminogen activator inhibitor-1 function and regulation. *Compr Physiol*. 2016;6:1873-1896.
- 1383.** Wang L, Chen L, Liu Z, et al. PAI-1 exacerbates white adipose tissue dysfunction and metabolic dysregulation in high fat diet-induced obesity. *Front Pharmacol*. 2018;9:1087. <https://doi.org/10.3389/fphar.2018.01087>
- 1384.** Cigolini M, Tonoli M, Borgato L, et al. Expression of plasminogen activator inhibitor-1 in human adipose tissue: a role for TNF-alpha? *Atherosclerosis*. 1999;143:81-90.
- 1385.** Venugopal J, Hanashiro K, Nagamine Y. Regulation of PAI-1 gene expression during adipogenesis. *J Cell Biochem*. 2007;101:369-380.
- 1386.** Eriksson P, Reynisdottir S, Lönnqvist F, Stemme V, Hamsten A, Arner P. Adipose tissue secretion of plasminogen activator inhibitor-1 in non-obese and obese individuals. *Diabetologia*. 1998;41:65-71.
- 1387.** Schäfer K, Fujisawa K, Konstantinides S, Loskutoff DJ. Disruption of the plasminogen activator inhibitor 1 gene reduces the adiposity and improves the metabolic profile of genetically obese and diabetic ob/ob mice. *FASEB J*. 2001;15:1840-1842.

- 1388.** Ma LJ, Mao SL, Taylor KL, et al. Prevention of obesity and insulin resistance in mice lacking plasminogen activator inhibitor 1. *Diabetes*. 2004;53:336-346.
- 1389.** Isoppo de Souza C, Rosa DD, et al. Association of adipokines and adhesion molecules with indicators of obesity in women undergoing mammography screening. *Nutr Metab (Lond)*. 2012;9(1):97. <https://doi.org/10.1186/1743-7075-9-97>
- 1390.** Orenes-Piñero E, Pineda J, Roldán V, et al. Effects of body mass index on the lipid profile and biomarkers of inflammation and a fibrinolytic and prothrombotic state. *J Atheroscler Thromb*. 2015;22:610-619.
- 1391.** Folsom AR, Qamhieh HT, Wing RR, et al. Impact of weight loss on plasminogen activator inhibitor (PAI-1), factor VII, and other hemostatic factors in moderately overweight adults. *Arterioscler Thromb*. 1993;13:162-169.
- 1392.** Bilgic Gazioglu S, Akan G, Atalar F, Erten G. PAI-1 and TNF-alpha profiles of adipose tissue in obese cardiovascular disease patients. *Int J Clin Exp Pathol*. 2015;8:15919-15925.
- 1393.** Kim MK, Jang EH, Hong OK, et al. Changes in serum levels of bone morphogenic protein 4 and inflammatory cytokines after bariatric surgery in severely obese Korean patients with type 2 diabetes. *Int J Endocrinol*. 2013;2013:681205. <https://doi.org/10.1155/2013/681205>
- 1394.** Ingelsson E, Pencina MJ, Tofler GH, et al. Multimarker approach to evaluate the incidence of the metabolic syndrome and longitudinal changes in metabolic risk factors: the Framingham Offspring Study. *Circulation*. 2007;116:984-992.
- 1395.** Bakhshi H, Michelhaugh SA, Bruce SA, et al. Association between proteomic biomarkers and myocardial fibrosis measured by MRI: the Multi-Ethnic Study of Atherosclerosis. *EBioMedicine*. 2023;90:104490. <https://doi.org/10.1016/j.ebiom.2023.104490>
- 1396.** Li S, Kong F, Xu X, Song S, Wu Y, Tong J. Identification and exploration of aging-related subtypes and distinctive role of SERPINE1 in heart failure based on single-cell and bulk RNA sequencing data. *J Gene Med*. 2024;26(1):e3631. <https://doi.org/10.1002/jgm.3631>
- 1397.** de Boer RA, Naylor M, deFilippi CR, et al. Association of cardiovascular biomarkers with incident heart failure with preserved and reduced ejection fraction. *JAMA Cardiol*. 2018;3:215-224.
- 1398.** Suthahar N, Meems LMG, et al. Relationship between body mass index, cardiovascular biomarkers and incident heart failure. *Eur J Heart Fail*. 2021;23:396-402.
- 1399.** Winter MP, Kleber ME, Koller L, et al. Prognostic significance of tPA/PAI-1 complex in patients with heart failure and preserved ejection fraction. *Thromb Haemost*. 2017;117:471-478.
- 1400.** Wang D, Liu J, Zhong L, et al. The effect of sodium-glucose cotransporter 2 inhibitors on biomarkers of inflammation: A systematic review and meta-analysis of randomized controlled trials. *Front Pharmacol*. 2022;13:1045235. <https://doi.org/10.3389/fphar.2022.1045235>
- 1401.** Forst T, Michelson G, Ratter F, et al. Addition of liraglutide in patients with Type 2 diabetes well controlled on metformin monotherapy improves several markers of vascular function. *Diabet Med*. 2012;29(9):1115-1118. <https://doi.org/10.1111/j.1464-5491.2012.03589.x>
- 1402.** Goodfield NE, Newby DE, Ludlam CA, Flapan AD. Effects of acute angiotensin II type 1 receptor antagonism and angiotensin converting enzyme inhibition on plasma fibrinolytic parameters in patients with heart failure. *Circulation*. 1999;99:2983-2985.
- 1403.** Tiryaki O, Usalan C, Buyukhatipoglu H. Effect of combined angiotensin-converting enzyme and aldosterone inhibition on plasma plasminogen activator inhibitor type 1 levels in chronic hypertensive patients. *Nephrology (Carlton)*. 2010;15:211-215.
- 1404.** Gill RM, Jones BD, Corbly AK, et al. Cardiac diastolic dysfunction in conscious dogs with heart failure induced by chronic coronary microembolization. *Am J Physiol Heart Circ Physiol*. 2006;291:H3154-H3158.
- 1405.** Flevariatis P, Khan SS, Eren M, et al. Plasminogen activator inhibitor type i controls cardiomyocyte transforming growth factor- $\beta$  and cardiac fibrosis. *Circulation*. 2017;136:664-679.
- 1406.** Gupta KK, Donahue DL, Sandoval-Cooper MJ, Castellino FJ, Plopis VA. Plasminogen activator inhibitor-1 protects mice against cardiac fibrosis by inhibiting urokinase-type plasminogen activator-mediated plasminogen activation. *Sci Rep*. 2017;7(1):365. <https://doi.org/10.1038/s41598-017-00418-y>
- 1407.** Ghosh AK, Bradham WS, Gleaves LA, et al. Genetic deficiency of plasminogen activator inhibitor-1 promotes cardiac fibrosis in aged mice: involvement of constitutive transforming growth factor-beta signaling and endothelial-to-mesenchymal transition. *Circulation*. 2010;122:1200-1209.
- 1408.** Takeshita K, Hayashi M, Iino S, et al. Increased expression of plasminogen activator inhibitor-1 in cardiomyocytes contributes to cardiac fibrosis after myocardial infarction. *Am J Pathol*. 2004;164:449-456.
- 1409.** Riecke-Hoch M, Hoes MF, Pfeffer TJ, et al. In peripartum cardiomyopathy plasminogen activator inhibitor-1 is a potential new biomarker with controversial roles. *Cardiovasc Res*. 2020;116:1875-1886.
- 1410.** Ghosh AK, Vaughan DE. PAI-1 in tissue fibrosis. *J Cell Physiol*. 2012;227:493-507.
- 1411.** Flevariatis P, Vaughan D. The role of plasminogen activator inhibitor type-1 in fibrosis. *Semin Thromb Hemost*. 2017;43:169-177.
- 1412.** Ohkura N, Shirakura M, Nakatani E, Oishi K, Atsumi G. Associations between plasma PAI-1 concentrations and its expressions in various organs in obese model mice. *Thromb Res*. 2012;130:e301-e304.
- 1413.** Chen R, Yan J, Liu P, Wang Z, Wang C. Plasminogen activator inhibitor links obesity and thrombotic cerebrovascular diseases: the roles of PAI-1 and obesity on stroke. *Metab Brain Dis*. 2017;32:667-673.
- 1414.** Thanikachalam PV, Ramamurthy S, Mallapur P, et al. Modulation of IL-33/ST2 signaling as a potential new therapeutic target for cardiovascular diseases. *Cytokine Growth Factor Rev*. 2023;71:72-94-104.
- 1415.** Hasan A, Kochumon S, Al-Ozairi E, Tuomilehto J, Ahmad R. Association between adipose tissue interleukin-33 and immunometabolic markers in individuals with varying degrees of glycemia. *Dis Markers*. 2019;2019:7901062. <https://doi.org/10.1155/2019/7901062>
- 1416.** Torres SV, Man K, Elmazzahi T, et al. Two regulatory T cell populations in the visceral adipose tissue shape systemic metabolism. *Nat Immunol*. 2024;25:496-511.
- 1417.** Sitzia C, Vianello E, Dozio E, et al. Unveiling IL-33/ST2 pathway unbalance in cardiac remodeling due to obesity in Zucker fatty rats. *Int J Mol Sci*. 2023;24(3):1991. <https://doi.org/10.3390/ijms24031991>
- 1418.** Zhao XY, Zhou L, Chen Z, et al. The obesity-induced adipokine sST2 exacerbates adipose T (reg) and ILC2 depletion and promotes insulin resistance. *Sci Adv*. 2020;6(20):eaay6191. <https://doi.org/10.1126/sciadv.aay6191>
- 1419.** Tang H, Liu N, Feng X, et al. Circulating levels of IL-33 are elevated by obesity and positively correlated with metabolic disorders in Chinese adults. *J Transl Med*. 2021;19(1):52. <https://doi.org/10.1186/s12967-021-02711-x>
- 1420.** Martínez-Martínez E, Cachofero V, Rousseau E, et al. Interleukin-33/ST2 system attenuates aldosterone-induced adipogenesis and inflammation. *Mol Cell Endocrinol*. 2015;411:20-27.
- 1421.** Miller AM, Asquith DL, Hueber AJ, et al. Interleukin-33 induces protective effects in adipose tissue inflammation during obesity in mice. *Circ Res*. 2010;107:650-658.
- 1422.** Zeyda M, Wernly B, Demyanets S, et al. Severe obesity increases adipose tissue expression of interleukin-33 and its receptor ST2, both predominantly detectable in endothelial cells of human adipose tissue. *Int J Obes (Lond)*. 2013;37:658-665.
- 1423.** Demyanets S, Kaun C, Kaider A, et al. The pro-inflammatory marker soluble suppression of tumorigenicity-2 (ST2) is reduced especially in diabetic morbidly obese patients undergoing bariatric surgery. *Cardiovasc Diabetol*. 2020;19(1):26. <https://doi.org/10.1186/s12933-020-01001-y>
- 1424.** Simeone P, Tripaldi R, Michelsen A, et al. Effects of liraglutide vs. lifestyle changes on soluble suppression of tumorigenesis-2 (sST2) and galectin-3 in obese subjects with prediabetes or type 2 diabetes after comparable weight loss. *Cardiovasc Diabetol*. 2022;21(1):36. <https://doi.org/10.1186/s12933-022-01469-w>
- 1425.** Gruzdeva O, Uchashova E, Dyleva Y, et al. Relationships between epicardial adipose tissue thickness and adipofibroblast indicator profiles post-myocardial infarction. *Cardiovasc Diabetol*. 2018;17(1):40. <https://doi.org/10.1186/s12933-018-0679-y>
- 1426.** Vianello E, Dozio E, Bandera F, et al. Dysfunctional EAT thickness may promote maladaptive heart remodeling in CVD patients

- through the ST2-IL33 system, directly related to EPAC protein expression. *Sci Rep.* 2019;9(1):10331. <https://doi.org/10.1038/s41598-019-46676-w>
- 1427.** Seki K, Sanada S, Kudinova AY, et al. Interleukin-33 prevents apoptosis and improves survival after experimental myocardial infarction through ST2 signaling. *Circ Heart Fail.* 2009;2:684-691.
- 1428.** Veeraveedu PT, Sanada S, Okuda K, et al. Ablation of IL-33 gene exacerbate myocardial remodeling in mice with heart failure induced by mechanical stress. *Biochem Pharmacol.* 2017;138:73-80.
- 1429.** Sanada S, Hakuno D, Higgins LJ, Schreiter ER, McKenzie AN, Lee RT. IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system. *J Clin Invest.* 2007;117:1538-1549.
- 1430.** Asensio-Lopez MC, Lax A, Fernandez Del Palacio MJ, et al. Yin-Yang 1 transcription factor modulates ST2 expression during adverse cardiac remodeling post-myocardial infarction. *J Mol Cell Cardiol.* 2019;130:216-233.
- 1431.** Asensio-Lopez MC, Sassi Y, Soler F, et al. The miRNA199a/SIRT1/P300/Yy1/sST2 signaling axis regulates adverse cardiac remodeling following MI. *Sci Rep.* 2021;11(1):3915. <https://doi.org/10.1038/s41598-021-82745-9>
- 1432.** Martínez-Martínez E, Miana M, Jurado-López R, et al. A role for soluble ST2 in vascular remodeling associated with obesity in rats. *PLoS One.* 2013;8(11):e79176. <https://doi.org/10.1371/journal.pone.0079176>
- 1433.** Vianello E, Dozio E, Tacchini L, Frati L, Corsi Romanelli MM. ST2/IL-33 signaling in cardiac fibrosis. *Int J Biochem Cell Biol.* 2019;116:105619. <https://doi.org/10.1016/j.biocel.2019.105619>
- 1434.** Matilla L, Arrieta V, Jover E, et al. Soluble St2 induces cardiac fibroblast activation and collagen synthesis via neuropilin-1. *Cells.* 2020;9(7):1667. <https://doi.org/10.3390/cells9071667>
- 1435.** Bansal N, Zelnick L, Go A, et al. Cardiac biomarkers and risk of incident heart failure in chronic kidney disease: the CRIC (Chronic Renal Insufficiency Cohort) Study. *J Am Heart Assoc.* 2019;8(21):e012336. <https://doi.org/10.1161/JAHA.119.012336>
- 1436.** Barautat M, Fournier P, Peacock WF, et al. sST2 adds to the prognostic value of Gal-3 and BNP in chronic heart failure. *Acta Cardiol.* 2020;75:739-747.
- 1437.** Shi Y, Liu J, Liu C, et al. Diagnostic and prognostic value of serum soluble suppression of tumorigenicity-2 in heart failure with preserved ejection fraction: A systematic review and meta-analysis. *Front Cardiovasc Med.* 2022;9:937291. <https://doi.org/10.3389/fcvm.2022.937291>
- 1438.** Demyanets S, Kaun C, Pentz R, et al. Components of the interleukin-33/ST2 system are differentially expressed and regulated in human cardiac cells and in cells of the cardiac vasculature. *J Mol Cell Cardiol.* 2013;60:16-26.
- 1439.** AbouEzzeddine OF, McKie PM, Dunlay SM, et al. Suppression of tumorigenicity 2 in heart failure with preserved ejection fraction. *J Am Heart Assoc.* 2017;6(2):e004382. <https://doi.org/10.1161/JAHF.116.004382>
- 1440.** Bartunek J, Delrue L, Van Durme F, et al. Nonmyocardial production of ST2 protein in human hypertrophy and failure is related to diastolic load. *J Am Coll Cardiol.* 2008;52:2166-2174.
- 1441.** Truong QA, Januzzi JL, Szymonifka J, et al. Coronary sinus biomarker sampling compared to peripheral venous blood for predicting outcomes in patients with severe heart failure undergoing cardiac resynchronization therapy: the BIOCRT study. *Heart Rhythm.* 2014;11:2167-2175.
- 1442.** Kaye DM, Mariani JA, van Empel V, Maeder MT. Determinants and implications of elevated soluble ST2 levels in heart failure. *Int J Cardiol.* 2014;176:1242-1243.
- 1443.** Chen WY, Hong J, Gannon J, Kakkar R, Lee RT. Myocardial pressure overload induces systemic inflammation through endothelial cell IL-33. *Proc Natl Acad Sci U S A.* 2015;112:7249-7254.
- 1444.** Hofmann MA, Drury S, Fu C, et al. RAGE mediates a novel proinflammatory axis: a central cell surface receptor for S100/calgranulin polypeptides. *Cell.* 1999;97:889-901.
- 1445.** Donato R, Sorci G, Riuzzi F, et al. S100B's double life: intracellular regulator and extracellular signal. *Biochim Biophys Acta.* 2009;1793:1008-1022.
- 1446.** Sorci G, Bianchi R, Riuzzi F, et al. S100B protein, a damage-associated molecular pattern protein in the brain and heart, and beyond. *Cardiovasc Psychiatry Neurol.* 2010;2010:656481. <https://doi.org/10.1155/2010/656481>
- 1447.** Leclerc E, Fritz G, Vetter SW, Heizmann CW. Binding of S100 proteins to RAGE: an update. *Biochim Biophys Acta.* 2009;1793:993-1007.
- 1448.** Li D, Li K, Chen G, et al. S100B suppresses the differentiation of C3H/10T1/2 murine embryonic mesenchymal cells into osteoblasts. *Mol Med Rep.* 2016;14:3878-3886.
- 1449.** Michetti F, Dell'Anna E, Tiberio G, Cocchia D. Immunochemical and immunocytochemical study of S-100 protein in rat adipocytes. *Brain Res.* 1983;262:352-356.
- 1450.** Netto CB, Conte S, Leite MC, et al. Serum S100B protein is increased in fasting rats. *Arch Med Res.* 2006;37:683-686.
- 1451.** Gonçalves CA, Leite MC, Guerra MC. Adipocytes as an important source of serum S100B and possible roles of this protein in adipose tissue. *Cardiovasc Psychiatry Neurol.* 2010;2010:790431. <https://doi.org/10.1155/2010/790431>
- 1452.** Steiner J, Schiltz K, Walter M, et al. S100B serum levels are closely correlated with body mass index: an important caveat in neuropsychiatric research. *Psychoneuroendocrinology.* 2010;35:321-324.
- 1453.** Buckman LB, Anderson-Baucum EK, Hasty AH, Ellacott KL. Regulation of S100B in white adipose tissue by obesity in mice. *Adipocyte.* 2014;3:215-220.
- 1454.** Son KH, Son M, Ahn H, et al. Age-related accumulation of advanced glycation end-
- products-albumin, S100 $\beta$ , and the expressions of advanced glycation end product receptor differ in visceral and subcutaneous fat. *Biochem Biophys Res Commun.* 2016;477:271-276.
- 1455.** Monden M, Koyama H, Otsuka Y, et al. Receptor for advanced glycation end products regulates adipocyte hypertrophy and insulin sensitivity in mice: involvement of Toll-like receptor 2. *Diabetes.* 2013;62:478-489.
- 1456.** Fujiya A, Nagasaki H, Seino Y, et al. The role of S100B in the interaction between adipocytes and macrophages. *Obesity (Silver Spring).* 2014;22:371-379.
- 1457.** Arivazhagan L, Popp CJ, Ruiz HH, et al. The RAGE/DIAPH1 axis: mediator of obesity and proposed biomarker of human cardiometabolic disease. *Cardiovasc Res.* 2024;119:2813-2824.
- 1458.** Feng Z, Du Z, Shu X, et al. Role of RAGE in obesity-induced adipose tissue inflammation and insulin resistance. *Cell Death Discov.* 2021;7(1):305. <https://doi.org/10.1038/s41420-021-00711-w>
- 1459.** Renovato-Martins M, Moreira-Nunes C, Atella GC, Barja-Fidalgo C, Moraes JA. Obese adipose tissue secretion induces inflammation in preadipocytes: role of toll-like receptor-4. *Nutrients.* 2020 Sep 16;12(9):2828. <https://doi.org/10.3390/nu12092828>
- 1460.** Steiner J, Myint AM, Schiltz K, et al. S100B serum levels in schizophrenia are presumably related to visceral obesity and insulin resistance. *Cardiovasc Psychiatry Neurol.* 2010;2010:480707. <https://doi.org/10.1155/2010/480707>
- 1461.** Kheirouri S, Ebrahimi E, Alizadeh M. Association of S100B serum levels with metabolic syndrome and its components. *Acta Med Port.* 2018;31:201-206.
- 1462.** Holtkamp K, Bührén K, Ponath G, et al. Serum levels of S100B are decreased in chronic starvation and normalize with weight gain. *J Neural Transm (Vienna).* 2008;115:937-940.
- 1463.** Wilson RA, Arivazhagan L, Ruiz HH, et al. Pharmacological antagonism of receptor for advanced glycation end products signaling promotes thermogenesis, healthful body mass and composition, and metabolism in mice. *Obesity (Silver Spring).* 2023;31:1825-1843.
- 1464.** Tikellis C, Thomas MC, Harcourt BE, et al. Cardiac inflammation associated with a Western diet is mediated via activation of RAGE by AGEs. *Am J Physiol Endocrinol Metab.* 2008;295:E323-E330.
- 1465.** Gao ZQ, Yang C, Wang YY, et al. RAGE upregulation and nuclear factor-kappaB activation associated with ageing rat cardiomyocyte dysfunction. *Gen Physiol Biophys.* 2008;27:152-158.
- 1466.** Zhang L, Yang X, Jiang G, et al. HMGB1 enhances mechanical stress-induced cardiomyocyte hypertrophy in vitro via the RAGE/ERK1/2 signaling pathway. *Int J Mol Med.* 2019;44:885-892.
- 1467.** Petrova R, Yamamoto Y, Muraki K, et al. Advanced glycation endproduct-induced calcium handling impairment in mouse cardiac myocytes. *J Mol Cell Cardiol.* 2002;34:1425-1431.

- 1468.** Liu Z, Zhang Y, Pan S, et al. Activation of RAGE-dependent endoplasmic reticulum stress associates with exacerbated postmyocardial infarction ventricular arrhythmias in diabetes. *Am J Physiol Endocrinol Metab.* 2021;320:E539-E550.
- 1469.** Nelson MB, Swensen AC, Winden DR, Bodine JS, Bikman BT, Reynolds PR. Cardiomyocyte mitochondrial respiration is reduced by receptor for advanced glycation end-product signaling in a ceramide-dependent manner. *Am J Physiol Heart Circ Physiol.* 2015;309:H63-H69.
- 1470.** Tsoporis JN, Izhar S, Leong-Poi H, Desjardins JF, Huttunen HJ, Parker TG. S100B interaction with the receptor for advanced glycation end products (RAGE): a novel receptor-mediated mechanism for myocyte apoptosis postinfarction. *Circ Res.* 2010;106:93-101.
- 1471.** Liang B, Zhou Z, Yang Z, et al. AGEs-RAGE axis mediates myocardial fibrosis via activation of cardiac fibroblasts induced by autophagy in heart failure. *Exp Physiol.* 2022;107:879-891.
- 1472.** Zhu W, Tsang S, Browe DM, et al. Interaction of beta1-adrenoceptor with RAGE mediates cardiomyopathy via CaMKII signaling. *JCI Insight.* 2016;1(1):e84969. <https://doi.org/10.1172/jci.insight.84969>
- 1473.** Liu Y, Yu M, Zhang Z, et al. Blockade of receptor for advanced glycation end products protects against systolic overload-induced heart failure after transverse aortic constriction in mice. *Eur J Pharmacol.* 2016;791:535-543.
- 1474.** Gao W, Zhou Z, Liang B, et al. Inhibiting receptor of advanced glycation end products attenuates pressure overload-induced cardiac dysfunction by preventing excessive autophagy. *Front Physiol.* 2018;9:1333. <https://doi.org/10.3389/fphys.2018.01333>
- 1475.** Raposeiras-Rouibin S, Rodiño-Janeiro BK, Grigorian-Shamagian L, et al. Soluble receptor of advanced glycation end products levels are related to ischaemic aetiology and extent of coronary disease in chronic heart failure patients, independent of advanced glycation end products levels: New Roles for Soluble RAGE. *Eur J Heart Fail.* 2010;12:1092-1100.
- 1476.** Koyama Y, Takeishi Y, Niizeki T, et al. Soluble Receptor for advanced glycation end products (RAGE) is a prognostic factor for heart failure. *J Card Fail.* 2008;14:133-139.
- 1477.** Li JP, Lu L, Wang LJ, Zhang FR, Shen WF. Increased serum levels of S100B are related to the severity of cardiac dysfunction, renal insufficiency and major cardiac events in patients with chronic heart failure. *Clin Biochem.* 2011;44:984-988.
- 1478.** Bayraktar A, Canpolat U, Demiri E, et al. New insights into the mechanisms of diastolic dysfunction in patients with type 2 diabetes. *Scand Cardiovasc J.* 2015;49:142-148.
- 1479.** Scavello F, Zeni F, Milano G, et al. Soluble receptor for advanced glycation end-products regulates age-associated cardiac fibrosis. *Int J Biol Sci.* 2021;17(10):2399-2416.
- 1480.** Lim S, Lee ME, Jeong J, et al. sRAGE attenuates angiotensin II-induced cardiomyocyte hypertrophy by inhibiting RAGE-NFKappaB-NLRP3 activation. *Inflamm Res.* 2018;67:691-701.
- 1481.** Miranda ER, Somal VS, Mey JT, et al. Circulating soluble RAGE isoforms are attenuated in obese, impaired-glucose-tolerant individuals and are associated with the development of type 2 diabetes. *Am J Physiol Endocrinol Metab.* 2017;313:E631-E640.
- 1482.** Volz HC, Seidel C, Laochachewin D, et al. HMGB1: the missing link between diabetes mellitus and heart failure. *Basic Res Cardiol.* 2010;105:805-820.
- 1483.** Abedini A, Derk J, Schmidt AM. The receptor for advanced glycation endproducts is a mediator of toxicity by IAPP and other proteotoxic aggregates: Establishing and exploiting common ground for novel amyloidosis therapies. *Protein Sci.* 2018;27:1166-1180.
- 1484.** Meijer K, de Vries M, Al-Lahham S, et al. Human primary adipocytes exhibit immune cell function: adipocytes prime inflammation independent of macrophages. *PLoS One.* 2011;6(3):e17154. <https://doi.org/10.1371/journal.pone.0017154>
- 1485.** Winkler G, Kiss S, Keszhelyi L, et al. Expression of tumor necrosis factor (TNF)-alpha protein in the subcutaneous and visceral adipose tissue in correlation with adipocyte cell volume, serum TNF-alpha, soluble serum TNF-receptor-2 concentrations and C-peptide level. *Eur J Endocrinol.* 2003;149:129-135.
- 1486.** Fair JN. Release of interleukins and other inflammatory cytokines by human adipose tissue is enhanced in obesity and primarily due to the nonfat cells. *Vitam Horm.* 2006;74:443-477.
- 1487.** Uysal KT, Wiesbrock SM, Marino MW, Hotamisligil GS. Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. *Nature.* 1997;389:610-614.
- 1488.** Schreyer SA, Chua SC Jr, LeBoeuf RC. Obesity and diabetes in TNF-alpha receptor-deficient mice. *J Clin Invest.* 1998;102:402-411.
- 1489.** Gong M, Liu C, Zhang L, Zhang H, Pan J. Loss of the TNF $\alpha$  function inhibits Wnt/ $\beta$ -catenin signaling, exacerbates obesity development in adolescent spontaneous obese mice. *Mol Cell Biochem.* 2014;391:59-66.
- 1490.** Negrin KA, Roth Flach RJ, DiStefano MT, et al. IL-1 signaling in obesity-induced hepatic lipogenesis and steatosis. *PLoS One.* 2014;9(9):e107265. <https://doi.org/10.1371/journal.pone.0107265>
- 1491.** Whitham M, Pal M, Petzold T, et al. Adipocyte-specific deletion of IL-6 does not attenuate obesity-induced weight gain or glucose intolerance in mice. *Am J Physiol Endocrinol Metab.* 2019;317:E597-E604.
- 1492.** Jermendy A, Korner A, Kovacs M, et al. Association between toll-like receptor polymorphisms and serum levels of tumor necrosis factor-alpha and its soluble receptors in obese children. *Med Sci Monit.* 2010;16:CR180-CR185.
- 1493.** Juge-Aubry CE, Somm E, Giusti V, et al. Adipose tissue is a major source of interleukin-1 receptor antagonist: upregulation in obesity and inflammation. *Diabetes.* 2003;52:1104-1110.
- 1494.** Park HS, Park JY, Yu R. Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF-alpha and IL-6. *Diabetes Res Clin Pract.* 2005;69:29-35.
- 1495.** Yalçın T, Oğuz SH, Bayraktar M, Rakıcıoğlu N. Anthropometric measurements and serum TNF-alpha, IL-6 and adiponectin in type 2 diabetes. *Diabetol Int.* 2021;13:396-406.
- 1496.** Frühbeck G, Catalán V, Ramírez B, et al. Serum levels of IL-1 RA increase with obesity and type 2 diabetes in relation to adipose tissue dysfunction and are reduced after bariatric surgery in parallel to adiposity. *J Inflamm Res.* 2022;15:1331-1345.
- 1497.** Roytblat L, Rachinsky M, Fisher A, et al. Raised interleukin-6 levels in obese patients. *Obes Res.* 2000;8:673-675.
- 1498.** Hanna A, Frangogiannis NG. Inflammatory cytokines and chemokines as therapeutic targets in heart failure. *Cardiovasc Drugs Ther.* 2020;34:849-863.
- 1499.** Sun M, Chen M, Dawood F, et al. Tumor necrosis factor-alpha mediates cardiac remodeling and ventricular dysfunction after pressure overload state. *Circulation.* 2007;115:1398-1407.
- 1500.** Chen F, Chen D, Zhang Y, et al. Interleukin-6 deficiency attenuates angiotensin II-induced cardiac pathogenesis with increased myocyte hypertrophy. *Biochem Biophys Res Commun.* 2017;494:534-541.
- 1501.** Higashikuni Y, Tanaka K, Kato M, et al. Toll-like receptor-2 mediates adaptive cardiac hypertrophy in response to pressure overload through interleukin-1beta upregulation via nuclear factor kappaB activation. *J Am Heart Assoc.* 2013;2(6):e000267. <https://doi.org/10.1161/JAHA.113.000267>
- 1502.** Srinivas BK, Bourdi A, O'Regan JD, et al. Interleukin-1beta disruption protects male mice from heart failure with preserved ejection fraction pathogenesis. *J Am Heart Assoc.* 2023;12(14):e029668. <https://doi.org/10.1161/JAHA.122.029668>
- 1503.** Liu H, Huang Y, Zhao Y, et al. Inflammatory macrophage interleukin-1 $\beta$  mediates high-fat diet-induced heart failure with preserved ejection fraction. *JACC Basic Transl Sci.* 2022;8:174-185.
- 1504.** Lai NC, Gao MH, Tang E, et al. Pressure overload-induced cardiac remodeling and dysfunction in the absence of interleukin 6 in mice. *Lab Invest.* 2012;92:1518-1526.
- 1505.** Manilall A, Mokotedi L, Gunter S, et al. Tumor necrosis factor-alpha mediates inflammation-induced early-stage left ventricular systolic dysfunction. *J Cardiovasc Pharmacol.* 2023;81:411-422.
- 1506.** Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. *N Engl J Med.* 1990;323:236-241.
- 1507.** Hudzik B, Szkodzinski J, Romanowski W, et al. Serum interleukin-6 concentration reflects the extent of asymptomatic left ventricular dysfunction and predicts progression to heart failure in patients with stable coronary artery disease. *Cytokine.* 2011;54:266-271.

- 1508.** Alogna A, Koepf KE, Sabbah M, et al. Interleukin-6 in patients with heart failure and preserved ejection fraction. *JACC Heart Fail.* 2023;11:1549-1561.
- 1509.** Saraste A, Voipio-Pulkki LM, Heikkilä P, Laine P, Nieminen MS, Pulkki K. Soluble tumor necrosis factor receptor levels identify a subgroup of heart failure patients with increased cardiomyocyte apoptosis. *Clin Chim Acta.* 2002;320: 65-67.
- 1510.** Misso E, Campbell A, Lebel B. Cytokine inhibitors in patients with heart failure and impaired functional capacity. *Jpn Circ J.* 1997;61: 749-754.
- 1511.** Mann DL, McMurray JJ, Packer M, et al. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). *Circulation.* 2004;109:1594-1602.
- 1512.** Chung ES, Packer M, Lo KH, et al. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. *Circulation.* 2003;107:3133-3140.
- 1513.** Klein B, Brailly H. Cytokine-binding proteins: stimulating antagonists. *Immunol Today.* 1995;16:216-220.
- 1514.** Bai J, Li X, Shi Z, Pan H, et al. Changes in the structure, function, and fat content of the heart in patients with obesity after bariatric surgery—a prospective magnetic resonance imaging study. *Obes Surg.* 2025;35:9-18.
- 1515.** Henry JA, Abdesselam I, Deal O, et al. The effect of bariatric surgery type on cardiac reverse remodeling. *Int J Obes (Lond).* 2024;48:808-814.
- 1516.** Torriani M, Oliveira AL, Azevedo DC, Bredella MA, Yu EW. Effects of Roux-en-Y gastric bypass surgery on visceral and subcutaneous fat density by computed tomography. *Obes Surg.* 2015;25:381-385.
- 1517.** Meyer-Gerspach AC, Peterli R, Moor M, et al. Quantification of liver, subcutaneous, and visceral adipose tissues by MRI before and after bariatric surgery. *Obes Surg.* 2019;29:2795-2805.
- 1518.** Osorio-Conles Ó, Vidal J, de Hollanda A. Impact of bariatric surgery on adipose tissue biology. *J Clin Med.* 2021;10(23):5516. <https://doi.org/10.3390/jcm10235516>
- 1519.** Trachta P, Dostálová I, Haluzíková D, et al. Laparoscopic sleeve gastrectomy ameliorates mRNA expression of inflammation-related genes in subcutaneous adipose tissue but not in peripheral monocytes of obese patients. *Mol Cell Endocrinol.* 2014;383:96-102.
- 1520.** Illán-Gómez F, González-Ortega M, Orea-Soler I, et al. Obesity and inflammation: change in adiponectin, C-reactive protein, tumour necrosis factor-alpha and interleukin-6 after bariatric surgery. *Obes Surg.* 2012;22:950-955.
- 1521.** Oliveras A, Molina L, Goday A, et al. Effect of bariatric surgery on cardiac structure and function in obese patients: role of the renin-angiotensin system. *J Clin Hypertens (Greenwich).* 2021;23:181-192.
- 1522.** Ghannim H, Monte S, Caruana J, Green K, Abuaysheh S, Dandona P. Decreases in neprilysin and vasoconstrictors and increases in vasodilators following bariatric surgery. *Diabetes Obes Metab.* 2018;20:2029-2033.
- 1523.** Jahansouz C, Xu H, Kizy S, et al. Serum FABP4 concentrations decrease after Roux-en-Y gastric bypass but not after intensive medical management. *Surgery.* 2019;165:571-578.
- 1524.** Bidares M, Safari-Kish B, Malekzadeh-Shoushtari H, Azarbajeyani N, Nosouhi G, Aziz M. Assessing the impact of bariatric surgery on retinol-binding protein 4 (RBP4): a systematic review and meta-analysis. *Obes Surg.* 2024;34: 1855-1865.
- 1525.** Fiorotti AM, Gomes ACA, Bortoli AM, et al. Dynamic changes in adiponectin and resistin drive remission of cardiometabolic risk biomarkers in individuals with obesity following bariatric surgery. *Pharmaceuticals (Basel).* 2024;17(2):215. <https://doi.org/10.3390/ph17020215>
- 1526.** Salman AA, Sultan AAEA, Abdallah A, et al. Effect of weight loss induced by laparoscopic sleeve gastrectomy on liver histology and serum adipokine levels. *J Gastroenterol Hepatol.* 2020;35:1769-1773.
- 1527.** Zanato V, Lombardi AM, Busetto L, et al. Weight loss reduces anti-ADAMTS13 autoantibodies and improves inflammatory and coagulative parameters in obese patients. *Endocrine.* 2017;56:521-527.
- 1528.** Klein S, Mittendorfer B, Eagon JC, et al. Gastric bypass surgery improves metabolic and hepatic abnormalities associated with nonalcoholic fatty liver disease. *Gastroenterology.* 2006;130:1564-1572.
- 1529.** Rubino F, Gagner M, Gentiletti P, et al. The early effect of the Roux-en-Y gastric bypass on hormones involved in body weight regulation and glucose metabolism. *Ann Surg.* 2004;240: 236-242.
- 1530.** Pardina E, Ferrer R, Baena-Fustegueras JA, et al. The relationships between IGF-1 and CRP, NO, leptin, and adiponectin during weight loss in the morbidly obese. *Obes Surg.* 2010;20:623-632.
- 1531.** Ibrahim DM, Mohamed NR, Fouad TA, Soliman AF. Short-term impact of laparoscopic sleeve gastrectomy on serum cartonectin and vaspin levels in obese subjects. *Obes Surg.* 2018;28:3237-3245.
- 1532.** Wolf RM, Jaffe AE, Steele KE, et al. Cytokine, chemokine, and cytokine receptor changes are associated with metabolic improvements after bariatric surgery. *J Clin Endocrinol Metab.* 2019;104:947-956.
- 1533.** De Luca A, Delaye JB, Fauchier G, et al. 3-Month post-operative increase in FGF21 is predictive of one-year weight loss after bariatric surgery. *Obes Surg.* 2023;33:2468-2474.
- 1534.** Karki S, Farb MG, Myers S, Apovian C, Hess DT, Gokce N. Effect of bariatric weight loss on the adipose lipolytic transcriptome in obese humans. *Mediators Inflamm.* 2015;2015:106237. <https://doi.org/10.1155/2015/106237>
- 1535.** Di Vincenzo A, Granzotto M, Trevellin E, et al. Sleeve gastrectomy preferentially increases GDF15 plasma levels in patients with obesity but without metabolic syndrome. *Obes Surg.* 2025;35: 341-344.
- 1536.** Brock J, Schmid A, Karrasch T, et al. Progranulin serum levels and gene expression in subcutaneous vs visceral adipose tissue of severely obese patients undergoing bariatric surgery. *Clin Endocrinol (Oxf).* 2019;91:400-410.
- 1537.** Hughes D, Aminian A, Tu C, et al. Impact of bariatric surgery on left ventricular structure and function. *J Am Heart Assoc.* 2024;13(1):e031505. <https://doi.org/10.1161/JAHA.123.031505>
- 1538.** Crane JD, Joy G, Knott KD, et al. The impact of bariatric surgery on coronary microvascular function assessed using automated quantitative perfusion CMR. *JACC Cardiovasc Imaging.* 2024;17:1305-1316.
- 1539.** Henry JA, Abdesselam I, Deal O, et al. Changes in epicardial and visceral adipose tissue depots following bariatric surgery and their effect on cardiac geometry. *Front Endocrinol (Lausanne).* 2023;14:109277. <https://doi.org/10.3389/fendo.2023.109277>
- 1540.** Kindel TL, Foster T, Harmann L, Strande J. Sleeve gastrectomy in Obese Zucker rats restores cardiac function and geometry toward a lean phenotype independent of weight loss. *J Card Fail.* 2019;25:372-379.
- 1541.** Benotti PN, Wood GC, Carey DJ, et al. Gastric bypass surgery produces a durable reduction in cardiovascular disease risk factors and reduces the long-term risks of congestive heart failure. *J Am Heart Assoc.* 2017;6(5): e005126. <https://doi.org/10.1161/JAHA.116.005126>
- 1542.** Romero Funes D, Gutierrez Blanco D, Botero-Fonnegra C, et al. Bariatric surgery decreases the number of future hospital admissions for diastolic heart failure in subjects with severe obesity: a retrospective analysis of the US National Inpatient Sample database. *Surg Obes Relat Dis.* 2022;18:1-8.
- 1543.** Goodfriend TL, Kelley DE, Goodpaster BH, Winters SJ. Visceral obesity and insulin resistance are associated with plasma aldosterone levels in women. *Obes Res.* 1999;7:355-362.
- 1544.** Vecchiola A, Fuentes CA, Solar I, et al. Eplerenone implantation improved adipose dysfunction averting RAAS activation and cell division. *Front Endocrinol (Lausanne).* 2020;11:223. <https://doi.org/10.3389/fendo.2020.00223>
- 1545.** Karashima S, Yoneda T, Kometani M, et al. Comparison of eplerenone and spironolactone for the treatment of primary aldosteronism. *Hypertens Res.* 2016;39:133-137.
- 1546.** Karashima S, Yoneda T, Kometani M, et al. Angiotensin II receptor blocker combined with eplerenone or hydrochlorothiazide for hypertensive patients with diabetes mellitus. *Clin Exp Hypertens.* 2016;38:565-570.
- 1547.** Ferreira JP, Rossignol P, Claggett BL, et al. Weight changes in heart failure with preserved

- ejection fraction: findings from TOPCAT. *Clin Res Cardiol.* 2022;111:451-459.
- 1548.** Bender SB, DeMarco VG, Padilla J, et al. Mineralocorticoid receptor antagonism treats obesity-associated cardiac diastolic dysfunction. *Hypertension.* 2015;65:1082-1088.
- 1549.** Kamari Y, Shimon I, Koren F, Peleg E, Sharabi Y, Grossman E. High-salt diet increases plasma adiponectin levels independent of blood pressure in hypertensive rats: the role of the renin-angiotensin-aldosterone system. *J Hypertens.* 2010;28:95-101.
- 1550.** Matsumoto S, Takebayashi K, Aso Y. The effect of spironolactone on circulating adipocytokines in patients with type 2 diabetes mellitus complicated by diabetic nephropathy. *Metabolism.* 2006;55:1645-1652.
- 1551.** Javaheri A, Diab A, Zhao L, et al. Proteomic analysis of effects of spironolactone in heart failure with preserved ejection fraction. *Circ Heart Fail.* 2022;15(9):e009693. <https://doi.org/10.1161/CIRCHEARTFAILURE.121.009693>
- 1552.** Monzo L, Kobayashi M, Ferreira JP, et al. Echocardiographic and biomarker characteristics in diabetes, coronary artery disease or both: insights from HOMAGE trial. *Cardiovasc Diabetol.* 2025;24(1):111. <https://doi.org/10.1186/s12933-025-02609-8>
- 1553.** Wada T, Kenmochi H, Miyashita Y, et al. Spironolactone improves glucose and lipid metabolism by ameliorating hepatic steatosis and inflammation and suppressing enhanced gluconeogenesis induced by high-fat and high-fructose diet. *Endocrinology.* 2010;151:2040-2049.
- 1554.** Ma J, Sun F, Wang J, et al. Effects of aldosterone on chemerin expression and secretion in 3T3-L1 adipocytes. *Exp Clin Endocrinol Diabetes.* 2018;126:187-193.
- 1555.** Ma J, Albornoz F, Yu C, Byrne DW, Vaughan DE, Brown NJ. Differing effects of mineralocorticoid receptor-dependent and -independent potassium-sparing diuretics on fibrinolytic balance. *Hypertension.* 2005;46:313-320.
- 1556.** Sawathiparnich P, Murphey LJ, Kumar S, Vaughan DE, Brown NJ. Effect of combined AT1 receptor and aldosterone receptor antagonism on plasminogen activator inhibitor-1. *J Clin Endocrinol Metab.* 2003;88:3867-3873.
- 1557.** Olivier A, Pitt B, Gireld N, et al. Effect of eplerenone in patients with heart failure and reduced ejection fraction: potential effect modification by abdominal obesity. Insight from the EMPHASIS-HF trial. *Eur J Heart Fail.* 2017;19:1186-1197.
- 1558.** Butt JH, Henderson AD, Jhund PS, et al. Finerenone, obesity, and heart failure with mildly reduced/preserved ejection fraction: prespecified analysis of FINEARTS-HF. *J Am Coll Cardiol.* 2025;85:140-155.
- 1559.** Elkholey K, Papadimitriou L, Butler J, Thadani U, Stavrakis S. Effect of obesity on response to spironolactone in patients with heart failure with preserved ejection fraction. *Am J Cardiol.* 2021;146:36-47.
- 1560.** Killion EA, Chen M, Falsey JR, et al. Chronic glucose-dependent insulinotropic polypeptide receptor (GIPR) agonism desensitizes adipocyte GIPR activity mimicking functional GIPR antagonism. *Nat Commun.* 2020;11(1):4981. <https://doi.org/10.1038/s41467-020-18751-8>
- 1561.** Vendrell J, El Bekay R, Peral B, et al. Study of the potential association of adipose tissue GLP-1 receptor with obesity and insulin resistance. *Endocrinology.* 2011;152:4072-4079.
- 1562.** Górska J, Śliwa A, Grucia A, et al. Glucagon-like peptide-1 receptor agonist stimulates mitochondrial bioenergetics in human adipocytes. *Acta Biochim Pol.* 2017;64:423-429.
- 1563.** Martins FF, Marinho TS, Cardoso LEM, et al. Semaglutide (GLP-1 receptor agonist) stimulates browning on subcutaneous fat adipocytes and mitigates inflammation and endoplasmic reticulum stress in visceral fat adipocytes of obese mice. *Cell Biochem Funct.* 2022;40:903-913.
- 1564.** Xu F, Lin B, Zheng X, et al. GLP-1 receptor agonist promotes brown remodelling in mouse white adipose tissue through SIRT1. *Diabetologia.* 2016;59:1059-1069.
- 1565.** Lee YS, Park MS, Choung JS, et al. Glucagon-like peptide-1 inhibits adipose tissue macrophage infiltration and inflammation in an obese mouse model of diabetes. *Diabetologia.* 2012;55:2456-2468.
- 1566.** Vaittinen M, Ilha M, Herbers E, et al. Liraglutide demonstrates a therapeutic effect on mitochondrial dysfunction in human SGBS adipocytes in vitro. *Diabetes Res Clin Pract.* 2023;199:110635. <https://doi.org/10.1016/j.diabres.2023.110635>
- 1567.** Brachs S, Soll D, Beer F, et al. Hormonal regulation of human adipose tissue lipolysis: impact of adipose GIP system in overweight and obesity. *Eur J Endocrinol.* 2025;192:91-99.
- 1568.** Yu X, Chen S, Funcke JB, et al. The GIP receptor activates futile calcium cycling in white adipose tissue to increase energy expenditure and drive weight loss in mice. *Cell Metab.* 2025;37:187-204.
- 1569.** Gastaldelli A, Cusi K, Fernández Landó L, Bray R, Brouwers B, Rodríguez Á. Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial. *Lancet Diabetes Endocrinol.* 2022;10:393-406.
- 1570.** Akoumianakis I, Zagaliotis A, Konstantarakí M, Filippatos TD. GLP-1 analogs and regional adiposity: A systematic review and meta-analysis. *Obes Rev.* 2023;24(8):e13574. <https://doi.org/10.1111/obr.13574>
- 1571.** Malavazos AE, Iacobellis G, Dozio E, et al. Human epicardial adipose tissue expresses glucose-dependent insulinotropic polypeptide, glucagon, and glucagon-like peptide-1 receptors as potential targets of pleiotropic therapies. *Eur J Prev Cardiol.* 2023;30:680-693.
- 1572.** Myasoedova VA, Parisi V, Moschetta D, et al. Efficacy of cardiometabolic drugs in reduction of epicardial adipose tissue: a systematic review and meta-analysis. *Cardiovasc Diabetol.* 2023;22(1):23. <https://doi.org/10.1186/s12933-023-01738-2>
- 1573.** Cai H, Dai C, Liu J, Chen S. Liraglutide combined with HIIT preserves contractile apparatus and blunts the progression of heart failure in diabetic cardiomyopathy rats. *Sci Rep.* 2025;15(1):5051. <https://doi.org/10.1038/s41598-025-85699-4>
- 1574.** Almutairi M, Gopal K, Greenwell AA, et al. The GLP-1 receptor agonist liraglutide increases myocardial glucose oxidation rates via indirect mechanisms and mitigates experimental diabetic cardiomyopathy. *Can J Cardiol.* 2021;37:140-150.
- 1575.** Kuo CY, Tsou SH, Kornelius E, et al. The protective effects of liraglutide in reducing lipid droplets accumulation and myocardial fibrosis in diabetic cardiomyopathy. *Cell Mol Life Sci.* 2025;82(1):39. <https://doi.org/10.1007/s00018-024-05558-9>
- 1576.** Simental-Mendía LE, Sánchez-García A, Linden-Torres E, Simental-Mendía M. Impact of glucagon-like peptide-1 receptor agonists on adiponectin concentrations: a meta-analysis of randomized controlled trials. *Br J Clin Pharmacol.* 2021;87:4140-4149.
- 1577.** Samms RJ, Christe ME, Collins KA, et al. GIPR agonism mediates weight-independent insulin sensitization by tirzepatide in obese mice. *J Clin Invest.* 2021;131(12):e146353. <https://doi.org/10.1172/JCI146353>
- 1578.** El Bekay R, Coín-Aragüez L, Fernández-García D, et al. Effects of glucagon-like peptide-1 on the differentiation and metabolism of human adipocytes. *Br J Pharmacol.* 2016;173:1820-1834.
- 1579.** Cantini G, Di Franco A, Samavat J, Forti G, Mannucci E, Luconi M. Effect of liraglutide on proliferation and differentiation of human adipose stem cells. *Mol Cell Endocrinol.* 2015;402:43-50.
- 1580.** Koldemir Gündüz M, Kaymak G, Kanbur E, Berikten D, Şener H. Exenatide increases CTRP3 gene expression in adipose cells by inhibiting adipogenesis and induces apoptosis. *Toxicol In Vitro.* 2022;85:105479. <https://doi.org/10.1016/j.tiv.2022.105479>
- 1581.** Li X, Jiang L, Yang M, Wu Y, Sun S, Sun J. GLP-1 receptor agonist increases the expression of CTRP3, a novel adipokine, in 3T3-L1 adipocytes through PKA signal pathway. *J Endocrinol Invest.* 2015;38:73-79.
- 1582.** Yan P, Li L, Yang M, et al. Effects of the long-acting human glucagon-like peptide-1 analog liraglutide on plasma omentin-1 levels in patients with type 2 diabetes mellitus. *Diabetes Res Clin Pract.* 2011;92:368-374.
- 1583.** Liu R, Ding X, Wang Y, Wang M, Peng Y. Glucagon-like peptide-1 upregulates visfatin expression in 3T3-L1 adipocytes. *Horm Metab Res.* 2013;45:646-651.
- 1584.** Li D, Xu X, Zhang Y, et al. Liraglutide treatment causes upregulation of adiponectin and downregulation of resistin in Chinese type 2 diabetes. *Diabetes Res Clin Pract.* 2015;110(2):224-228.
- 1585.** Dai C, Zhu W. Effects of GLP-1 receptor agonists on asprosin levels in normal weight or overweight/obesity patients with type 2 diabetes mellitus. *Medicine (Baltimore).* 2022;101(43):e31334. <https://doi.org/10.1097/MD.00000000000031334>

- 1586.** Zhou B, Dong C, Zhao B, et al. (E(X)-4)(2)-Fc, an effective long-acting GLP-1 receptor agonist, reduces obesity-related inflammation by inhibiting leptin expression. *Biochem Biophys Res Commun.* 2020;529:562-568.
- 1587.** Wajdlich M, Nowicki M. The impact of GLP-1 receptor agonist liraglutide on blood pressure profile, hydration, natriuresis in diabetic patients with severely impaired kidney function. *Sci Rep.* 2024;14(1):5002. <https://doi.org/10.1038/s41598-024-55724-z>
- 1588.** Touceda V, Fontana Estevez F, Cacciagiù L, et al. Liraglutide improves adipose tissue remodeling and mitochondrial dynamics in a visceral obesity model induced by a high-fat diet. *Curr Res Pharmacol Drug Discov.* 2024;6:100185. <https://doi.org/10.1016/j.crpdr.2024.100185>
- 1589.** Li P, Tang Z, Wang L, Feng B. Glucagon-like peptide-1 analogue liraglutide ameliorates atherosclerosis via inhibiting advanced glycation end product-induced receptor for advanced glycosylation end product expression in apolipoprotein-E deficient mice. *Mol Med Rep.* 2017;16:3421-3426.
- 1590.** Vergès B, Duvillard L, Pais de Barros JP, et al. Liraglutide increases the catabolism of apolipoprotein B100-containing lipoproteins in patients with type 2 diabetes and reduces protein convertase subtilisin/kexin type 9 expression. *Diabetes Care.* 2021;44:1027-1037.
- 1591.** Xu W, Sang YQ, Liu XK, et al. Effect of glucagon-like peptide-1 receptor agonist on insulin secretion index and serum Wnt5a protein in patients with new-onset type 2 diabetes mellitus. *J Diabetes Metab Disord.* 2023;22:539-545.
- 1592.** Liu J, Yang K, Xiao W, et al. GLP-1 receptor agonists stimulate ANGPTL8 production through the PI3K/Akt pathway in a GLP-1 receptor-dependent manner. *Peptides.* 2018;106:83-90.
- 1593.** Zhang N, Liu C, Zhang Y, et al. Liraglutide regulates lipid metabolism via FGF21- LKB1-AMPK- ACC1 pathway in white adipose tissues and macrophage of type 2 diabetic mice. *Biochem Biophys Res Commun.* 2021;548:120-126.
- 1594.** Le TDV, Fathi P, Watters AB, et al. Fibroblast growth factor-21 is required for weight loss induced by the glucagon-like peptide-1 receptor agonist liraglutide in male mice fed high carbohydrate diets. *Mol Metab.* 2023;72:101718. <https://doi.org/10.1016/j.molmet.2023.101718>
- 1595.** Li H, Donelan W, Wang F, et al. GLP-1 induces the expression of FNDC5 derivatives that execute lipolytic actions. *Front Cell Dev Biol.* 2021;9:777026. <https://doi.org/10.3389/fcell.2021.777026>
- 1596.** Rafiullah M, Benabdulkamel H, Masood A, et al. Urinary proteome differences in patients with type 2 diabetes pre and post liraglutide treatment. *Curr Issues Mol Biol.* 2023;45:1407-1421.
- 1597.** Su K, Yi B, Yao BQ, et al. Liraglutide attenuates renal tubular ectopic lipid deposition in rats with diabetic nephropathy by inhibiting lipid synthesis and promoting lipolysis. *Pharmacol Res.* 2020;156:104778. <https://doi.org/10.1016/j.phrs.2020.104778>
- 1598.** Valenzuela-Vallejo L, Chrysafi P, Bello-Ramos J, Bsata S, Mantzoros CS. Circulating total and intact GDF-15 levels are not altered in response to weight loss induced by liraglutide or lorcaserin treatment in humans with obesity. *Metabolism.* 2022;133:155237. <https://doi.org/10.1016/j.metabol.2022.155237>
- 1599.** Butler J, Shah SJ, Petrie MC, et al. Semaglutide versus placebo in people with obesity-related heart failure with preserved ejection fraction: a pooled analysis of the STEP-HFpEF and STEP-HFpEF DM randomised trials. *Lancet.* 2024;403:1635-1648.
- 1600.** Borlaug BA, Zile MR, Kramer CM, et al. Impact of body mass index, central adiposity, and weight loss on the benefits of tirzepatide in HFpEF: the SUMMIT trial. *J Am Coll Cardiol.* 2025;86:242-255. <https://doi.org/10.1016/j.jacc.2025.04.059>
- 1601.** Borlaug BA, Kitzman DW, Davies MJ, et al. Semaglutide in HFpEF across obesity class and by body weight reduction: a prespecified analysis of the STEP-HFpEF trial. *Nat Med.* 2023;29:2358-2365.
- 1602.** Solomon SD, Ostrominski JW, Wang X, et al. Effect of semaglutide on cardiac structure and function in patients with obesity-related heart failure. *J Am Coll Cardiol.* 2024;84:1587-1602.
- 1603.** Packer M. SGLT2 inhibitors produce cardiorenal benefits by promoting adaptive cellular reprogramming to induce a state of fasting mimicry: a paradigm shift in understanding their mechanism of action. *Diabetes Care.* 2020;43:508-511.
- 1604.** Swe MT, Thongnak L, Jaikumkao K, Pongchaidecha A, Chatsudhipong V, Lungkaphin A. Dapagliflozin not only improves hepatic injury and pancreatic endoplasmic reticulum stress, but also induces hepatic gluconeogenic enzymes expression in obese rats. *Clin Sci (Lond).* 2019;133:2415-2430.
- 1605.** Packer M. Critical reanalysis of the mechanisms underlying the cardiorenal benefits of SGLT2 inhibitors and reaffirmation of the nutrient deprivation signaling/autophagy hypothesis. *Circulation.* 2022;146:1383-1405.
- 1606.** Wang XX, Levi J, Luo Y, et al. SGLT2 protein expression is increased in human diabetic nephropathy: SGLT2 protein inhibition decreases renal lipid accumulation, inflammation, and the development of nephropathy in diabetic mice. *J Biol Chem.* 2017;292:5335-5348.
- 1607.** Yang X, Liu Q, Li Y, et al. The diabetes medication canagliflozin promotes mitochondrial remodelling of adipocyte via the AMPK-Sirt1-Pgc-1alpha signalling pathway. *Adipocyte.* 2020;9:484-494.
- 1608.** Xu L, Xu C, Liu X, et al. Empagliflozin induces white adipocyte browning and modulates mitochondrial dynamics in KK Cg-Ay/J mice and mouse adipocytes. *Front Physiol.* 2021;12:745058. <https://doi.org/10.3389/fphys.2021.745058>
- 1609.** Lee JY, Lee M, Lee JY, et al. Ipragliflozin, an SGLT2 inhibitor, ameliorates high-fat diet-induced metabolic changes by upregulating energy expenditure through activation of the AMPK/SIRT1 pathway. *Diabetes Metab J.* 2021;45(6):921-932.
- 1610.** Wei D, Liao L, Wang H, Zhang W, Wang T, Xu Z. Canagliflozin ameliorates obesity by improving mitochondrial function and fatty acid oxidation via PPARalpha in vivo and in vitro. *Life Sci.* 2020;247:117414. <https://doi.org/10.1016/j.lfs.2020.117414>
- 1611.** Qu J, Tian L, Zhang M, Sun B, Chen L. SGLT2 inhibitor canagliflozin reduces visceral adipose tissue in db/db mice by modulating AMPK/KLF4 signaling and regulating mitochondrial dynamics to induce browning. *Mol Cell Endocrinol.* 2024;592:112320. <https://doi.org/10.1016/j.mce.2024.112320>
- 1612.** Takano M, Kondo H, Harada T, et al. Empagliflozin suppresses the differentiation/maturation of human epicardial preadipocytes and improves paracrine secretome profile. *JACC Basic Transl Sci.* 2023;8:1081-1097.
- 1613.** Díaz-Rodríguez E, Agra RM, Fernández ÁL, et al. Effects of dapagliflozin on human epicardial adipose tissue: modulation of insulin resistance, inflammatory chemokine production, and differentiation ability. *Cardiovasc Res.* 2018;114:336-346.
- 1614.** Xu L, Nagata N, Nagashimada M, et al. SGLT2 inhibition by empagliflozin promotes fat utilization and browning and attenuates inflammation and insulin resistance by polarizing M2 macrophages in diet-induced obese mice. *EBioMedicine.* 2017;20:137-149.
- 1615.** Ji W, Zhao M, Wang M, et al. Effects of canagliflozin on weight loss in high-fat diet-induced obese mice. *PLoS One.* 2017;12(6):e0179960. <https://doi.org/10.1371/journal.pone.0179960>
- 1616.** Hara K, Sakai Y, Tajiri Y, Nomura M. Beneficial effects of SGLT2 inhibitor on metabolic inflexibility and visceral fat amount in animal model of obese type 2 diabetes. *Heliyon.* 2022;8(10):e11012. <https://doi.org/10.1016/j.heliyon.2022.e11012>
- 1617.** Olagunju A, Yamani N, Kenny D, Mookadam M, Mookadam F, Unzek S. Potential for sodium-glucose cotransporter-2 inhibitors in the management of metabolic syndrome: a systematic review and meta-analysis. *World J Cardiol.* 2022;14:599-616.
- 1618.** Wang X, Wu N, Sun C, Jin D, Lu H. Effects of SGLT-2 inhibitors on adipose tissue distribution in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *Diabetol Metab Syndr.* 2023;15(1):113. <https://doi.org/10.1186/s13098-023-01085-y>
- 1619.** Liu X, Chen Y, Liu T, Cai L, Yang X, Mou C. The effects of sodium-glucose cotransporter 2 inhibitors on adipose tissue in patients with type 2 diabetes: A meta-analysis of randomized controlled trials. *Front Endocrinol (Lausanne).* 2023;14:1115321. <https://doi.org/10.3389/fendo.2023.1115321>
- 1620.** Koshizaka M, Ishikawa K, Ishibashi R, et al. Comparison of visceral fat reduction by ipragliflozin and metformin in elderly type 2 diabetes

- patients: sub-analysis of a randomized-controlled study.** *Diabetes Ther.* 2021;12:183-196.
- 1621.** Cinti F, Leccisotti L, Sorice GP, et al. Dapagliflozin treatment is associated with a reduction of epicardial adipose tissue thickness and epicardial glucose uptake in human type 2 diabetes. *Cardiovasc Diabetol.* 2023;22(1):349. <https://doi.org/10.1186/s12933-023-02091-0>
- 1622.** Sato T, Aizawa Y, Yuasa S, et al. The effect of dapagliflozin treatment on epicardial adipose tissue volume. *Cardiovasc Diabetol.* 2018;17(1):6. <https://doi.org/10.1186/s12933-017-0658-8>
- 1623.** Bao Y, Hu Y, Shi M, Zhao Z. SGLT2 inhibitors reduce epicardial adipose tissue more than GLP-1 agonists or exercise interventions in patients with type 2 diabetes mellitus and/or obesity: a systematic review and network meta-analysis. *Diabetes Obes Metab.* 2025;27:1096-1112.
- 1624.** Ferrannini G, Hach T, Crowe S, Sanghvi A, Hall KD, Ferrannini E. Energy balance after sodium-glucose cotransporter 2 inhibition. *Diabetes Care.* 2015;38:1730-1735.
- 1625.** Matsuba I, Kanamori A, Takihata M, et al. Canagliflozin increases calorie intake in type 2 diabetes without changing the energy ratio of the three macronutrients: CANA-K study. *Diabetes Technol Ther.* 2020;22:228-234.
- 1626.** Packer M, Wilcox CS, Testani JM. Critical analysis of the effects of SGLT2 inhibitors on renal tubular sodium, water and chloride homeostasis and their role in influencing heart failure outcomes. *Circulation.* 2023;148:354-372.
- 1627.** Kawata T, Iizuka T, Iemitsu K, et al. Ipragliflozin improves glycemic control and decreases body fat in patients with type 2 diabetes mellitus. *J Clin Med Res.* 2017;9:586-595.
- 1628.** Wang Y, Xia N. Influence of sodium-glucose cotransporter-2 inhibitors on plasma adiponectin in patients with type 2 diabetes: a meta-analysis of randomized controlled trials. *Horm Metab Res.* 2022;54:833-844.
- 1629.** Matsui T, Sotokawauchi A, Nishino Y, Koga Y, Yamagishi SI. Empagliflozin ameliorates renal and metabolic derangements in obese type 2 diabetic mice by blocking advanced glycation end product-receptor axis. *Mol Med.* 2025;31(1):88. <https://doi.org/10.1186/s10020-025-01138-0>
- 1630.** Osataphan S, Macchi C, Singhal G, et al. SGLT2 inhibition reprograms systemic metabolism via FGF21-dependent and -independent mechanisms. *JCI Insight.* 2019;4(5):e123130. <https://doi.org/10.1172/jci.insight.123130>
- 1631.** Di Vincenzo A, Granzotto M, Crescenzi M, Fioretto P, Vettor R, Rossato M. The effects of SGLT2 inhibitors on metabolic phenotype and FGF-21 expression from the adipose tissue and the liver are less pronounced in ob/ob mice. *BMC Endocr Disord.* 2025;25(1):63. <https://doi.org/10.1186/s12902-025-01879-3>
- 1632.** Berezin AA, Fushey IM, Berezin AE. The effect of SGLT2 inhibitor dapagliflozin on serum levels of apelin in T2DM patients with heart failure. *Biomedicines.* 2022;10(7):1751. <https://doi.org/10.3390/biomedicines10071751>
- 1633.** Jiang A, Feng Z, Yuan L, Zhang Y, Li Q, She Y. Effect of sodium-glucose co-transporter-2 inhibitors on the levels of serum asporin in patients with newly diagnosed type 2 diabetes mellitus. *Diabetol Metab Syndr.* 2021;13(1):34. <https://doi.org/10.1186/s13098-021-00652-5>
- 1634.** Buttice L, Ghani M, Suthakar J, et al. The effect of sodium-glucose cotransporter-2 inhibitors on inflammatory biomarkers: a meta-analysis of randomized controlled trials. *Diabetes Obes Metab.* 2024;26:2706-2721.
- 1635.** Shaheer A, Kumar A, Menon P, Jallo M, Basha S. Effect of add-on therapy of sodium-glucose cotransporter 2 inhibitors and dipeptidyl peptidase 4 inhibitors on adipokines in type 2 diabetes mellitus. *J Clin Med Res.* 2021;13:355-362.
- 1636.** Sakurai S, Jojima T, Iijima T, Tomaru T, Usui I, Aso Y. Empagliflozin decreases the plasma concentration of plasminogen activator inhibitor-1 (PAI-1) in patients with type 2 diabetes: Association with improvement of fibrinolysis. *J Diabetes Complications.* 2020;34(11):107703. <https://doi.org/10.1016/j.jdiacomp.2020.107703>
- 1637.** Szekeres Z, Sandor B, Bognar Z, et al. Clinical study of metabolic parameters, leptin and the SGLT2 inhibitor empagliflozin among patients with obesity and type 2 diabetes. *Int J Mol Sci.* 2023;24(5):4405. <https://doi.org/10.3390/ijms24054405>
- 1638.** Mohebi R, Liu Y, Hansen MK, et al. Insulin growth factor axis and cardio-renal risk in diabetic kidney disease: an analysis from the CREDENCE trial. *Cardiovasc Diabetol.* 2023;22(1):176. <https://doi.org/10.1186/s12933-023-01916-2>
- 1639.** Adamson C, Welsh P, Docherty KF, et al. IGFBP-7 and outcomes in heart failure with reduced ejection fraction: findings from DAPA-HF. *JACC Heart Fail.* 2023;11:291-304.
- 1640.** Januzzi JL Jr, Butler J, Jarolim P, et al. Effects of canagliflozin on cardiovascular biomarkers in older adults with type 2 diabetes. *J Am Coll Cardiol.* 2017;70:704-712.
- 1641.** Furuhashi M, Matsumoto M, Hiramitsu S, et al. Possible increase in serum FABP4 level despite adiposity reduction by canagliflozin, an SGLT2 inhibitor. *PLoS One.* 2016;11(4):e0154482. <https://doi.org/10.1371/journal.pone.0154482>
- 1642.** Mori K, Tsuchiya K, Nakamura S, et al. Ipragliflozin-induced adipose expansion inhibits cuff-induced vascular remodeling in mice. *Cardiovasc Diabetol.* 2019;18(1):83. <https://doi.org/10.1186/s12933-019-0886-1>
- 1643.** Chen D, Shi J, Wu Y, et al. Dapagliflozin alleviates high-fat-induced obesity cardiomyopathy by inhibiting ferroptosis. *ESC Heart Fail.* 2025;12:1358-1373.
- 1644.** Borlaug BA, Reddy YNV, Braun A, et al. Cardiac and metabolic effects of dapagliflozin in heart failure with preserved ejection fraction: the CAMEO-DAPA trial. *Circulation.* 2023;148:834-844.
- 1645.** Adamson C, Kondo T, Jhund PS, et al. Dapagliflozin for heart failure according to body mass index: the DELIVER trial. *Eur Heart J.* 2022;43:4406-4417.
- 1646.** Siddiqi TJ, Anker SD, Filippatos G, et al. Health status across major subgroups of patients with heart failure and preserved ejection fraction. *Eur J Heart Fail.* 2023;25:1623-1631.
- 1647.** Oyama K, Raz I, Cahn A, et al. Obesity and effects of dapagliflozin on cardiovascular and renal outcomes in patients with type 2 diabetes mellitus in the DECLARE-TIMI 58 trial. *Eur Heart J.* 2022;43:2958-2967.
- 1648.** Sarzani R, Marcucci P, Salvi F, et al. Angiotensin II stimulates and atrial natriuretic peptide inhibits human visceral adipocyte growth. *Int J Obes (Lond).* 2008;32:259-267.
- 1649.** Tsukuda K, Mogi M, Iwanami J, et al. Enhancement of adipocyte browning by angiotensin ii type 1 receptor blockade. *PLoS One.* 2016;11(12):e0167704. <https://doi.org/10.1371/journal.pone.0167704>
- 1650.** Muñoz MC, Giani JF, Dominici FP, Turyn D, Toblli JE. Long-term treatment with an angiotensin II receptor blocker decreases adipocyte size and improves insulin signaling in obese Zucker rats. *J Hypertens.* 2009;27:2409-2420.
- 1651.** Mori Y, Itoh Y, Tajima N. Angiotensin II receptor blockers downsize adipocytes spontaneously type 2 diabetic rats with visceral fat obesity. *Am J Hypertens.* 2007;20:431-436.
- 1652.** Kurata A, Nishizawa H, Kihara S, et al. Blockade of angiotensin II type-I receptor reduces oxidative stress in adipose tissue and ameliorates adipocytokine dysregulation. *Kidney Int.* 2006;70:1717-1724.
- 1653.** Kouryama R, Suganami T, Nishida J, et al. Attenuation of diet-induced weight gain and adiposity through increased energy expenditure in mice lacking angiotensin II type 1a receptor. *Endocrinology.* 2005;146:3481-3489.
- 1654.** Rodriguez R, Lee AY, Godoy-Lugo JA, et al. Chronic AT(1) blockade improves hyperglycemia by decreasing adipocyte inflammation and decreasing hepatic PCK1 and G6PC1 expression in obese rats. *Am J Physiol Endocrinol Metab.* 2021;321:E714-E727.
- 1655.** Murakami K, Wada J, Ogawa D, et al. The effects of telmisartan treatment on the abdominal fat depot in patients with metabolic syndrome and essential hypertension: Abdominal fat Depot Intervention Program of Okayama (ADPO). *Diab Vas Dis Res.* 2013;10:93-96.
- 1656.** Shiota A, Shimabukuro M, Fukuda D, et al. Activation of AMPK-Sirt1 pathway by telmisartan in white adipose tissue: a possible link to anti-metabolic effects. *Eur J Pharmacol.* 2012;692:84-90.
- 1657.** Furuhashi M, Ura N, Higashira K, et al. Blockade of the renin-angiotensin system increases adiponectin concentrations in patients with essential hypertension. *Hypertension.* 2003;42:76-81.
- 1658.** Hung WW, Hsieh TJ, Lin T, et al. Blockade of the renin-angiotensin system ameliorates apelin production in 3T3-L1 adipocytes. *Cardiovasc Drugs Ther.* 2011;25:3-12.
- 1659.** Kim DY, Choi MJ, Ko TK, et al. Angiotensin AT(1) receptor antagonism by losartan stimulates

- 1660.** Furukoshi M, Mita T, Moniwa N, et al. Angiotensin II receptor blockers decrease serum concentration of fatty acid-binding protein 4 in patients with hypertension. *Hypertens Res*. 2015;38:252-259.
- 1661.** Skurk T, Lee YM, Hauner H. Angiotensin II and its metabolites stimulate PAI-1 protein release from human adipocytes in primary culture. *Hypertension*. 2001;37:1336-1340.
- 1662.** Cole BK, Keller SR, Wu R, Carter JD, Nadler JL, Nunemaker CS. Valsartan protects pancreatic islets and adipose tissue from the inflammatory and metabolic consequences of a high-fat diet in mice. *Hypertension*. 2010;55:715-721.
- 1663.** Ushijima K, Takuma M, Ando H, et al. Effects of telmisartan and valsartan on insulin sensitivity in obese diabetic mice. *Eur J Pharmacol*. 2013;698:505-510.
- 1664.** Verboven K, Hansen D, Moro C, et al. Attenuated atrial natriuretic peptide-mediated lipolysis in subcutaneous adipocytes of obese type 2 diabetic men. *Clin Sci (Lond)*. 2016;130:1105-1114.
- 1665.** Rydén M, Bäckdahl J, Petrus P, et al. Impaired atrial natriuretic peptide-mediated lipolysis in obesity. *Int J Obes (Lond)*. 2016;40:714-720.
- 1666.** Souza SC, Chau MD, Yang Q, et al. Atrial natriuretic peptide regulates lipid mobilization and oxygen consumption in human adipocytes by activating AMPK. *Biochem Biophys Res Commun*. 2011;410:398-403.
- 1667.** Kimura H, Nagoshi T, Oi Y, et al. Treatment with atrial natriuretic peptide induces adipose tissue browning and exerts thermogenic actions in vivo. *Sci Rep*. 2021;11(1):17466. <https://doi.org/10.1038/s41598-021-96970-9>
- 1668.** Kimura H, Nagoshi T, Yoshii A, et al. The thermogenic actions of natriuretic peptide in brown adipocytes: the direct measurement of the intracellular temperature using a fluorescent thermoprobe. *Sci Rep*. 2017;7(1):12978. <https://doi.org/10.1038/s41598-017-13563-1>
- 1669.** Carper D, Coué M, Nascimento EBM, et al. Atrial natriuretic peptide orchestrates a coordinated physiological response to fuel non-shivering thermogenesis. *Cell Rep*. 2020;32(8):108075. <https://doi.org/10.1016/j.celrep.2020.108075>
- 1670.** Wang L, Tang Y, Herman MA, Spurney RF. Pharmacologic blockade of the natriuretic peptide clearance receptor promotes weight loss and enhances insulin sensitivity in type 2 diabetes. *Transl Res*. 2023;255:140-151.
- 1671.** Wu W, Shi F, Liu D, et al. Enhancing natriuretic peptide signaling in adipose tissue, but not in muscle, protects against diet-induced obesity and insulin resistance. *Sci Signal*. 2017;10(489):eaaam6870. <https://doi.org/10.1126/scisignal.aam6870>
- 1672.** Tsukamoto O, Fujita M, Kato M, et al. Natriuretic peptides enhance the production of adiponectin in human adipocytes and in patients with chronic heart failure. *J Am Coll Cardiol*. 2009;53:2070-2077.
- 1673.** Moro C, Klincakova E, Lolmède K, et al. Atrial natriuretic peptide inhibits the production of adipokines and cytokines linked to inflammation and insulin resistance in human subcutaneous adipose tissue. *Diabetologia*. 2007;50:1038-1047.
- 1674.** Birkenfeld AL, Boschmann M, Engeli S, et al. Atrial natriuretic peptide and adiponectin interactions in man. *PLoS One*. 2012;7(8):e43238. <https://doi.org/10.1371/journal.pone.0043238>
- 1675.** Daniels MA, Fischer-Posovszky P, Boschmann M, et al. Atrial natriuretic peptide and leptin interactions in healthy men. *Front Endocrinol (Lausanne)*. 2023;14:1195677. <https://doi.org/10.3389/fendo.2023.1195677>
- 1676.** Moraña-Fernández S, Vázquez-Abuín X, Aragón-Herrera A, et al. Cardiometabolic effects of sacubitril/valsartan in a rat model of heart failure with preserved ejection fraction. *Biochem Pharmacol*. 2024;230(Pt 1):116571. <https://doi.org/10.1016/j.bcp.2024.116571>
- 1677.** Tanaka T, Tsutamoto T, Sakai H, et al. Effect of atrial natriuretic peptide on adiponectin in patients with heart failure. *Eur J Heart Fail*. 2008;10:360-366.
- 1678.** Arfsten H, Goliasch G, Bartko PE, et al. Increased concentrations of bioactive adrenomedullin subsequently to angiotensin-receptor/neprilysin-inhibitor treatment in chronic systolic heart failure. *Br J Clin Pharmacol*. 2021;87:916-924.
- 1679.** Murphy SP, Prescott MF, Camacho A, et al. Atrial natriuretic peptide and treatment with sacubitril/valsartan in heart failure with reduced ejection fraction. *JACC Heart Fail*. 2021;9:127-136.
- 1680.** McKinnie SM, Fischer C, Tran KM, et al. The metalloprotease neprilysin degrades and inactivates apelin peptides. *Chembiochem*. 2016;17:1495-1498.
- 1681.** Rice GI, Thomas DA, Grant PJ, Turner AJ, Hooper NM. Evaluation of angiotensin-converting enzyme (ACE), its homologue ACE2 and neprilysin in angiotensin peptide metabolism. *Biochem J*. 2004;383:45-51.
- 1682.** Nougué H, Pezel T, Picard F, et al. Effects of sacubitril/valsartan on neprilysin targets and the metabolism of natriuretic peptides in chronic heart failure: a mechanistic clinical study. *Eur J Heart Fail*. 2019;21:598-605.
- 1683.** Simko F, Baka T, Stanko P, et al. Sacubitril/valsartan and ivabradine attenuate left ventricular remodeling and dysfunction in spontaneously hypertensive rats: different interactions with the renin-angiotensin-aldosterone system. *Bio-medicines*. 2022;10(8):1844. <https://doi.org/10.3390/biomedicines10081844>
- 1684.** Anand IS, Rector TS, Cleland JG, et al. Prognostic value of baseline plasma amino-terminal pro-brain natriuretic peptide and its interactions with irbesartan treatment effects in patients with heart failure and preserved ejection fraction: findings from the I-PRESERVE trial. *Circ Heart Fail*. 2011;4:569-577.
- 1685.** Harrington J, Mentz R, Adams K, et al. The relationship between obesity status and change in NT-proBNP with angiotensin-neprilysin inhibition in patients with mildly reduced or preserved ejection fraction and recent worsening heart failure event: results from the PARAGLIDE-HF Trial. *Circulation*. 2024;150(Suppl 1). [https://doi.org/10.1161/circ.150.suppl\\_1.4140480](https://doi.org/10.1161/circ.150.suppl_1.4140480)
- 1686.** Scott NJA, Prickett TCR, Charles CJ, Frampton CM, Richards AM, Rademaker MT. Augmentation of natriuretic peptide bioactivity via combined inhibition of neprilysin and phosphodiesterase-9 in heart failure. *JACC Heart Fail*. 2023;11:227-239.
- 1687.** Mishra S, Sadagopan N, Dunkerly-Eyring B, et al. Inhibition of phosphodiesterase type 9 reduces obesity and cardiometabolic syndrome in mice. *J Clin Invest*. 2021;131(21):e148798. <https://doi.org/10.1172/JCI148798>
- 1688.** Richards DA, Aronovitz MJ, Liu P, et al. CRD-733, a novel PDE9 (phosphodiesterase 9) inhibitor, reverses pressure overload-induced heart failure. *Circ Heart Fail*. 2021;14(1):e007300. <https://doi.org/10.1161/CIRCH-EARTFAILURE.120.007300>
- 1689.** Yang L, Jia X, Fang D, et al. Metformin inhibits lipid droplets fusion and growth via reduction in cidec and its regulatory factors in rat adipose-derived stem cells. *Int J Mol Sci*. 2022;23(11):5986. <https://doi.org/10.3390/ijms23115986>
- 1690.** Pescador N, Francisco V, Vázquez P, et al. Metformin reduces macrophage HIF1alpha-dependent proinflammatory signaling to restore brown adipocyte function in vitro. *Redox Biol*. 2021;48:102171. <https://doi.org/10.1016/j.redox.2021.102171>
- 1691.** Luo T, Nocon A, Fry J, et al. AMPK activation by metformin suppresses abnormal extracellular matrix remodeling in adipose tissue and ameliorates insulin resistance in obesity. *Diabetes*. 2016;65:2295-2310.
- 1692.** Sakae T, Dorayappan KDP, Zingarelli R, et al. Obesity-induced extracellular vesicles proteins drive the endometrial cancer pathogenesis: therapeutic potential of HO-3867 and metformin. *Oncogene*. 2024;43:3586-3597.
- 1693.** Kim EK, Lee SH, Lee SY, et al. Metformin ameliorates experimental-obesity-associated autoimmune arthritis by inducing FGF21 expression and brown adipocyte differentiation. *Exp Mol Med*. 2018;50(1):e432. <https://doi.org/10.1038/emm.2017.245>
- 1694.** Glueck CJ, Fontaine RN, Wang P, et al. Metformin reduces weight, centripetal obesity, insulin, leptin, and low-density lipoprotein cholesterol in nondiabetic, morbidly obese subjects with body mass index greater than 30. *Metabolism*. 2001;50:856-861.
- 1695.** Haber R, Zarzour F, Ghezzawi M, et al. The impact of metformin on weight and metabolic parameters in patients with obesity: a systematic review and meta-analysis of randomized controlled trials. *Diabetes Obes Metab*. 2024;26:1850-1867.
- 1696.** Caton PW, Kieswich J, Taqoob MM, Holness MJ, Sugden MC. Metformin opposes

- impaired AMPK and SIRT1 function and deleterious changes in core clock protein expression in white adipose tissue of genetically-obese db/db mice. *Diabetes Obes Metab.* 2011;13:1097-1104.
- 1697.** Zulian A, Cancello R, Girola A, et al. In vitro and in vivo effects of metformin on human adipose tissue adiponectin. *Obes Facts.* 2011;4:27-33.
- 1698.** Bauer S, Weigert J, Neumeier M, et al. Low-abundant adiponectin receptors in visceral adipose tissue of humans and rats are further reduced in diabetic animals. *Arch Med Res.* 2010;41:75-82.
- 1699.** Tan BK, Adya R, Farhatullah S, Chen J, Lehnert H, Randeva HS. Metformin treatment may increase omentin-1 levels in women with polycystic ovary syndrome. *Diabetes.* 2010;59:3023-3031.
- 1700.** Elbarbary NS, Ismail EAR, Ghallab MA. Effect of metformin as an add-on therapy on neuregulin-4 levels and vascular-related complications in adolescents with type 1 diabetes: A randomized controlled trial. *Diabetes Res Clin Pract.* 2022;186:109857. <https://doi.org/10.1016/j.diabres.2022.109857>
- 1701.** Tan BK, Chen J, Hu J, et al. Metformin increases the novel adipokine cartonectin/CTRP3 in women with polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2013;98:E1891-E1900.
- 1702.** Eriksson A, Attvall S, Bonnier M, et al. Short-term effects of metformin in type 2 diabetes. *Diabetes Obes Metab.* 2007;9:483-489.
- 1703.** Klein J, Westphal S, Kraus D, et al. Metformin inhibits leptin secretion via a mitogen-activated protein kinase signalling pathway in brown adipocytes. *J Endocrinol.* 2004;183:299-307.
- 1704.** Song J, Ren P, Zhang L, Wang XL, Chen L, Shen YH. Metformin reduces lipid accumulation in macrophages by inhibiting FOXO1-mediated transcription of fatty acid-binding protein 4. *Biochem Biophys Res Commun.* 2010;393:89-94.
- 1705.** Gokulakrishnan K, Pandey GK, Sathishkumar C, et al. Augmentation of RBP4/STR4 signaling leads to insulin resistance and inflammation and the plausible therapeutic role of vildagliptin and metformin. *Mol Biol Rep.* 2021;48:4093-4106.
- 1706.** Rea R, Donnelly R. Effects of metformin and oleic acid on adipocyte expression of resistin. *Diabetes Obes Metab.* 2006;8:105-109.
- 1707.** Morita N, Hosaka T, Kitahara A, et al. Novel mechanisms modulating palmitate-induced inflammatory factors in hypertrophied 3T3-L1 adipocytes by AMPK. *J Diabetes Res.* 2018;2018:9256482. <https://doi.org/10.1155/2018/9256482>
- 1708.** He G, Pedersen SB, Bruun JM, Lihn AS, Richelsen B. Metformin, but not thiazolidinediones, inhibits plasminogen activator inhibitor-1 production in human adipose tissue in vitro. *Horm Metab Res.* 2003;35:18-23.
- 1709.** Esteghamati A, Ghasemisefde M, Mousavizadeh M, Noshad S, Nakjavani M. Pioglitazone and metformin are equally effective in reduction of chemerin in patients with type 2 diabetes. *J Diabetes Investig.* 2014;5:327-332.
- 1710.** Goldberg RB, Bray GA, Marcovina SM, et al. Non-traditional biomarkers and incident diabetes in the Diabetes Prevention Program: comparative effects of lifestyle and metformin interventions. *Diabetologia.* 2019;62:58-69.
- 1711.** Magalhães FMV, Pestana RMC, Ferreira CN, et al. GDF-15 levels in patients with polycystic ovary syndrome treated with metformin: a combined clinical and in silico pathway analysis. *Arch Endocrinol Metab.* 2024;68:e230416. <https://doi.org/10.20945/2359-4292-2023-0416>
- 1712.** Tan BK, Heutling D, Chen J, et al. Metformin decreases the adipokine vaspin in overweight women with polycystic ovary syndrome concomitant with improvement in insulin sensitivity and a decrease in insulin resistance. *Diabetes.* 2008;57:1501-1507.
- 1713.** Telagareddy R, Kumar PR, Pattanaik SR, et al. Serum irisin in polycystic ovary syndrome and its alteration with metformin intervention. *Indian J Endocrinol Metab.* 2024;28:91-97.
- 1714.** Yang S, Lv Q, Luo T, et al. Metformin inhibits expression and secretion of PEDF in adipocyte and hepatocyte via promoting AMPK phosphorylation. *Mediators Inflamm.* 2013;2013:429207. <https://doi.org/10.1155/2013/429207>
- 1715.** UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet.* 1998;352:854-865.
- 1716.** Güneş H, Güneş H, Özmen Ş, Çelik E, Temiz F. Effects of metformin on epicardial adipose tissue and atrial electromechanical delay of obese children with insulin resistance. *Cardiol Young.* 2020;30:1429-1432.
- 1717.** Slater RE, Strom JG, Methawasin M, et al. Metformin improves diastolic function in an HFpEF-like mouse model by increasing titin compliance. *J Gen Physiol.* 2019;151:42-52.
- 1718.** Lai YC, Tabima DM, Dube JJ, et al. SIRT3-AMP-activated protein kinase activation by nitrite and metformin improves hyperglycemia and normalizes pulmonary hypertension associated with heart failure with preserved ejection fraction. *Circulation.* 2016;133:717-731.
- 1719.** Gu J, Yin ZF, Zhang JF, Wang CQ. Association between long-term prescription of metformin and the progression of heart failure with preserved ejection fraction in patients with type 2 diabetes mellitus and hypertension. *Int J Cardiol.* 2020;306:140-145.
- 1720.** Halabi A, Sen J, Huynh Q, Marwick TH. Metformin treatment in heart failure with preserved ejection fraction: a systematic review and meta-regression analysis. *Cardiovasc Diabetol.* 2020;19(1):124. <https://doi.org/10.1186/s12933-020-01100-w>
- 1721.** Packer M. Qiliqiangxin: a multifaceted holistic treatment for heart failure or a pharmacological probe for the identification of cardioprotective mechanisms? *Eur J Heart Fail.* 2023;25:2130-2143.
- 1722.** Jeong S, Yoon M. Fenofibrate inhibits adipocyte hypertrophy and insulin resistance by activating adipose PPARalpha in high fat diet-induced obese mice. *Exp Mol Med.* 2009;41:397-405.
- 1723.** Toyoda T, Kamei Y, Kato H, et al. Effect of peroxisome proliferator-activated receptor-alpha ligands in the interaction between adipocytes and macrophages in obese adipose tissue. *Obesity (Silver Spring).* 2008;16:1199-1207.
- 1724.** Frias FT, Rocha KCE, de Mendonça M, et al. Fenofibrate reverses changes induced by high-fat diet on metabolism in mice muscle and visceral adipocytes. *J Cell Physiol.* 2018;233:3515-3528.
- 1725.** Rachid TL, Penna-de-Carvalho A, Bringhenti I, et al. PPAR- $\alpha$  agonist elicits metabolically active brown adipocytes and weight loss in diet-induced obese mice. *Cell Biochem Funct.* 2015;33:249-256.
- 1726.** Shin Y, Lee M, Lee D, Jang J, Shin SS, Yoon M. Fenofibrate regulates visceral obesity and nonalcoholic steatohepatitis in obese female ovariectomized C57BL/6J mice. *Int J Mol Sci.* 2021;22(7):3675. <https://doi.org/10.3390/ijms22073675>
- 1727.** Patel NG, Holder JC, Smith SA, Kumar S, Eggo MC. Differential regulation of lipogenesis and leptin production by independent signaling pathways and rosiglitazone during human adipocyte differentiation. *Diabetes.* 2003;52:43-50.
- 1728.** Matsuura N, Asano C, Nagasawa K, et al. Effects of pioglitazone on cardiac and adipose tissue pathology in rats with metabolic syndrome. *Int J Cardiol.* 2015;179:360-369.
- 1729.** Civelek E, Karaman EF, Özden S, Uydeş Doğan BS, Kaleli Durman D. Effect of pioglitazone on endoplasmic reticulum stress and autophagy response in the perivascular adipose tissue of type 2 diabetic rats. *PPAR Res.* 2025;2025:9645836. <https://doi.org/10.1155/ppar/9645836>
- 1730.** Kubota N, Terauchi Y, Miki H, et al. PPAR gamma mediates high-fat diet-induced adipocyte hypertrophy and insulin resistance. *Mol Cell.* 1999;4:4597-4609.
- 1731.** Picard F, Kurtev M, Chung N, et al. Sirt1 promotes fat mobilization in white adipocytes by repressing PPAR-gamma. *Nature.* 2004;429:771-776.
- 1732.** Yu P, Wang W, Guo W, et al. Pioglitazone-enhanced brown fat whitening contributes to weight gain in diet-induced obese mice. *Exp Clin Endocrinol Diabetes.* 2023;131:595-604.
- 1733.** Sikder K, Shukla SK, Patel N, Singh H, Rafiq K. High fat diet upregulates fatty acid oxidation and ketogenesis via intervention of PPAR-gamma. *Cell Physiol Biochem.* 2018;48:1317-1331.
- 1734.** Lim S, Lee SH, Min KW, et al. A multicentre, double-blind, placebo-controlled, randomized, parallel comparison, phase 3 trial to evaluate the efficacy and safety of pioglitazone add-on therapy in type 2 diabetic patients treated with metformin and dapagliflozin. *Diabetes Obes Metab.* 2024;26:2188-2198.

- 1735.** Xie G, Wang Y, Xu Q, et al. Knockdown of adiponectin promotes the adipogenesis of goat intramuscular preadipocytes. *Anim Biotechnol*. 2022;33:408-416.
- 1736.** Nishimoto H, Yamamoto A, Furukawa S, Wakisaka S, Maeda T. C1q/TNF-related protein 3 expression and effects on adipocyte differentiation of 3T3-L1 cells. *Cell Biol Int*. 2017;41:197-203.
- 1737.** Xiao XH, Wang YD, Qi XY, et al. Zinc alpha glycoprotein protects against obesity-induced hepatic steatosis. *Int J Obes (Lond)*. 2018;42:1418-1430.
- 1738.** Zhu HJ, Ding HH, Deng JY, et al. Inhibition of preadipocyte differentiation and adipogenesis by zinc-alpha2-glycoprotein treatment in 3T3-L1 cells. *J Diabetes Investig*. 2013;6(4):252-260.
- 1739.** Zhou B, Wang X, Wang Y, Liu D. FNDC5 attenuates atherosclerotic plaque formation and regulates PPARalpha/HO-1 in ApoE-/ mice. *J Vasc Res*. 2023;60:172-182.
- 1740.** Fisher FM, Kleiner S, Douris N, et al. FGF21 regulates PGC-1alpha and browning of white adipose tissues in adaptive thermogenesis. *Genes Dev*. 2012;26:271-281.
- 1741.** Akingbemi BT. Adiponectin receptors in energy homeostasis and obesity pathogenesis. *Prog Mol Biol Transl Sci*. 2013;114:317-342.
- 1742.** Yoon MJ, Lee GY, Chung JJ, Ahn YH, Hong SH, Kim JB. Adiponectin increases fatty acid oxidation in skeletal muscle cells by sequential activation of AMP-activated protein kinase, p38 mitogen-activated protein kinase, and peroxisome proliferator-activated receptor alpha. *Diabetes*. 2006;55:2562-2570.
- 1743.** Abu-Odeh M, Zhang Y, Reilly SM, et al. FGF21 promotes thermogenic gene expression as an autocrine factor in adipocytes. *Cell Rep*. 2021;35(13):109331. <https://doi.org/10.1016/j.celrep.2021.109331>
- 1744.** Fujii N, Uta S, Kobayashi M, Sato T, Okita N, Higami Y. Impact of aging and caloric restriction on fibroblast growth factor 21 signaling in rat white adipose tissue. *Exp Gerontol*. 2019;118:55-64.
- 1745.** Wölkart G, Schrammel A, Dörffel K, Haemmerle G, Zechner R, Mayer B. Cardiac dysfunction in adipose triglyceride lipase deficiency: treatment with a PPARalpha agonist. *Br J Pharmacol*. 2012;165:380-389.
- 1746.** Wu H, Wei L, Bao Y, Lu J, et al. Fenofibrate reduces serum retinol-binding protein-4 by suppressing its expression in adipose tissue. *Am J Physiol Endocrinol Metab*. 2009;296:E628-E634.
- 1747.** Oki K, Koide J, Nakanishi S, Nakashima R, Yamane K. Fenofibrate increases high molecular weight adiponectin in subjects with hypertriglyceridemia. *Endocr J*. 2007;54:431-435.
- 1748.** Zirlin A, Ernst S, Leugers A, et al. Inhibition by fibrates of plasminogen activator inhibitor type-1 expression in human adipocytes and pre-adipocytes. *Thromb Haemost*. 2009;101:1060-1069.
- 1749.** Zhao SP, Wu J. Fenofibrate reduces tumor necrosis factor-alpha serum concentration and adipocyte secretion of hypercholesterolemic rabbits. *Clin Chim Acta*. 2004;347:145-150.
- 1750.** Bednarski TK, Duda MK, Dobrzyn P. Alterations of lipid metabolism in the heart in spontaneously hypertensive rats precedes left ventricular hypertrophy and cardiac dysfunction. *Cells*. 2022;11(19):3032. <https://doi.org/10.3390/cells11193032>
- 1751.** Smets PJ, Teunissen BE, Willemse PH, et al. Cardiac hypertrophy is enhanced in PPAR alpha-/- mice in response to chronic pressure overload. *Cardiovasc Res*. 2008;78:79-89.
- 1752.** Loichot C, Jesel L, Tesse A, et al. Deletion of peroxisome proliferator-activated receptor-alpha induces an alteration of cardiac functions. *Am J Physiol Heart Circ Physiol*. 2006;291:H161-H166.
- 1753.** Brigadeau F, Gelé P, Wibaux M, et al. The PPARalpha activator fenofibrate slows down the progression of the left ventricular dysfunction in porcine tachycardia-induced cardiomyopathy. *J Cardiovasc Pharmacol*. 2007;49:408-415.
- 1754.** Castiglioni L, Gelosa P, Muluhie M, et al. Fenofibrate reduces cardiac remodeling by mitochondrial dynamics preservation in a renovascular model of cardiac hypertrophy. *Eur J Pharmacol*. 2024;978:176767. <https://doi.org/10.1016/j.ejphar.2024.176767>
- 1755.** Son NH, Park TS, Yamashita H, et al. Cardiomyocyte expression of PPARgamma leads to cardiac dysfunction in mice. *J Clin Invest*. 2007;117:2791-2801.
- 1756.** Duan SZ, Ivashchenko CY, Russell MW, Milstone DS, Mortensen RM. Cardiomyocyte-specific knockout and agonist of peroxisome proliferator-activated receptor-gamma both induce cardiac hypertrophy in mice. *Circ Res*. 2005;97:372-379.
- 1757.** Fang X, Stroud MJ, Ouyang K, et al. Adipocyte-specific loss of PPARgamma attenuates cardiac hypertrophy. *JCI Insight*. 2016;1(16):e89908. <https://doi.org/10.1172/jci.insight.89908>
- 1758.** Zhou Y, Luo P, Chang HH, et al. Clofibrate attenuates blood pressure and sodium retention in DOCA-salt hypertension. *Kidney Int*. 2008;74:1040-1048.
- 1759.** Chraibi A, Renaud S. PPARgamma-induced stimulation of amiloride-sensitive sodium current in renal collecting duct principal cells is serum and insulin dependent. *Cell Physiol Biochem*. 2014;33:581-593.
- 1760.** Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet*. 2005;366:1279-1289.
- 1761.** Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet*. 2009;373:2125-2135.
- 1762.** Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. *Lancet*. 2007;370:1129-1136.
- 1763.** Kalliora C, Drosatos K. The glitazars paradox: cardiotoxicity of the metabolically beneficial dual PPARalpha and PPARgamma activation. *J Cardiovasc Pharmacol*. 2020;76:514-526.
- 1764.** Han CL, Qu CZ. Cardiovascular risk and safety evaluation of a dual peroxisome proliferator-activated receptor-alpha/gamma agonist, aleglitazar, in patients with type 2 diabetes: a meta-analysis. *J Cardiovasc Pharmacol*. 2020;75:351-357.
- 1765.** Hassan NF, Hassan AH, El-Ansary MR. Cytokine modulation by etanercept ameliorates metabolic syndrome and its related complications induced in rats administered a high-fat high-fructose diet. *Sci Rep*. 2022;12(1):20227. <https://doi.org/10.1038/s41598-022-24593-9>
- 1766.** Lv Z, Chen X, Chen P, et al. Colchicine prevents ventricular arrhythmias vulnerability in diet-induced obesity rats. *Biochem Biophys Res Commun*. 2022;610:127-132.
- 1767.** Chen CY, Tsai CY, Lee PC, Lee SD. Long-term etanercept therapy favors weight gain and ameliorates cachexia in rheumatoid arthritis patients: roles of gut hormones and leptin. *Curr Pharm Des*. 2013;19:1956-1964.
- 1768.** Hmamouchi I, Roux C, Paternotte S, Kolta S, Dougados M, Briot K. Early increase of abdominal adiposity in patients with spondyloarthritis receiving anti-tumor necrosis factor-alpha treatment. *J Rheumatol*. 2014;41:1112-1117.
- 1769.** Engvall IL, Tengstrand B, Brismar K, Hafström I. Infliximab therapy increases body fat mass in early rheumatoid arthritis independently of changes in disease activity and levels of leptin and adiponectin: a randomised study over 21 months. *Arthritis Res Ther*. 2010;12(5):R197. <https://doi.org/10.1186/ar3169>
- 1770.** Lo J, Bernstein LE, Canavan B, et al. Effects of TNF-alpha neutralization on adipocytokines and skeletal muscle adiposity in the metabolic syndrome. *Am J Physiol Endocrinol Metab*. 2007;293:E102-E109.
- 1771.** Ferraz-Amaro I, Arce-Franco M, Muñiz J, et al. Systemic blockade of TNF-alpha does not improve insulin resistance in humans. *Horm Metab Res*. 2011;43:801-808.
- 1772.** Yarur AJ, Bruss A, Moosekri A, et al. Higher intra-abdominal visceral adipose tissue mass is associated with lower rates of clinical and endoscopic remission in patients with inflammatory bowel diseases initiating biologic therapy: results of the Constellation study. *Gastroenterology*. 2023;165:963-975.
- 1773.** Lim Z, Welman CJ, Raymond W, Thin L. The effect of adiposity on anti-tumor necrosis factor-alpha levels and loss of response in Crohn's disease patients. *Clin Transl Gastroenterol*. 2020;11(9):e00233. <https://doi.org/10.14309/ctg.0000000000000233>

- 1774.** Ottaviani S, Gardette A, Tubach F, et al. Body mass index and response to infliximab in rheumatoid arthritis. *Clin Exp Rheumatol.* 2015;33:478-483.
- 1775.** Ibáñez Vodnizza SE, Nurmohamed MT, et al. Fat mass lowers the response to tumor necrosis factor-alpha blockers in patients with ankylosing spondylitis. *J Rheumatol.* 2017;44:1355-1361.
- 1776.** van Asseldonk EJ, Stienstra R, Koenen TB, Joosten LA, Netea MG, Tack CJ. Treatment with Anakinra improves disposition index but not insulin sensitivity in nondiabetic subjects with the metabolic syndrome: a randomized, double-blind, placebo-controlled study. *J Clin Endocrinol Metab.* 2011;96:2119-2126.
- 1777.** Somm E, Henrichot E, Pernin A, et al. Decreased fat mass in interleukin-1 receptor antagonist-deficient mice: impact on adipogenesis, food intake, and energy expenditure. *Diabetes.* 2005;54:3503-3509.
- 1778.** Schimmel RJ. Inhibition of free fatty acid mobilization by colchicine. *J Lipid Res.* 1974;15: 206-210.
- 1779.** Levine JA, Sarrafan-Chaharsoughi Z, Patel TP, et al. Effects of colchicine on lipolysis and adipose tissue inflammation in adults with obesity and metabolic syndrome. *Obesity (Silver Spring).* 2022;30:358-368.
- 1780.** Demidowich AP, Levine JA, Onyekaba GI, et al. Effects of colchicine in adults with metabolic syndrome: a pilot randomized controlled trial. *Diabetes Obes Metab.* 2019;21:1642-1651.
- 1781.** Ruscitti P, Ursini F, Cipriani P, et al. IL-1 inhibition improves insulin resistance and adipokines in rheumatoid arthritis patients with comorbid type 2 diabetes: An observational study. *Medicine (Baltimore).* 2019;98(7):e14587. <https://doi.org/10.1097/MD.00000000000014587>
- 1782.** Everett BM, Cornel JH, Lainscak M, et al. Anti-inflammatory therapy with canakinumab for the prevention of hospitalization for heart failure. *Circulation.* 2019;139:1289-1299.
- 1783.** Van Tassell BW, Trankle CR, Canada JM, et al. IL-1 blockade in patients with heart failure with preserved ejection fraction. *Circ Heart Fail.* 2018;11(8):e005036. <https://doi.org/10.1161/CIRCHEARTFAILURE.118.005036>
- 1784.** Deftereos S, Giannopoulos G, Panagopoulou V, et al. Anti-inflammatory treatment with colchicine in stable chronic heart failure: a prospective, randomized study. *JACC Heart Fail.* 2014;2:131-137.
- 1785.** Pascual-Figal D, Núñez J, Pérez-Martínez MT, et al. Colchicine in acutely decompensated heart failure: the COLICA trial. *Eur Heart J.* 2024;45:4826-4836.
- 1786.** Shaikh S, Hamza M, Neppala S, et al. Colchicine for secondary prevention in patients with acute coronary syndrome: a systematic review and meta-analysis. *Int J Cardiol.* 2025;425: 133045. <https://doi.org/10.1016/j.ijcard.2025.133045>
- 1787.** Ridker PM, Devalaraja M, Baeres FMM, et al. IL-6 inhibition with ziltivekimab in patients at high atherosclerotic risk (RESCUE): a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet.* 2021;397:2060-2069.
- 1788.** Petrie M, Borlaug B, Buchholtz K, et al. HERMES: Effects of ziltivekimab versus placebo on morbidity and mortality in patients with heart failure with mildly reduced or preserved ejection fraction and systemic inflammation. *J Card Fail.* 2024;30(1):126. <https://doi.org/10.1016/j.cardfail.2023.10.024>
- 1789.** Laurindo LF, Laurindo LF, Rodrigues VD, et al. Unraveling the rationale and conducting a comprehensive assessment of AdipoRon (adiponectin receptor agonist) as a candidate drug for diabetic nephropathy and cardiomyopathy prevention and intervention-a systematic review. *Naunyn Schmiedebergs Arch Pharmacol.* 2025;398:165-177.
- 1790.** Barbalho SM, Méndez-Sánchez N, Fornari Laurindo L. AdipoRon and ADP355, adiponectin receptor agonists, in metabolic-associated fatty liver disease (MAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. *Biochem Pharmacol.* 2023;218:115871. <https://doi.org/10.1016/j.bcp.2023.115871>
- 1791.** Sassi Ørum K, Tagmose TM, Olsen J, et al. Development of zalfermin, a long-acting proteolytically stabilized FGF21 analog. *J Med Chem.* 2024;67:11769-11788.
- 1792.** Harrison SA, Frias JP, Lucas KJ, et al. Safety and efficacy of eruxerifin in combination with a GLP-1 receptor agonist in patients with NASH/MASH and type 2 diabetes in a randomized Phase 2 study. *Clin Gastroenterol Hepatol.* 2025;23:103-113.
- 1793.** Smith WB, Nguyen D, Clough T, et al. A growth differentiation factor 15 receptor agonist in randomized placebo-controlled trials in healthy or obese persons. *J Clin Endocrinol Metab.* 2025;110:771-786.
- 1794.** Benichou O, Coskun T, Gonciarz MD, et al. Discovery, development, and clinical proof of mechanism of LY3463251, a long-acting GDF15 receptor agonist. *Cell Metab.* 2023;35:274-286.
- 1795.** Sonnenberg SB, Rane AA, Liu CJ, et al. Delivery of an engineered HGF fragment in an extracellular matrix-derived hydrogel prevents negative LV remodeling post-myocardial infarction. *Biomaterials.* 2015;45:56-63.
- 1796.** Coroniti R, Fario R, Nuno DJ, Otvos L, Scilaro L, Surmacz E. Designer leptin receptor antagonist Allo-acα inhibits VEGF effects in ophthalmic neoangiogenesis models. *Front Mol Biosci.* 2016;3:67. <https://doi.org/10.3389/fmolb.2016.00067>
- 1797.** Munikumar M, Krishna VS, Reddy VS, Rajeswari B, Sriram D, Rao MV. In silico design of small peptides antagonist against leptin receptor for the treatment of obesity and its associated immune-mediated diseases. *J Mol Graph Model.* 2018;82:20-36.
- 1798.** Jonas M, Simon AJ, Gilburd B, Schneiderman J. Intrarenal anti-leptin treatment attenuates ischemia and reperfusion injury. *Am J Nephrol.* 2023;54:337-348.
- 1799.** Mukherjee A, Chiang CY, Daifotis HA, et al. Adipocyte-induced FABP4 expression in ovarian cancer cells promotes metastasis and mediates carboplatin resistance. *Cancer Res.* 2020;80: 1748-1761.
- 1800.** Yu H, Wang Z, Zhu B, et al. A humanized Anti-YKL-40 antibody inhibits tumor development. *Biochem Pharmacol.* 2024;225:116335. <https://doi.org/10.1016/j.bcp.2024.116335>
- 1801.** Peng Z, Wang X, Zhu Q, et al. CMKLR1 antagonist alpha-NETA protects against diabetic nephropathy in mice. *Kidney Blood Press Res.* 2023;48:405-413.
- 1802.** Ning S, Liu C, Lou W, et al. Bioengineered BERA-Wnt5a siRNA targeting Wnt5a/FZD2 signaling suppresses advanced prostate cancer tumor growth and enhances enzalutamide treatment. *Mol Cancer Ther.* 2022;21:1594-1607.
- 1803.** Jadhav PK, Schiffler MA, Gavardinas K, et al. Discovery of cathepsin S inhibitor LY3000328 for the treatment of abdominal aortic aneurysm. *ACS Med Chem Lett.* 2014;5:1138-1142.
- 1804.** Peng K, Liu H, Yan B, et al. Inhibition of cathepsin S attenuates myocardial ischemia/reperfusion injury by suppressing inflammation and apoptosis. *J Cell Physiol.* 2021;236:1309-1320.
- 1805.** Xu X, Khoong YM, Gu S, et al. Investigating the potential of LSKL peptide as a novel hypertrophic scar treatment. *Biomed Pharmacother.* 2020;124:109824. <https://doi.org/10.1016/j.bioph.2020.109824>
- 1806.** Kong W, Zhu L, Li T, et al. Azeliragon inhibits PAK1 and enhances the therapeutic efficacy of AKT inhibitors in pancreatic cancer. *Eur J Pharmacol.* 2023;948:175703. <https://doi.org/10.1016/j.ejphar.2023.175703>
- 1807.** Ye S, Ma F, Mahmood DFD, Vera PL. Modulation of persistent bladder pain in mice: The role of macrophage migration inhibitory factor, high mobility group box-1, and downstream signaling pathways. *Bladder (San Franc).* 2024;11 (2):e2120001. <https://doi.org/10.14440/bladder.2024.0015>
- 1808.** Li N, Hang W, Shu H, Zhou N. Pirfenidone alleviates cardiac fibrosis induced by pressure overload via inhibiting TGF-beta1/Smad3 signaling pathway. *J Cell Mol Med.* 2022;26:4548-4555.
- 1809.** Sandoval-Rodriguez A, Monroy-Ramirez HC, Meza-Rios A, et al. Pirfenidone Is an agonistic ligand for PPARalpha and improves NASH by activation of SIRT1/LKB1/pAMPK. *Hepatol Commun.* 2020;4:434-449.
- 1810.** Gutiérrez-Cuevas J, Sandoval-Rodriguez A, Monroy-Ramirez HC, et al. Prolonged-release pirfenidone prevents obesity-induced cardiac steatosis and fibrosis in a mouse NASH model. *Cardiovasc Drugs Ther.* 2021;35:927-938.
- 1811.** Lewis GA, Dodd S, Clayton D, Bedson E, et al. Pirfenidone in heart failure with preserved ejection fraction: a randomized phase 2 trial. *Nat Med.* 2021;27:1477-1482.

- 1812.** Frias JP, Deenadayalan S, Erichsen L, et al. Efficacy and safety of co-administered once-weekly cagrilintide 2·4 mg with once-weekly semaglutide 2·4 mg in type 2 diabetes: a multicentre, randomised, double-blind, active-controlled, phase 2 trial. *Lancet*. 2023;402:720-730.
- 1813.** Despa S, Margulies KB, Chen L, et al. Hyperamylinemia contributes to cardiac dysfunction in obesity and diabetes: a study in humans and rats. *Circ Res*. 2012;110:598-608.
- 1814.** James WP, Caterson ID, Coutinho W, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *N Engl J Med*. 2010;363:905-917.
- 1815.** Topol EJ, Bousser MG, Fox KA, et al. Rimonabant for prevention of cardiovascular events (CRESCENDO): a randomised, multicentre, placebo-controlled trial. *Lancet*. 2010;376:517-523.
- 1816.** Shah NR, Braverman ER. Measuring adiposity in patients: the utility of body mass index (BMI), percent body fat, and leptin. *PLoS One*. 2012;7(4):e33308. <https://doi.org/10.1371/journal.pone.0033308>
- 1817.** Brydon L, O'Donnell K, Wright CE, Wawrzyniak AJ, Wardle J, Steptoe A. Circulating leptin and stress-induced cardiovascular activity in humans. *Obesity (Silver Spring)*. 2008;16:2642-2647.
- 1818.** Cicero AF, Magni P, Lentini P, et al. Sex hormones and adipokines in healthy pre-menopausal, post-menopausal and elderly women, and in age-matched men: data from the Brisighella Heart study. *J Endocrinol Invest*. 2011;34:e158-e162.

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**KEY WORDS** adipokines, heart failure with a preserved ejection fraction, obesity, visceral adiposity

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**APPENDIX** For supplemental material, please see the online version of this paper.