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Diabetes-associated cardiac fibrosis: cellular effectors, molecular mechanisms and therapeutic opportunities

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Abstract

Both type 1 and type 2 diabetes are associated with cardiac fibrosis that may reduce myocardial compliance, contribute to the pathogenesis of heart failure, and trigger arrhythmic events. Diabetes-associated fibrosis is mediated by activated cardiac fibroblasts, but may also involve fibrogenic actions of macrophages, cardiomyocytes and vascular cells. The molecular basis responsible for cardiac fibrosis in diabetes remains poorly understood. Hyperglycemia directly activates a fibrogenic program, leading to accumulation of advanced glycation end-products (AGEs) that crosslink extracellular matrix proteins, and transduce fibrogenic signals through reactive oxygen species generation, or through activation of Receptor for AGEs (RAGE)-mediated pathways. Pro-inflammatory cytokines and chemokines may recruit fibrogenic leukocyte subsets in the cardiac interstitium. Activation of transforming growth factor-β/Smad signaling may activate fibroblasts inducing deposition of structural extracellular matrix proteins and matricellular macromolecules. Adipokines, endothelin-1 and the renin-angiotensin-aldosterone system have also been implicated in the diabetic myocardium. This manuscript reviews our current understanding of the cellular effectors and molecular pathways that mediate fibrosis in diabetes. Based on the pathophysiologic mechanism, we propose therapeutic interventions that may attenuate the diabetes-associated fibrotic response and discuss the challenges that may hamper clinical translation.

1. INTRODUCTION

Epidemiologic studies have documented a strong association between diabetes and heart failure [1]. Data from the Framingham study demonstrated a 2-fold higher risk of heart failure in male diabetics and a 5-fold increase in risk in female patients with diabetes [2]. In the Reduction of Atherothrombosis for Continued Health (REACH) registry, an international study of patients with established atherothrombotic disease, or at high risk for of atherothrombosis, diabetics exhibited a 33% higher risk of hospitalization due to heart

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failure [3]. Moreover, diabetes adversely affects prognosis in patients with heart failure. In the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program, diabetes was an independent predictor of morbidity and mortality in patients with heart failure, in both groups with systolic dysfunction and with preserved ejection fraction [4].

Despite its high clinical significance and important contribution to morbidity and mortality, diabetes-associated heart failure remains understudied [5]. From a pathophysiologic perspective, the increased incidence of heart failure in diabetics can be attributed to several factors. First, patients with diabetes have an increased incidence of coronary artery disease and develop atherosclerotic lesions at a younger age, often exhibiting multivessel disease and involvement of distal coronary segments. Second, hypertension is commonly found in both type 1 and type 2 diabetics [6] and may also be involved in the pathogenesis of diabetes-associated heart failure. Third, diabetes can cause distinct pathologic alterations in the myocardium, independent of its effects on blood pressure and coronary atherosclerosis. Histopathologic studies in myocardial samples from patients with diabetes [7] suggested a distinct entity, termed “diabetic cardiomyopathy” that may occur in the absence of coronary disease or other concomitant conditions and may contribute to the development of heart failure. In both human patients and in animal models of diabetes, interstitial and perivascular fibrosis are prominent characteristics of diabetic cardiomyopathy. Deposition of extracellular matrix proteins in the cardiac interstitium, and cross-linking of the matrix increase myocardial stiffness and may mediate diastolic dysfunction in the diabetic myocardium. Considering the high prevalence of heart failure with preserved ejection fraction (HFpEF) in diabetics, fibrotic myocardial remodeling may be critically implicated in the pathogenesis of diabetes-associated heart failure. The current manuscript reviews our understanding of the pathophysiology of diabetic cardiac fibrosis. We identify the cellular effectors mediating fibrosis in the diabetic heart, and discuss the molecular signals that may activate the fibrogenic response. Finally, we propose therapeutic interventions that may attenuate myocardial fibrosis, targeting heart failure in diabetic patients.

2. CARDIAC FIBROSIS IN DIABETICS

Extensive evidence has documented the presence of myocardial fibrosis in patients with diabetes. Cardiac magnetic resonance imaging often identifies myocardial scars (replacement fibrosis) in diabetics without a history of myocardial infarction; these findings likely reflect silent coronary events [8],[9]. Numerous histopathologic studies have demonstrated that cardiac fibrosis in diabetic patients occurs independently of coronary atherosclerosis or hypertension. Regan and co-workers showed that patients with adult-onset diabetes may exhibit extensive perivascular, interstitial, and even replacement fibrosis, in the absence of hypertension or coronary artery disease [10]. Myocardial fibrosis in diabetics is often accompanied by cardiomyocyte hypertrophy and by evidence of microvascular abnormalities, such as thickening of the capillary basement membrane [11]. Diabetes-associated interstitial fibrosis is associated with accumulation of type I and III collagen, involves both left [12],[13] and right ventricle [14], and has been described in both type 1 and type 2 diabetes [15],[16]. Relations between diabetes-associated fibrosis and cardiac function have not been systematically investigated. However, in a study examining biopsies

from patients with heart failure in the absence of coronary disease, diabetes was associated with increased collagen levels only in patients with reduced ejection fraction [17]. Diabetes is also associated with accentuation of fibrotic changes in patients with other cardiac conditions. In patients with aortic stenosis, diabetes was associated with worse myocardial stiffness and increased myocardial collagen content [18].

3. FIBROSIS IN ANIMAL MODELS OF DIABETES

Animal models of diabetes provide strong support to the association between diabetes and myocardial fibrosis. The severity of cardiac fibrosis and left ventricular dysfunction in experimental models of diabetes is dependent on the species, genetic background, gender and age of the animals studied, the etiology of diabetes and the presence of concomitant pathophysiologic conditions (such as hypertension, dyslipidemias, etc.) [19].

Streptozotocin-induced diabetes models have been extensively used to investigate the complications of type 1 diabetes. In rodent models, steptozotocin induces β cell toxicity and death, and triggers a T cell-mediated immune response, simulating human insulin-dependent diabetes [20]. In both mice and rats, streptozotocin-induced diabetes is associated with interstitial myocardial fibrosis, accompanied by cardiomyocyte hypertrophy, induction of pro-fibrotic and hypertrophy-associated genes, and microvascular rarefaction [21],[22],[23], [24],[25]. In contrast, in a genetic model of insulin-dependent type 1 diabetes, the *Ins2*$^{WT/C96Y}$ Akita mouse, diastolic dysfunction was associated with a lipotoxic cardiomyopathy, in the absence of significant cardiac fibrosis and cardiomyocyte hypertrophy [26].

Pro-fibrotic effects of type 1 diabetes on the myocardium have also been demonstrated in large animal models. Mongrel dogs rendered diabetic through administration of alloxan developed significant myocardial fibrosis [27]. Alloxan-induced insulin-dependent diabetes had similar effects on rhesus monkeys, causing a 2-fold increase in left ventricular collagen content, in the absence of hypertrophy [28].

Cardiac fibrosis has also been documented in experimental models of type 2 diabetes (Figure 1). db/db mice express a truncated leptin receptor and are resistant to the central effects of leptin. These animals develop severe obesity at 1–2 months of age, associated with overt diabetes. Both histochemical staining techniques and biochemical assays have consistently documented cardiac fibrosis in db/db mice at 4–6 months of age [29],[30],[31], accompanied by cardiomyocyte hypertrophy and diastolic dysfunction [32],[31]. Leptin-deficient ob/ob animals also develop severe obesity, insulin resistance and cardiac hypertrophy at a young age [33]. However, evidence demonstrating fibrotic remodeling in ob/ob hearts has been inconsistent. 20-week old ob/ob in a C57BL/6J background exhibited significant perivascular cardiac fibrosis associated with elevated expression of Transforming Growth Factor (TGF)-β1 and Plasminogen activator inhibitor (PAI)-1, indicating activation of matrix-preserving pathways [34]. In contrast, another study demonstrated that 36-week-old ob/ob mice exhibited cardiac hypertrophy and diastolic dysfunction, but had comparable collagen content with lean WT animals [35]. Gender-specific effects, the relative sensitivity of various techniques used to assess fibrosis, and differences in the diets fed to the animals

may explain the conflicting findings. Genetic models of type diabetes in the rat also exhibit cardiac fibrosis. Zucker rats have a leptin receptor missense mutation and develop severe obesity and insulin resistance. These animals have perivascular myocardial fibrosis, associated with cardiomyocyte hypertrophy [36] and diastolic dysfunction [37].

The effects of diet-induced type 2 diabetes and metabolic syndrome on the myocardial interstitium are more subtle. Male C57/BL6J mice fed a high-fat/high-carbohydrate diet developed diabetes associated with ventricular hypertrophy, interstitial fibrosis and diastolic dysfunction after 6–8 months of feeding [38],[39]. Feeding of male C57/BL6J mice with a high-fat diet required 16 months for development of significant cardiac hypertrophy and myocardial fibrosis [40].

Animal model experiments support the clinical evidence suggesting that diabetes accentuates fibrosis induced by other pathophysiologic conditions. Streptozotocin-induced insulin-dependent diabetes increased hypertensive myocardial fibrosis in rats [41]. Moreover, non-insulin dependent diabetes in mice increased myocardial susceptibility to hypertensive hypertrophy and fibrosis [42].

4. THE CELL BIOLOGY OF DIABETES-ASSOCIATED CARDIAC FIBROSIS

The adult mammalian myocardium contains large populations of non-cardiomyocytes, enmeshed into the interstitial matrix network, including fibroblasts, pericytes vascular smooth muscle cells, endothelial cells, mast cells, macrophages and dendritic cells. Although fibroblasts, as the main matrix-producing cells, are considered critical cellular effectors of fibrosis, other populations of myocardial cells may also contribute to the fibrotic process by modulating fibroblast phenotype and function (Figure 2). Although the cell biological basis of cardiac fibrosis has been extensively investigated in models of myocardial infarction and cardiac pressure overload [43], much less is known regarding the cells responsible for diabetes-associated fibrotic cardiac remodeling.

The fibroblasts

As the main matrix-producing cells in the cardiac interstitium, fibroblasts are critically involved in all cardiac fibrotic conditions [44],[45]. In the infarcted and remodeling myocardium, fibroblasts undergo myofibroblast transdifferentiation, expressing contractile proteins, such as α-smooth muscle actin (α-SMA), and synthesizing large amounts of extracellular matrix proteins [46],[47],[48],[49]. Although diabetes-associated cardiac fibrosis likely involves expansion and activation of the resident fibroblast population, whether fibroblasts in diabetic hearts undergo a similar process of myofibroblast conversion remains unknown. In vitro studies characterizing fibroblasts isolated from diabetic hearts provide robust evidence of activation. Cardiac fibroblasts harvested from obese diabetic Zucker rat hearts exhibited greater ability to contract gels, increased proliferative activity, and elevated α-SMA expression, consistent with a myofibroblast phenotype [50]. Cardiac fibroblasts isolated from db/db mice exhibited a matrix-preserving phenotype, associated with increased expression of collagen and protease inhibitors [51]. Atrial fibroblasts derived from patients with type 2 diabetes also showed evidence of activation, exhibiting high collagen synthesis [52]. Hyperglycemia, activation of the Renin-angiotensin-aldosterone

(RAAS) system and fibrogenic growth factors induced by metabolic dysregulation may be involved in activation of cardiac fibroblasts in diabetic hearts.

Monocytes and macrophages

The myocardium contains a resident macrophage population [53],[54] that is enriched following cardiac injury through recruitment of monocytes [55],[56]. Macrophages are highly plastic cells, capable of acquiring a fibrogenic phenotype that may activate fibroblasts following myocardial injury, or pressure overload [57],[58],[59]. Infiltration of the diabetic myocardium with monocytes and macrophages has been demonstrated in models of type 1 and type 2 diabetes [60],[61],[62]; these cells may contribute to fibrotic remodeling of the ventricle by secreting a wide range of fibrogenic mediators. Whether recruitment or activation of fibrogenic subsets of monocytes/macrophages mediates fibrosis in diabetic hearts has not been directly tested.

Lymphocytes

A growing body of evidence suggests that lymphocyte subpopulations modulate fibroblast phenotype [63], and may mediate fibrotic responses in the remodeling myocardium [64], [65]. Whether alterations in lymphocyte phenotype are implicated in the pathogenesis of diabetes-associated cardiac fibrosis remains unknown.

Endothelial cells and pericytes

In the infarcted and in the pressure overloaded heart, endothelial to mesenchymal transition (EndMT) contributes to cardiac fibrosis, by providing an additional pool of activated fibroblasts [66],[67]. In models of type 1 diabetes, associative evidence supports the involvement of EndMT in the expansion of fibroblasts in the cardiac interstitium [68]. Pericytes are also capable of myofibroblast conversion and may acquire a fibroblast-like phenotype in diabetic states [69]. Moreover, vascular cells may participate in cardiac fibrosis by secreting mediators that activate fibroblasts. Hard documenting the involvement of vascular cells in diabetes-associated fibrosis is lacking.

Mast cells

Mast cells are capable of producing fibrogenic growth factors and proteases and have been implicated in the pathogenesis of cardiac fibrosis in models of myocardial infarction, cardiac pressure overload and cytokine overexpression [70],[71],[72]. In a mouse model of type 1 diabetes, delayed accumulation of mast cells has been implicated in defective healing [73]. Whether mast cells are involved in diabetes-associated cardiac fibrosis remains unknown.

Cardiomyocytes

Cardiomyocytes may play a critical role in diabetes-associated cardiac fibrosis through several distinct mechanisms. First, diabetes and metabolic dysfunction may exert toxic effects on the cardiomyocytes, eventually leading to irreversible injury and cell death [74], [75]. Fibrosis in diabetics may reflect replacement of dead cardiomyocytes with fibrous tissue, rather than direct activation of fibroblasts or immune cells. Second, hyperglycemia may promote a fibrogenic phenotype in cardiomyocytes, inducing synthesis and release of

growth factors and cytokines that induce fibroblast proliferation and activation. Third, cardiomyocytes in diabetic hearts may express pro-inflammatory mediators that trigger fibrosis through activation of immune cells. Robust experimental data supporting these cellular mechanisms are lacking.

5. MOLECULAR SIGNALS IMPLICATED IN DIABETES-ASSOCIATED CARDIAC FIBROSIS

Experimental evidence suggests that diabetes-associated cardiac fibrosis may involve activation of several distinct, but overlapping, fibrogenic pathways, including neurohumoral signals, inflammatory cytokines and growth factors, endothelin-1, adipokines, reactive oxygen species (ROS) and deposition of matricellular proteins in the cardiac interstitium. It is likely that the significance of each one of these pathways may be dependent on the severity and pathophysiologic basis of diabetes and on the presence of concommittant conditions, such as dyslipidemia and hypertension.

Hyperglycemia activates a pro-fibrotic program

In vitro, high glucose stimulates fibroblast proliferation, promotes myofibroblast transdifferentiation, and activates transcription and secretion of extracellular matrix proteins [76],[77],[78]. The stimulatory effects of glucose have been attributed to activation of angiotensin II and TGF-β signaling [79],[76], ROS generation [80] and subsequent stimulation of Erk [81] pathways. However, the significance of these findings in vivo is unclear, as robust evidence demonstrating that diabetes-associated myocardial fibrosis is due to hyperglycemia is lacking. Although clinical data examining relations between serum glucose and cardiac fibrosis are lacking, randomized controlled trials do not support the notion that intensive glycemic control reduces the incidence of heart failure in diabetics [1]. Moreover, correction of hyperglycemia does not consistently attenuate diabetes-associated fibrosis in extracardiac tissues. In rats with streptozotocin-induced type 1 diabetes, tight glycemic control did not affect the development of renal fibrosis [82]. Thus, the role of hyperglycemia in mediating fibrotic remodeling of the diabetic heart remains unclear.

Neurohumoral activation

Diabetes activates the myocardial RAAS; increased activity of local RAAS in diabetic hearts may induce a pro-fibrotic program in cardiac fibroblasts, while promoting functional abnormalities in cardiomyocytes [83]. In vivo studies have documented increased myocardial levels of angiotensin II and augmented density of angiotensin II type 1 (AT1) receptors in experimental models of type 1 and type 2 diabetes [84],[85]. Most of the evidence on the role of angiotensin signaling in diabetes-associated cardiac fibrosis is derived from pharmacologic inhibition studies. In three different models of type 2 diabetes (Zucker rats, db/db and ob/ob mice) ACE inhibition decreased collagen deposition, and reduced perivascular coronary fibrosis, attenuating TGF-β levels [86],[32]. Experiments using AT1 blockers suggested that the profibrotic effects of angiotensin II in diabetes are mediated through AT1 signaling [34], [87]. The protective effects of ACE inhibition and AT1 blockade in diabetes-associated cardiac fibrosis are also observed in models of type 1 diabetes [88].

Several molecular cascades may transduce pro-fibrotic angiotensin II signaling in the diabetic heart. First, angiotensin-mediated AT1 signaling may increase TGF-β expression and activation [89], stimulating Smad-dependent and Smad-independent signaling. Second, angiotensin II may accentuate TGF-β responses by inducing expression of the pro-fibrotic TGF-β co-receptor endoglin [90]. Third, AT1 activation may generate ROS in the diabetic myocardium promoting fibroblast activation [32],[91].

Aldosterone may also be an important downstream effector of angiotensin-mediated fibrogenic actions on the myocardium [92]. Experimental evidence suggests that aldosterone antagonism attenuates fibrosis in a rat model of type 1 diabetes [93] and in a mouse model of diet-induced obesity [94]. Clinical studies support an important role for aldosterone signaling in myocardial fibrosis associated with diabetes and obesity. In a prospective randomized controlled clinical study, a 6-month course of the aldosterone antagonist spironolactone in patients with obesity, but without other comorbidities, reduced levels of serological markers of collagen synthesis and improved myocardial compliance and diastolic function [95].

Pro-inflammatory cytokines and chemokines

Activation of immune pathways and induction of pro-inflammatory signaling are associated with fibrosis [96]. Pro-inflammatory cytokines (such as Tumor Necrosis Factor (TNF)-α, and Interleukin (IL)-1β) modulate fibroblast phenotype and have been implicated in the pathogenesis of heart failure. In cardiac fibroblasts, TNF-α stimulation induces proliferation and enhances collagen synthesis [97]. IL-1β on the other hand, delays myofibroblast conversion, promoting α matrix-degrading pro-inflammatory fibroblast phenotype [98]. In a model of streptozotocin-induced type 1 diabetes TNF-α and IL-1β were upregulated in the myocardium [99],[100]. However, experiments examining the effects of cytokine inhibition in rodent models of diabetes have produced conflicting results [101],[102] that may be explained by differences in experimental models, the specific anti-cytokine strategy used, and different methodologies for assessment of cardiac remodeling. The cellular targets of TNF-α and the molecular signals responsible for activation of a pro-fibrotic program in the diabetic heart remain unknown.

Chemokines may also be implicated in cardiac fibrosis through recruitment of fibrogenic monocyte subsets, or through direct actions on fibroblasts [103]. The CC chemokine Monocyte Chemoattractant Protein (MCP)-1/CCL2 mediates ischemic cardiac fibrosis, predominantly through effects on macrophages [104],[55]. Moreover, the CXC chemokine Stromal cell-Derived Factor (SDF)-1/CXCL12 may promote fibrosis by mediating recruitment of bone marrow-derived cells [105]. Evidence suggesting a role for chemokine-mediated pathways in diabetes-associated cardiac fibrosis is limited. Although myocardial MCP-1 expression was increased in a rat model of type 2 diabetes [106], whether induction of the chemokine plays a critical role in fibrosis of the diabetic heart has not been investigated. SDF-1 blockade through inhibition of its receptor CXCR4 attenuated cardiac fibrosis in rodent models of type 1 and type 2 diabetes [107].

TGF-β

TGF-βs are highly pleiotropic mediators that have been extensively implicated in the pathogenesis of tissue fibrosis [108],[109]. TGF-β1 mediates myofibroblast transdifferentiation, stimulates matrix transcription, and promotes a matrix-preserving phenotype in fibroblasts by inducing synthesis of protease inhibitors [108]. Increased myocardial expression of TGF-β has been consistently reported in models of type 1 and type 2 diabetes and is associated with cardiac fibrosis [100],[110],[111],[86]. TGF-β induction in diabetic hearts may be mediated through angiotensin II activation [86], or may involve direct actions of high glucose and leptin on TGF-β transcription, secretion, and activation [112],[113].

Because TGF-β exerts a wide range of actions on all cell types involved in cardiac remodeling, dissecting its biological actions on the diabetic heart is challenging. Pro-fibrotic actions of TGF-β may involve both Smad-dependent and Smad-independent pathways [114],[115]. Experiments using a mouse model of type 2 diabetes demonstrated that global loss of Smad3 reduces cardiac fibrosis and improves myocardial compliance, attenuating myocardial oxidative stress [31]. Whether the pro-fibrotic actions of Smad3 in the diabetic heart reflect direct actions on cardiac fibroblasts, or effects on cardiomyocytes, immune and vascular cells remains unknown.

Endothelin (ET)-1

ET-1, is a potent vasoconstrictor and pro-fibrotic peptide, produced by vascular endothelial cells in response to stimulation with cytokines, angiotensin II, or hypoxia. Experimental evidence suggests that ET-1 expression is induced in experimental models of type 1 and type 2 diabetes [68],[116]. In streptozotocin-induced diabetic mice, endothelial cell-specific loss of ET-1 attenuated myocardial fibrosis, reducing endothelial to mesenchymal transdifferentiation [68]

Oxidative stress

ROS generation is has been extensively implicated in the pathogenesis of cardiac fibrosis Fibrogenic actions of angiotensin II, cytokines and growth factors are, at least in part, dependent on ROS. Extensive evidence demonstrates accentuated oxidative stress in experimental models of type 1 and type 2 diabetes [117]. Streptozotocin-induced diabetic rats exhibited increased glutathione oxidation and augmented lipid hydroperoxide levels in the myocardium [118]. In db/db hearts, mitochondrial generation of ROS is markedly increased and is associated with peroxidation of lipids and proteins [119]. Hyperglycemia and insulin resistance may increase myocardial ROS generation in diabetic animals. Moreover, diabetes is associated with attenuated myocardial activation of antioxidant enzymes, such as manganese superoxide dismutase and glutathione peroxidase 1 [120], [121], suggesting that defective free radical scavenging may also contribute to the accentuated oxidative stress.

The role of oxidative stress in diabetes-associated cardiac fibrosis is supported predominantly by pharmacologic interventions. In models of type 1 or type 2 diabetes, various pharmacological approaches that inhibit oxidative stress, or reduce the level of

oxidative modification attenuated cardiac interstitial fibrosis [122], reduced cardiomyocyte hypertrophy, and decreased diastolic dysfunction [39],[32].

The advanced glycation end-products (AGE)/Receptor for AGE (RAGE) axis

After prolonged exposure to aldose sugars, proteins and lipids undergo non-enzymatic glycation and oxidation, leading to formation of AGEs [123]. In diabetic tissues, accelerated accumulation of AGEs may mediate inflammation and fibrosis. AGEs accumulate in both intracellular and extracellular space and may play a key role in diabetes-associated cardiac fibrosis through several distinct mechanisms. First, AGEs crosslink collagens and laminins in the extracellular matrix and may reduce cardiac compliance, causing diastolic dysfunction. Second, AGEs may bind to RAGEs, cell surface receptors that when activated modulate cellular phenotype. In fibroblasts, AGE/RAGE signaling stimulates inflammatory gene synthesis, accentuates expression of matrix proteins, and stimulates proliferation [124]. The pro-fibrotic effects of RAGE may be mediated, at least in part, through TGF-β [125] and AT-1 cascades [126]. Third, AGEs generate ROS and may promote fibrosis by increasing oxidative stress. Fourth, AGEs may modulate macrophage phenotype inducing a pro-fibrotic program. The in vivo role of these potential mechanisms in mediating diabetes-associated cardiac fibrosis has not been systematically studied. In db/db mice, RAGE blockade protected from the development of diastolic dysfunction, attenuating myocardial collagen expression [127]. However, the cellular basis and molecular mechanisms for these effects remain unknown.

Adipokines—Adipose tissue does not serve only as a depot for stored fat, but also secretes large amounts of bioactive mediators, termed adipokines. Of these pleiotropic molecules, leptin and adiponectin have been implicated in the pathogenesis of tissue fibrosis.

Leptin is involved in the pathogenesis of cardiac remodeling in type 2 diabetes, obesity and metabolic dysfunction through effects on both cardiomyocytes and cardiac fibroblasts. In patients with uncomplicated obesity, elevated circulating leptin is associated with increased left ventricular mass [128]. Conflicting data are available on the effects of leptin on cardiomyocytes, suggesting both hypertrophic and anti-hypertrophic actions [129],[130]. Moreover, leptin is capable of activating fibroblasts, inducing activation of MMPs [131], [132]. In vivo, exogenous leptin administration in ob/ob mice significantly increased interstitial fibrosis [133]. The relative significance of the cellular actions of leptin on cardiomyocytes and fibroblasts in vivo remains unknown.

Adiponectin, an adipokine with anti-inflammatory, cardioprotective and anti-atherogenic properties [134],[135] may also regulate cardiac fibrosis. In vitro studies have suggested conflicting effects of adiponectin on fibroblast migration [136],[137]. In vivo, adiponectin exerted anti-fibrotic effects in a model of angiotensin-induced cardiac remodeling [138]. In db/db mice, exogenous adiponectin reduced cardiac hypertrophy activating AMPK signaling [139]. The role of adiponectin in diabetic cardiac fibrosis remains unknown.

The role of the matricellular proteins—Following injury, the extracellular matrix is enriched through deposition of matricellular proteins, extracellular macromolecules that do not play a structural role, but transduce signaling cascades, modulating cell:cell and

cell:matrix interactions. Several members of the matricellular family, including the thrombospondins (TSPs), tenascins-C and X, periostin, osteonectin, osteopontin, periostin, etc. are induced in the remodeling heart and regulate inflammatory, fibrotic and angiogenic responses [140]. TSP-1 is induced by high glucose [141] and is consistently upregulated in diabetes, obesity and metabolic dysfunction in both animal models and human patients [142],[143]. TSP-1 induction in the diabetic heart promotes matrix-preserving actions, while causing capillary rarefaction in db/db mice through effects on angiopoietin-2 synthesis [30]. Thus, induction of TSP-1 may mediate both fibrosis and vascular loss in the diabetic myocardium.

MicroRNAs—MicroRNAs (miRNAs) are short noncoding RNAs that function as regulators of gene expression and are involved in virtually all cellular responses. A growing body of evidence suggests a critical role for miRNAs in cardiac fibrosis [144]. miRNAs have multiple targets, including cytokines and growth factors, extracellular matrix proteins, proteases and matricellular macromolecules. Although published investigations suggest critical roles for several miRNAs in cardiac fibrosis induced by pressure overload or myocardial infarction, evidence indicating involvement of specific miRNAs in diabetes-associated cardiac fibrosis is limited. Recent studies investigated the myocardial miRNA landscape in a mouse model of type 1 diabetes [145],[146]. Diabetic hearts had alterations in levels of several miRNAs implicated in the pathogenesis of fibrosis, exhibiting upregulation of miR-125b and miR-199a, and downregulation of miR-150, miR-29b and miR-30a. Importantly, dysregulated expression of fibrosis-associated miRNAs remained altered in animals receiving insulin therapy to achieve intensive glycemic control [146]. Experimental studies examining whether these alterations play a causative role in the pathogenesis of diabetic cardiac fibrosis have not yet been performed. A recent investigation suggested that miR-133 downregulation may be involved in fibrotic remodeling of the diabetic heart. In a model of type 1 diabetes, cardiac fibrosis was associated with suppressed myocardial miR-133 expression; miR-133 overexpression attenuated the fibrotic response attenuating Erk and Smad activation [147].

6. TARGETING DIABETIC CARDIAC FIBROSIS: CHALLENGES AND OPPORTUNITIES

Clinical evidence suggests that diabetics with evidence of cardiac fibrosis, assessed through cardiac magnetic resonance imaging, have increased mortality and higher incidence of hospitalizations due to heart failure [148]. Several mechanisms may contribute to the increased risk. First, myocardial fibrosis may reduce ventricular compliance causing HFpEF. Second, diabetes-associated atrial fibrosis may induce atrial fibrillation, precipitating heart failure, and increasing the incidence of stroke. Third, ventricular fibrosis may be responsible for the increased risk of ventricular arrhythmias and sudden death observed in diabetic individuals [149]. Fourth, diabetes-related perturbation of the reparative response following infarction may result in faulty healing, adverse remodeling and development of post-infarction heart failure. Thus, on a theoretical basis, attenuation of cardiac fibrosis may reduce morbidity and mortality in diabetic patients.

Which strategies could be used to reduce cardiac fibrosis in diabetics? Considering the potentially critical involvement of high glucose in the pathogenesis of fibrosis, it would be reasonable to hypothesize that tight glycemic control may be effective in attenuation of cardiac fibrosis. Although poor glycemic control is associated with an increased incidence of heart failure [150], intensive glucose lowering failed to reduce cardiovascular events [151], the risk of heart failure [152] and the incidence of new-onset atrial fibrillation [153]. Unfortunately, relations between outcome and effects on cardiac fibrosis have not been studied.

Clearly, additional pharmacologic strategies are needed to inhibit and reverse fibrosis and to prevent the development of heart failure in diabetics. Established approaches inhibiting the RAAS through the use of ACE inhibitors, angiotensin receptor blockers and aldosterone antagonists may be valuable and have an excellent record of safety. Whether these approaches exert beneficial actions through attenuation of fibrosis is unclear. Novel pharmacologic strategies targeting the ROS system, AGE-mediated crosslinking, ET-1 or the TGF-β system hold significant promise. However, such approaches may also carry significant risks, due to the need for prolonged therapy and the importance of these molecular signals in homeostasis and tissue repair [154].

Attenuation of fibrotic remodeling following myocardial infarction may represent a more attractive therapeutic opportunity to reduce the risk of heart failure in diabetics. A brief therapeutic intervention may be effective in protecting the infarcted heart from excessive fibrosis in diabetic patients surviving an acute myocardial infarction. Clinical evidence suggests that diabetics have an increased incidence of post-infarction heart failure predominantly due to diastolic dysfunction [155]. Overactive angiotensin or TGF-β/Smad signaling may drive the reparative process towards an excessive fibrotic response. Dissection of the mechanisms responsible for defective cardiac repair in diabetics, and use of biomarkers or imaging studies to identify patients with specific pathophysiologic defects are needed to design personalized therapeutic approaches in order to reduce fibrosis and prevent the development of post-infarction heart failure [156].

7. CONCLUSIONS

Diabetes-associated cardiac fibrosis may be a major contributor to morbidity and mortality by causing heart failure and by increasing the incidence of arrhythmic events. Our understanding of the cellular events and molecular pathways involved in the pathogenesis of cardiac fibrosis remains limited. As a result, effective therapies targeting the fibrotic response in diabetic are lacking. Studies are needed to dissect the diabetes-associated molecular signals that activate fibroblasts in the cardiac interstitium, and to understand the fundamental basis for the link between metabolic dysfunction and fibrosis.

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Highlights

- Diabetes is associated with cardiac fibrosis.
- Diabetic cardiac fibrosis contributes to diastolic dysfunction and arrhythmogenesis.
- Activated fibroblasts are the main effector cells in diabetic fibrosis.
- Neurohumoral and inflammatory pathways may activate diabetic fibroblasts.
- Induction of matricellular proteins in the diabetic myocardium promotes fibrosis.

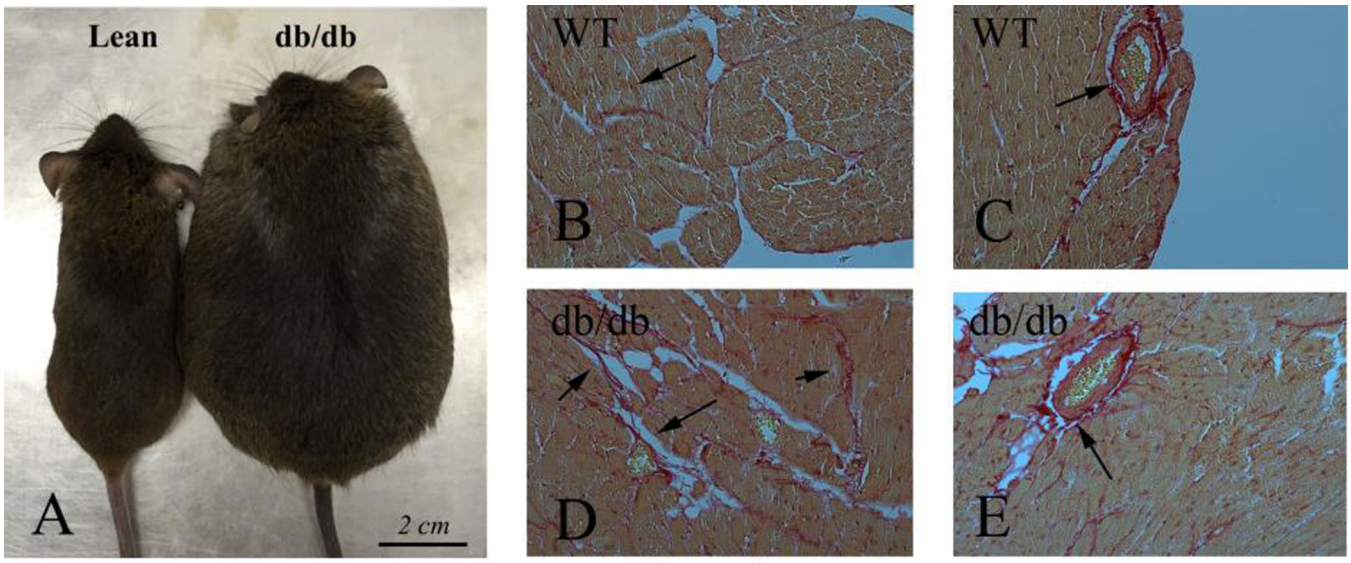

Figure 1.

Cardiac fibrosis in experimental models of diabetes. A. db/db mice develop severe obesity and diabetes, associated with myocardial fibrosis. B–E. Sirius red staining labels collagen (red – arrows) in the cardiac interstitium (B) and in perivascular areas (C) in lean and db/db mice (D–E). db/db animals exhibit expansion of the interstitial space (D) and perivascular accumulation of collagen (E).

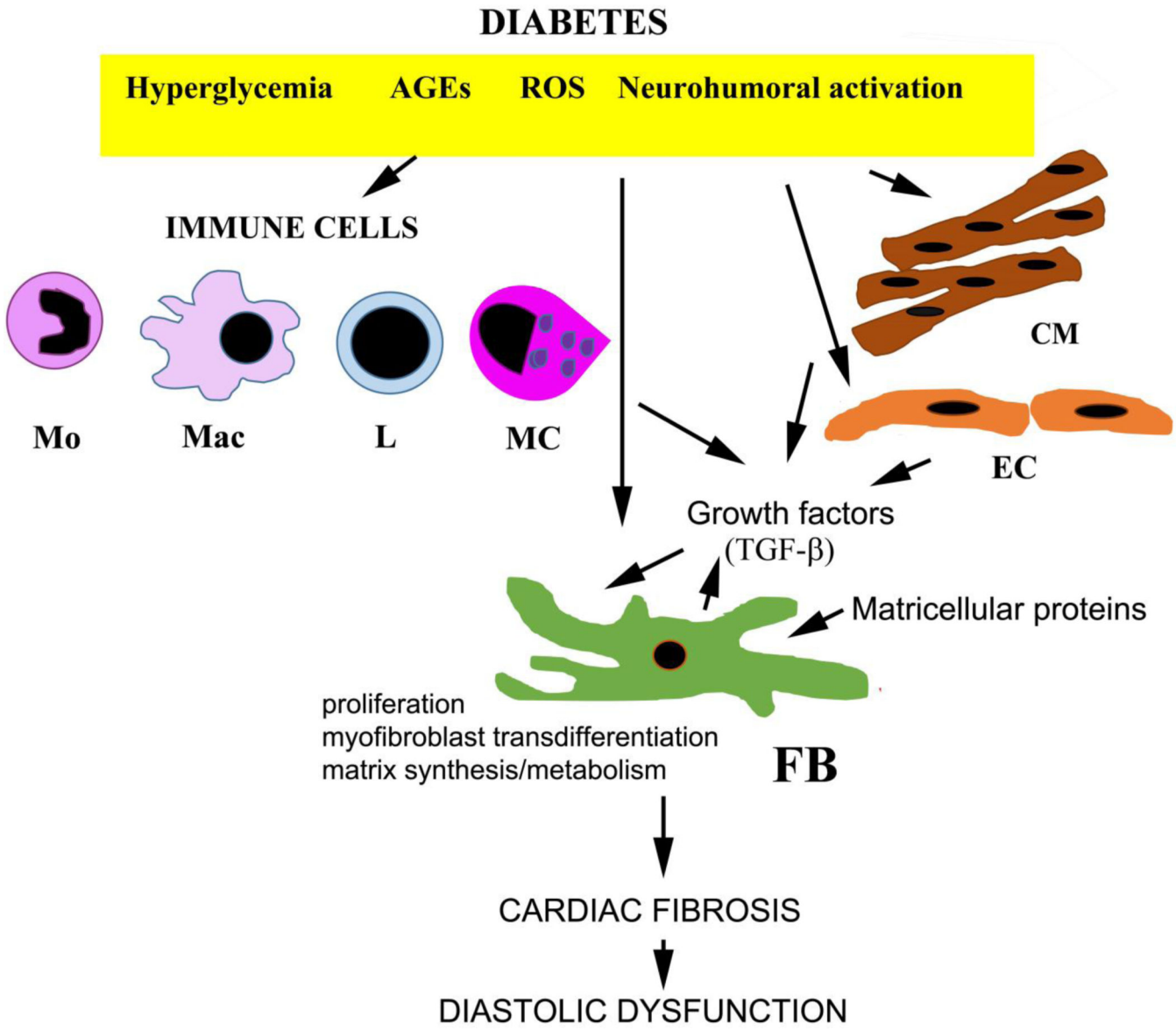

Figure 2.

The cell biology of diabetes-associated cardiac fibrosis. Diabetes-associated hyperglycemia, generation of advanced glycation end-products (AGEs) and reactive oxygen species (ROS) and neurohumoral activation directly activate resident cardiac fibroblasts and may induce a proliferative response and a matrix-synthetic phenotype. Induction and activation of fibrogenic growth factors (such as TGF-β) may play an important role in fibroblast stimulation. Immune cells (monocytes/Mo, macrophages/Mac, lymphocytes/L and mast cells/MC) may contribute to the fibrotic response by secreting pro-fibrotic mediators. Cardiomyocytes (CM) and endothelial cells (EC) may also secrete growth factors and modulate fibroblast phenotype. Endothelial cells and pericytes may transdifferentiate into fibroblasts contributing to the expansion of the fibroblast population in diabetic hearts.

Deposition of matricellular proteins (such as thrombospondin-1) in the diabetic myocardium may promote a pro-fibrotic phenotype in interstitial cells.