Biochemical Pharmacology 192 (2021) 114723

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Review

White adipose tissue dysfunction in obesity and aging

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ARTICLE INFO

Keywords:
Adipose tissue
Immune cells
Obesity
Aging

ABSTRACT

Both obesity and aging are associated with the development of metabolic diseases such as type 2 diabetes and cardiovascular disease. Chronic low-grade inflammation of adipose tissue is one of the mechanisms implicated in the progression of these diseases. Obesity and aging trigger adipose tissue alterations that ultimately lead to a pro-inflammatory phenotype of the adipose tissue-resident immune cells. Obesity and aging also share other features such as a higher visceral vs. subcutaneous adipose tissue ratio and a decreased lifespan. Here, we review the common characteristics of obesity and aging and the alterations in white adipose tissue and resident immune cells. We focus on the adipose tissue metabolic derangements in obesity and aging such as inflammation and adipose tissue remodeling.

1. Introduction

Inflammation is a central component of innate immunity [1], and is responsible for defending the body from various injuries, including infection and tissue damage, and restoring the integrity of affected tissues [2,3]. This response is characterized by increased blood flow, capillary dilatation, immune cell infiltration and the release of immunomodulatory molecules including cytokines and chemokines, which promote the neutralization of toxic agents and the repair of damaged tissue [4]. The resolution of inflammation is a process that enables tissues to return to homeostasis through immune cell reprogramming and the secretion of several anti-inflammatory mediators [5]. The activation of inflammation is essential for the preservation of cellular and organ integrity as a defense mechanism [1]. However, a chronic systemic inflammatory state, including low-grade inflammation, promotes the development of several diseases such as non-alcoholic fatty liver disease (NAFLD), cardiovascular disease (CVD), metabolic syndrome (MetS) and type 2 diabetes mellitus (T2D) [6,7], which are also age-related

Abbreviations: 4BL, B-cell subset expressing 4-1BBL; ADIPO-IR, Adipose tissue insulin resistance index; ASCs, Adipose stem cells; AT, Adipose tissue; ATMs, Adipose tissue infiltrated macrophages; BAT, Brown adipose tissue; BMI, Body mass index; Bregs, Regulatory B lymphocytes; CCL2, Chemokine (C-C motif) ligand 2; CCL5, Chemokine (C-C motif) ligand 5; CCR2, C-C chemokine receptor type 2; CD4, Cluster of differentiation 4; CD8, Cluster of differentiation 8; cDCs, Conventional dendritic cells; CLEC4C, C-Type lectin domain family 4 member C; CLS, Crown-like structures; CVD, Cardiovascular disease; DCs, Dendritic cells; DIO, Diet-induced obesity; ECM, Extracellular matrix; ERK, Extracellular signal-regulated kinase; G-CSF, Granulocyte colony-stimulating factor; HFD, High fat diet; HOMA2-IR, Physiological adjustments to a computer version of homeostatic model assessment; IFN-γ, Interferon gamma; IKK, IκB kinase; IL-1α, Interleukin 1 alpha; IL-1β, Interleukin 1 beta; IL-2, Interleukin 2; IL-6, Interleukin 6; IR, Insulin resistance; ISGs, Interferon-stimulated genes; M1, Classically activated macrophages, pro-inflammatory macrophages; M2, Alternative activated macrophages, anti-inflammatory macrophages; MetS, Metabolic syndrome; MIP-1β, Macrophage inflammatory protein 1 beta; NAFLD, Non-alcoholic fatty liver disease; NF-κB, Nuclear factor kappa B; p38 MAPK, p38 mitogen-activated protein kinases; pDCs, Plasmocytoid dendritic cells; PPARγ, Peroxisome proliferator-activated receptor gamma; SAT, Subcutaneous adipose tissue; SVF, Stromal vascular fraction; T2D, Type 2 diabetes mellitus; Th1, Type 1 T lymphocytes; Th17, Type 17 T lymphocytes; Th2, Type 2 T lymphocytes; TLR4, Toll-like receptor 4; TNF-α, Tumor necrosis factor alpha; Tregs, Regulatory T lymphocytes; VAT, Visceral adipose tissue; WAT, White adipose tissue; Wnt, Wingless-type MMTV integration site family.

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https://doi.org/10.1016/j.bcp.2021.114723
Received 31 May 2021; Received in revised form 30 July 2021; Accepted 3 August 2021
Available online 5 August 2021

diseases [8].

Overweight and aging are major global public health issues. Both promote the development of metabolic diseases associated with chronic low-grade inflammation [9]. These conditions are linked to higher rates of chronic diseases, which affect quality of life and public health costs [10,11]. Low-grade inflammation is associated with changes in body composition and immune cell phenotype [12–15]. This review describes the changes in adipose tissue (AT) and the common features present in obesity and aging, and their relationship with the development of several metabolic diseases.

2. Adipose tissue classification and distribution: Implications in obesity and aging

AT can be classified into brown adipose tissue (BAT) and white adipose tissue (WAT) [16]. BAT is mainly characterized by multilocular lipid droplets and a large number of mitochondria, which confer the ability to produce heat through non-shivering thermogenesis [17]. In contrast, WAT is comprised of large adipocytes with a single lipid droplet and with fewer mitochondria compared with BAT. This morphology confers on WAT the capacity for energy storage and homeostasis in response to nutritional demands [17]. In humans, WAT can be classified according to its distribution in two main depots: visceral WAT (VAT), which includes omental, mesenteric, retroperitoneal, gonadal, and pericardial WAT, and subcutaneous WAT (SAT), which is located under the skin. Both depots have been widely studied for their association with the development of insulin resistance (IR) and cardiometabolic risk [18,19]. However, each depot has different biochemical features and metabolic functions. In fact, it has been reported that AT distribution has a direct effect on the overall metabolism [20,21] and some studies have demonstrated that a high amount of VAT is associated with metabolic dysregulation [22,23], promoting glucose intolerance and IR [24]. *In vitro* assays have shown that adipocytes isolated from VAT have higher levels of lipid synthesis and lipolysis compared to SAT adipocytes [25,26]. In addition, the portal theory explains that all metabolites of VAT are released into the portal vein; therefore an increase in the amount of VAT could be responsible for metabolic complications associated with liver status [27,28]. Consequently, increased VAT mass is an independent factor in metabolic deterioration, and the size of this depot is directly associated with a poor prognosis in metabolic diseases [29].

On the other hand, some studies have proposed that an increase in SAT mass has a protective role and that it is inversely associated with glucose intolerance, IR and risk of T2D diagnosis [24,30]. In fact, a decrease in triglyceride accumulation in SAT results in increased lipid deposition in VAT, leading to metabolic complications [26,31,32]. Moreover, it has been demonstrated that pre-adipocytes isolated from SAT show different levels of expression of developmental genes compared with VAT precursors [20,33], suggesting that each depot plays a unique role in AT biology. Therefore, changes in the distribution of AT are relevant to understand its role in metabolism.

2.1. WAT changes in obesity

Obesity is characterized by the excessive accumulation of body fat in WAT (Fig. 1), mostly due to an imbalance between energy intake and expenditure. Hence, an increase in VAT and SAT mass leads to an increase in the body mass index (BMI), which is associated with the development of obesity-related co-morbidities [34]. However, the development of co-morbidities is mainly linked to AT distribution [35].

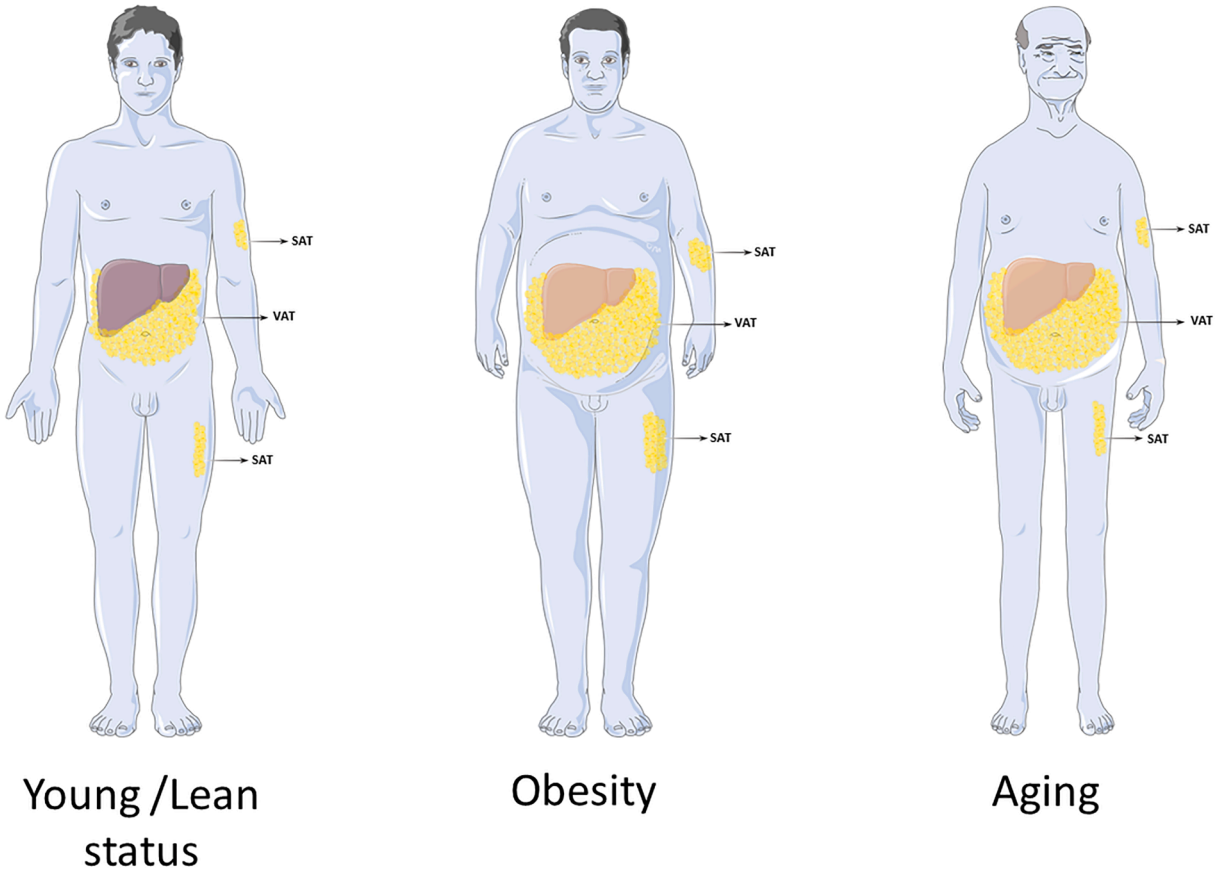

Fig. 1. Adipose tissue distribution changes with obesity and aging. In both males and females, the distribution of WAT is associated with the development of metabolic dysregulation. An increase in SAT, VAT, and the VAT/SAT ratio worsens the metabolic status of subjects with obesity. WAT redistribution occurs in the elderly, increasing the VAT/SAT ratio, and affecting metabolic status and life expectancy.

In fact, in humans, the percentage of VAT in obese subjects has a strong correlation with IR and poor glycemic control [30,36,37] and, in animal models, surgical removal of this tissue prevents IR and delays the development of T2D [38]. Furthermore, obese subjects have less SAT, which contributes to further deterioration of the insulin response and promotes the establishment of T2D [36,39]. In addition, insulin-sensitive obesity is linked to a smaller VAT depot at the same BMI, suggesting increased SAT [40] (Fig. 1). All this evidence indicates that both SAT and VAT contribute to the development of IR, but with contrasting roles. While an increase in SAT is associated with better metabolic status, an increase in VAT is linked with a worsening of metabolic status.

2.2. WAT changes in aging

Like obesity, aging is a principal contributor to metabolic deterioration, and is associated with the establishment of MetS [41]. Aging promotes WAT redistribution (Fig. 1), and in older subjects, a loss of SAT and higher amounts of VAT are observed [42,43]. This redistribution of WAT could be a factor contributing to the worse metabolic status of the elderly compared with their young counterparts. Despite the above finding, Preis et al. found that in older subjects ($\geq$50 years) there is a stronger association between SAT, insulin and HOMA-IR [37]. This suggests that in this population and contrary to what has commonly been assumed, SAT is associated with the development of IR.

It has also been reported that reducing WAT can extend life expectancy [44–46]. In fact, surgical VAT removal in rats improved glucose tolerance, reduced liver triglycerides and the incidence of renal disease and increased lifespan [47,48]. This suggests that fat accumulation in VAT is a main contributor to reducing life expectancy in aging.

Taking this evidence together, we propose that the distribution of AT directly contributes to the development of metabolic diseases in obesity and aging. At the same time, it has a direct impact on lifespan. For this reason, it is relevant to analyze the mechanisms involved in metabolic deterioration occurring in obesity and aging.

3. Adipose tissue-resident cells

WAT is composed by mature adipocytes and the stromal vascular fraction (SVF), which includes pre-adipocytes, fibroblasts, endothelial cells, stem cells and immune cells [49]. Each AT subpopulation changes according to metabolic status and aging. For this reason, we will further describe their specific contribution to AT metabolic function.

3.1. Mature adipocytes

One of the main cells present in WAT are mature adipocytes. These cells act as an energy reservoir and are capable of secreting endocrine molecules that regulate metabolism. Hypertrophy of adipocytes promotes hypoxia in WAT and, thus, induce WAT-inflammation, which is associated with metabolic disturbances [50]. In fact, adipocyte size is associated with the functionality of the WAT depots. In fact, VAT has larger adipocytes than SAT [51]. This suggests that adipocyte size is a determining factor for the pathogenic or protective role associated with VAT and SAT, respectively [22–24,30].

The energy imbalance that occurs in obesity leads to adipocyte hypertrophy which is linked with adipose tissue dysfunction and the development of metabolic complications [52]. In fact, obese subjects without metabolic complications have smaller and more numerous adipocytes in WAT, accompanied with lower degrees of inflammation and fibrosis, compared with their unhealthy counterparts [53–55].

In aging, there is a redistribution of WAT that promotes an increase in the size of VAT depot and that leads to larger adipocytes in VAT compared to SAT [42,43]. Thus, aging affects the secretion of pro-inflammatory molecules resulting in the development of metabolic diseases [42,56].

Taken together, this data suggests that the VAT larger adipocyte size present in both obesity and aging associated with comorbidities is an important factor that influences a worse metabolic status.

3.2. Pre-adipocytes

Pre-adipocytes are the precursor cells of adipocytes. They play an essential role in adipogenesis. It has been reported that their proliferative capacity is related to the fat depot from which they came, and the metabolic status and the age of the subjects [57]. For this reason, understanding the role of these cells in obesity and aging can provide us with tools to improve the metabolic status of both conditions.

When pre-adipocytes from SAT were analyzed, it was found that the adipogenic capacity of subcutaneous pre-adipocytes was higher than that of those from the visceral or omental depots, and that it was inversely correlated with higher VAT, fasting glycemia and VLDL-lipid content [58,59]. In this context, Tchoukalova and collaborators found that committed pre-adipocytes in lean women were significantly higher than in obese women (Fig. 2). However, women with a higher degree of obesity (BMI $>$ 35 kg/m^2) are more susceptible to apoptosis stimuli than lean women and women with a lower degree of obesity (BMI $<$ 35 kg/m^2) [60].

When visceral samples were analyzed, Andersen and collaborators found that pre-adipocytes from obese subjects with or without T2D showed lower expression of adipogenic markers during induced *in vitro* differentiation compared with lean subjects [61]. Moreover, pre-adipocytes from obese patients with T2D had impaired insulin signaling after differentiation, suggesting that pre-adipocyte programming depends on metabolic status and is retained after *in vitro* differentiation [61]. Similarly, in aged animal studies, the gene expression of markers associated with cell differentiation was diminished while the expression of markers associated with inflammation and stress was increased [62]. These data suggest that changes in pre-adipocytes in obesity and aging define the fate of mature cells, regulating the AT dysfunction observed in obese and elderly subjects.

Dietary interventions leading to weight loss increase the *in vitro* adipogenesis rate of pre-adipocytes, which is accompanied by enhanced expression of genes associated with this process. This indicates that weight loss could reprogram pre-adipocytes by improving their metabolic status [63]. In a similar outcome, pre-adipocytes from mice that underwent caloric restriction were prevented from entering premature senescence through an increase in microRNA processing machinery [64]. Moreover, when senescent pre-adipocytes were cleared from the AT of 18-month-old mice, adipogenic capacity and insulin sensitivity were enhanced [65].

Taken together, this data suggests that committed pre-adipocytes decline in number in obesity and aging, and that the adipogenic capacity of pre-adipocytes is related to their metabolic status (Table 1).

3.3. Stem cells

It has been reported that a subpopulation of the SVF, adipose stem cells (ASCs), can differentiate *in vitro* into mature adipocytes, myocytes, chondrocytes and osteocytes [66].

In the obesity field, some authors have focused their efforts on the association between ASCs and the inflammatory status in the obese population. In this context, Silva *et al.* found that VAT from obese patients that underwent bariatric surgery (BMI $>$ 40 kg/m^2) showed increased IL-6, CCL2 and G-CSF gene expression. However, after a lipid accumulation stimulus, cytokine levels were decreased, except for adiponectin, suggesting that ASCs differentially contribute to low-grade inflammation according to the origin of the fat depot [67]. Moreover, ASCs from obese subjects showed less proliferative capacity, premature senescence and increased cytokine secretion compared with non-obese subjects [68] (Table 1).

It is widely accepted that aging affects mesenchymal stem cell

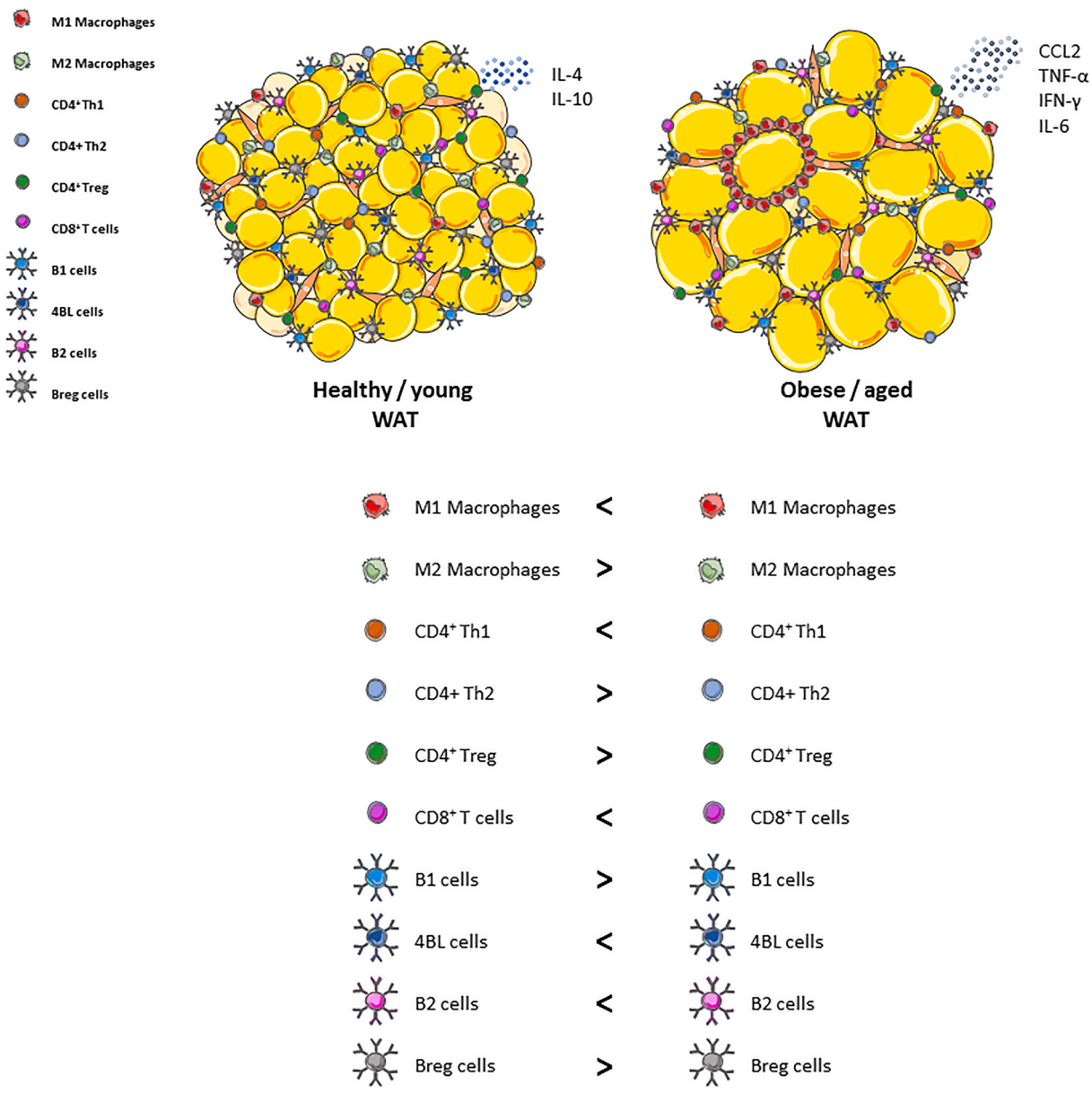

Fig. 2. Alterations in WAT-infiltrating immune cells during obesity and aging. Committed pre-adipocytes are more numerous in healthy WAT, promoting a better metabolic response. Moreover, infiltrated immune cells are responsible for maintaining homeostasis through the secretion of anti-inflammatory cytokines by M2, Tregs, Th2, Bregs and B1 cells, which helps to maintain insulin sensitivity. In obese or aged WAT, an increase in the number of infiltrating pro-inflammatory immune cells, such M1, Th1, $CD8^+$ T, 4BL and B2 cells, promotes adipose tissue dysfunction, which contributes to the development of insulin resistance.

physiology, altering cell proliferative capacity and plasticity and promoting cellular senescent characteristics [69,70]. When ASCs were isolated from the AT of animal models it was observed that old mice presented a reduction in cell proliferation, adipogenic differentiation, and insulin sensitivity and an increase in senescent markers, compared with their young counterparts [71,72]. In human models, Maredziak and collaborators studied ASCs isolated from the SAT of adults at different ages. They found that aged cells showed reduced proliferation rates and chondrogenic and osteogenic potential, and that this was accompanied by an increase in adipogenic differentiation and senescent behavior [73] (Table 1). Similarly, when SAT-derived ASCs from children, young adults and older adults were compared, Liu *et al.* found that aging promoted ASC senescence markers, and the age of donors was inversely correlated with the chondrogenic capacity, proliferation rate, migratory ability, and osteogenic differentiation capacity of ASCs. However, in contrast to Maredziak *et al.* they found that aging also had a negative effect on the capacity of ASCs for adipogenic differentiation [74]. Taken together, these studies suggest that ASCs from aged donors show a reduction in functionality.

All this evidence indicates that WAT-infiltrated ASCs in both obesity and aging have a senescent phenotype, affecting ASC differentiation towards adipocytes, which contributes to the metabolic impairment of adipose tissue.

3.4. Immune cells

3.4.1. Macrophages

This immune cell population was the first reported to infiltrate the AT. Interestingly, in 2003 researchers found differences in AT-infiltrated macrophages (ATMs) and their surface markers between lean and obese subjects, both in mice and humans [75]. ATMs can be broadly classified as M1, which has a pro-inflammatory phenotype, and M2, characterized by an immunosuppressive phenotype. Both subpopulations are present in AT in different proportions. The M1 phenotype is predominantly

Table 1
Overview of the WAT changes during obesity and aging.

Feautres	Obesity	Aging	Ref
Redistribution of WAT and co-morbidities			
VAT accumulation	↑	↑	[34]
SAT accumulation	↑	↓	[34]
Development of IR and T2D	↑ %VAT is correlated with IR and poor glycemic control. ↓ %SAT promotes T2D. ↓ VAT prevents IR and delays T2D development.	↓ in subjects ≥ 50 years with higher %SAT	[30,36,37 38,39]
Development of MetS	↑	↑ Correlates with lower %SAT and higher %VAT	[42,43,186–188]
Life expectancy	↓	↓ Correlates with %VAT	[44–48]
Composition of SVF			
Pre-adipocytes	Adipogenic capacity in SAT pre-adipocytes is higher than in VAT. ↑ Apoptosis ↓ Expression of adipogenic markers	Weight loss ↓ premature senescence ↓ Differentiation markers ↑ Inflammation and stress markers.	[58–65]
ASCs	↑ Inflammation ↓ Proliferative capacity ↑ Premature senescence ↑ Cytokine secretion	↓ Proliferative capacity ↓ Chondrogenic and osteogenic potential ↓ Insulin sensitivity	[67–73]
Immune cells			
Macrophages M1	↑ VAT and SAT ↑ WAT in subject with metabolic complications	↑ VAT ↑ M1/M2 ratio	[76,80,82,83,87,89,90]
Macrophages M2	↓ SAT (but not in VAT) ↑ with weight loss	↓ in WAT	[76,82,84,174,175]
$CD4^+$ Th1	↑ in DIO obese mice	↑ Th1/Th2 ratio	[100–103,106]
$CD4^+$ Th2	correlates with IL-10 ↓ in DIO mice	↑ in blood ↑ Th1/Th2 ratio	[109–111]
$CD4^+$ Treg	↓	↑	[90,112]
$CD8^+$ T cells	↑	↑	[114–117,119]
B1 cells	↓ B1 cells and can be converted to 4BL cells	↑ in VAT	[120,122–124,127,128]
B2 cells	↑ in DIO mice	↑ in VAT of old mice	[120,122,124]
Bregs	↑ in HFD-induced obese mice	–	[130]
DCs	↑ of cDCs was higher in SAT than VAT ↑ of pDCs in VAT	–	[132,177]
Adipose tissue metabolic derangements			
Inflammation	↑ Chronic low-grade WAT inflammation	↑ Chronic low-grade (inflammaging) in WAT	[6,126,139,141–144,189]
AT remodeling			
ECM in AT	↑ Collagen and fibrosis of AT	↑ Collagen and fibrosis of AT ↑ Ectopic accumulation of lipids	[159,161,163–169]
Apoptosis in AT	↑	↑	[171,178–182]

found in dysfunctional/obese WAT and in high proportions in subjects with metabolic complications [76]. In this context, hypertrophy of WAT increases CCL2 expression in adipocytes, the secretion of adipokines, adipocyte death and the recruitment of macrophages, which form crown-like structures (CLS) surrounding the dead adipocytes [77] (Fig. 2). On the other hand, M2 phenotype ATMs promote AT homeostasis, tissue remodeling, and insulin sensitivity and they are predominantly found in healthy/lean WAT [76,78,79].

3.4.1.1. Classical macrophage phenotype. One of the first studies of ATMs evaluated the infiltration of these cells in different fat depots in mouse models of obesity. Immunohistochemistry of SAT and VAT showed an increase in the number of pro-inflammatory macrophages infiltrating these depots, which was positively correlated with adipocyte size and animal weight [79,80]. Moreover, when these analyses were replicated in humans receiving a liquid formula diet (composed of 40% fat, 45% carbohydrate, and 15% protein) for 5–8 weeks, the authors found a positive correlation between BMI and M1 macrophage abundance in SAT and a positive correlation with adipocyte size [80]. Moreover, WAT-infiltrated ATMs are responsible for TNF-α, MCP-1, IFN-γ, iNOS and IL-6 expression in WAT [79–81].

In this context, it has been found that the total number of macrophages per gram of WAT is similar between SAT and VAT, in subjects with a similar BMI [82,83]. However, when overweight was analyzed, Lesna and collaborators found that BMI was directly correlated with the number of M1 phenotype cells and inversely with the M2 phenotype in SAT, but not in VAT [82]. Similarly, in immunohistological and flow cytometric analyses in women who underwent laparoscopic surgery, it was shown that M1 macrophages and the density of crown-like structures increased according to BMI and was correlated with IR in SAT and VAT (Fig. 2). In women with obesity, the number of pro-inflammatory macrophages was increased in SAT and VAT, with no differences in M2 macrophages between the two depots [84]. Likewise, it has been found that VAT infiltration by macrophages is correlated with BMI, *i.e.* the number of macrophages in the WAT in obese subjects is higher than in lean subjects [85,86] (Table 1). However, SAT M1 macrophages showed a higher infiltration and stronger correlation with BMI compared with VAT [87]. When M2 macrophages were studied, some authors demonstrated that TACI KO mice (mice that have a M2-phenotype macrophages) are protected from HFD-induced obesity outcomes [79,88]. In fact, they observed increased VAT M2 infiltration which is linked with obesity-induced comorbidities [79,88]. Moreover, adoptive transfer of TACI KO macrophages improved glucose metabolism in an obese host [79,88].

Like obesity, aging is also characterized by an increase in the number of M1 phenotype and a decrease of M2 phenotype macrophages in WAT (Fig. 2 and Table 1) [79]. In fact, the number of macrophages infiltrating SAT was correlated with adiposity and age, but not with insulin sensitivity in healthy subjects [89]. Additionally, a comparison of the number of ATMs in premenopausal and menopausal women found that the M1 phenotype was more numerous in VAT than in SAT in older subjects [83]. Animal studies demonstrated that the M1/M2 ratio increases with age, suggesting a decrease of M2 ATMs and promoting a pro-inflammatory phenotype in this tissue [79,90]. However, the proportion of ATMs decreased in aged mice and the macrophage phenotype showed a different range of activation states [91].

Studies evaluating the impact of weight loss on the number of ATMs showed a decrease in the M1 phenotype after weight loss intervention. Obese mice that underwent caloric restriction showed an initial increase in ATMs, without an increase in inflammatory gene expression, and then a significant decrease in this population [92]. Likewise, sleeve gastrectomy in obese mice led to an increase in the percentage of M2 macrophages in VAT, compared with pair-feed animals, while no changes were reported in inguinal WAT [93]. Conversely, weight loss in diet-induced obese (DIO) mice showed that the macrophage number and pro-inflammatory phenotype were maintained even after weight loss [94]. In humans, dietary intervention in overweight men (BMI 25–30 kg/m^2) with a body fat percentage > 25% led to a decrease in both M1 and M2 macrophages, accompanied by weight loss [95]. Three months after bariatric surgery obese pre-menopausal women showed a decrease in M1 and increase in M2 macrophages in SAT [84]. And finally, weight loss in obese post-menopausal women induced by a commercial very low caloric diet improved metabolic parameters and CLS density in SAT, with a decrease in the pro-inflammatory gene profile [96]. In summary, an increase in BMI is accompanied by higher macrophage infiltration in AT, and subsequently a deterioration in insulin sensitivity. Weight loss increases AT macrophage recruitment, as an initial step; however, the pro-inflammatory phenotype may be maintained or decrease according to the interventions and models under study. Further evidence is required to fully understand the effect of weight loss on macrophage infiltration in AT.

3.4.1.2. Macrophage-like pre-adipocytes. In animal and human models, Weisberg *et al.* found that gene expression of CD68 and the percentage of $CD68^+$, a marker of macrophage lineages, were correlated with BMI and adipocyte area (μm^2), respectively [80]. In fact, in mouse models of obesity, AT contained up to 80% of $F4/80^+$ cells, suggesting the high presence of both subtypes of macrophages [80]. However, recent findings showed that just 10–15% of cells in AT are macrophages [97,98]. In this context, Isakson *et al.* demonstrated that pre-adipocytes could acquire a macrophage-like phenotype [99]. They showed that pre-adipocytes isolated from AT biopsies and differentiated *in vitro* in the presence of TNF-α inhibited the canonical differentiation phenotype and induced an increase in macrophage-related gene expression [99]. On the other hand, when human adipogenesis of pre-adipocytes was tested in the presence or absence of macrophages isolated from the same sample, it was observed that macrophage removal significantly reduced adipogenesis and adipocytokine secretion from both depots [59].

Taken together, we suggest that ATMs promote adipogenesis in AT, maintaining healthy homeostasis. In addition, hypertrophy of the AT promotes a change in the pre-adipocyte phenotype, leading to an inflammatory profile (M1) that characterizes the dysfunction of the AT, and which is responsible for the development of the metabolic diseases found in obesity and aging.

3.4.2. T Cells

T cells play a central role in the immune response and can be classified according to their surface markers and immune responses [1]. T cells could be classified into $CD4^+$ and $CD8^+$ subsets, and the former can be subdivided into T regulatory (Tregs) and T helper lymphocytes (Th): Th1, Th2 and Th17. Both obesity and aging promote the infiltration of T cells in WAT, promoting a pro-inflammatory status and thus contributing to the development of metabolic diseases [79,100] (Table 1).

3.4.2.1. $CD4^+$ Th1 cells. There is little evidence regarding the presence of Th1 in AT. It has been reported that the Th1 profile in AT is induced in obese animals fed with HFD [101,102]. In a similar way, mice fed a HFD showed an increase in Th1 content in AT compared with lean controls [79,103]. Additionally, HFD-fed animals with a deficiency of Th1 cells or IFN-γ were protected against obesity-induced inflammation and IR, and adoptive transference of Th1 cells reverted the improved parameters [104,105]. This suggests that Th1 cells contribute to AT dysfunction in obesity [103]. To our knowledge, there is no evidence regarding the role of Th1 in aging. However, an increase in the Th1/Th2 ratio has been found in elderly subjects compared with young individuals [106] (Table 1).

All these studies show that the hypertrophy of adipose tissue, both in obesity and aging, promote the infiltration of Th1, which is associated with adipose tissue inflammation (Fig. 2).

3.4.2.2. $CD4^+$ Th2 cells. These T cells are responsible for the secretion of IL-4, IL-5 and IL-13 cytokines. This triggers M2 polarization, and the differentiation of beige adipocytes, which leads to the maintenance of AT thermogenesis [107,108]. Thus, Th2 cell infiltration is associated with an anti-inflammatory role in AT. It has been reported that Th2 cell infiltration in SAT and VAT is directly correlated with IL-10 secretion and inversely with IR [109]. Winer *et al.* demonstrated that DIO Rag1-null mice showed an increase in adiposity and worse glucose metabolism compared with wild-type mice, and that adoptive transference of $CD4^+$ T cells reversed this phenotype (Table 1). Moreover, the considerable IL-4 and IL-13 production observed in HFD-fed Rag1-null $CD4^+$ T cells could indicate that obesity and IR reversion may be attributable to the switch to a Th2 phenotype. Additionally, when transference was performed with $CD4^+$ T cells deficient in STAT6, a transcription factor essential for Th2 polarization, a loss of the protective effects of the adoptive transference was observed [104].

Contradictory evidence about Th2 cells has been reported in the elderly. Mansfield *et al.* showed that aged healthy subjects had increased levels of Th2 cells in the blood [110]. On the other hand, Sakata-Kaneko *et al.* showed that old healthy subjects had fewer Th2 cells, promoting Th1 development by suppressing Th2 development [111] (Table 1).

In summary, Th2 infiltration is a phenomenon that accompanies WAT hypertrophy and is associated with metabolic complications (Fig. 2).

3.4.2.3. $CD4^+$ T regulatory cells (Treg). T regulatory cells (Tregs) have an immunomodulatory role since they are responsible for the control of AT inflammation and the development of IR. Animal studies showed that there was a higher proportion of Tregs in SAT and VAT in lean compared to obese mice [112]. HFD-induced obesity causes a reduction in infiltrated-AT Tregs that is accompanied by a change in the signature of the residual Treg population [112] (Table 1).

Unlike obesity, aging promotes an increase in Treg infiltration in AT [79]. In fact, middle-age old mice have more resident VAT Tregs than young mice [90]. Furthermore, knockout of Tregs in AT prevented the development of age-associated IR [113] (Table 1).

Together, this evidence suggests that Tregs prevent AT inflammation in obesity (Fig. 2). However, in aging models, the number of Treg cells is increased, and for this reason, more evidence is necessary to determine their role in the aging process.

3.4.2.4. $CD8^+$ T cells. This T cell subtype is characterized by IFN-γ secretion, and its population increases in VAT and SAT in obesity and aging [79,109,114], promoting macrophage infiltration. In human studies CD8 gene expression in SAT correlates with BMI, suggesting that infiltration of $CD8^+$ lymphocytes is correlated with adiposity [114] (Table 1). In this context, mice fed a HFD showed an increase in $CD8^+$ cells in WAT, which preceded macrophage infiltration [115–117]. In fact, depletion of $CD8^+$ T cells improves glucose tolerance, insulin sensitivity and AT inflammation, which is blunted by the adoptive transfer of $CD8^+$ T cells [79,115].

Like obesity, $CD8^+$ infiltration in AT is also dependent on age [79]. In the elderly, $CD8^+$ T cell infiltration was induced by 4BL cells [118]. Accordingly, flow cytometry demonstrated that middle-aged mice had a higher percentage of $CD8^+$ cells compared with their young counterparts (Table 1). When the sex effect was studied, they found that females

had a higher number of $CD8^+$ activated T cells, as well as IFN-γ, CCL5 and MIP-1β levels in AT, compared with males [119].

Taken together, these data suggest that an increase in VAT (both in obesity and aging) promotes $CD8^+$ T cell infiltration (Fig. 2), which contributes to macrophage recruitment and M1 polarization, leading to inflammation of AT and thus contributing to the development of insulin resistance.

3.4.3. B cells

These cells are a component of the adaptive immune system that act by secreting antibodies, and thus modulate other cells [1]. They could be classified as B1, B2 and Bregs. An increase in the number of WAT-infiltrating B cells has been observed in obesity and aging [79,120,121].

3.4.3.1. B1 cells. There is conflicting information regarding the presence of B1 in AT. Shen *et al.* found B1a cells in WAT, but found fewer cells in HFD-fed mice accompanied by a reduction in IL-10 levels in WAT. Additionally, adoptive transfer of B1a cells into HFD-fed B cell-deficient mice improved IR, which suggests that these cells act as immune regulators and help to maintain AT homeostasis [122]. On the other hand, Winer *et al.* found an increase in B1 cells in VAT from mice after 4 weeks on a HFD and this was accompanied by a deterioration in metabolic status [120]. In this context, it has been reported that B1a cells can be converted into 4BL ($4–1BBL^+_{B1a\ cells}$) cells by $CCR2^+$ monocytes, which in turn induced IR, triggering 4-1BB receptor signaling. These B1-derived cells are implicated in obesity-induced VAT inflammation [123] (Fig. 2 and Table 1).

In VAT but not SAT, B1 accumulation was correlated with age in mice, suggesting that these cells contribute to age-associated metabolic diseases [79]. In fact, mice with impaired B cell function showed an improvement in aging-induced IR [124]. Inflammaging (low grade chronic inflammation that occurs in elderly [125,126] activates monocytes to convert innate B1a cells into 4BL cells, which then induce cytolytic $CD8^+$ T cells and insulin resistance in the elderly [118,127]. Additionally, inhibition of the conversion of B1a or depletion of 4BL cells reversed aging-associated IR [127,128] (Table 1).

Taken together, the above evidence suggests that conversion of B1a cells into 4BL cells could be one of the factors responsible for inducing insulin resistance in obesity and the elderly (Fig. 2).

3.4.3.2. B2 cells. HFD-fed mice showed an increase in the infiltration of B2 cells in WAT [79,120,122,124]. In this context, B-null mice showed an improvement in glucose metabolism that was reversed following adoptive transfer of B2 cells from wild type HFD donor mice into HFD-fed B cell-deficient mice, promoting IR and impaired glucose metabolism [122,124]. As in obesity, old mice had increased numbers of B2 cells in VAT [121,129] (Fig. 2 and Table 1).

3.4.3.3. Regulatory B cells (Bregs). It has been reported that the AT of HFD-induced obese mice was infiltrated with Breg cells that constitutively secreted IL-10. Adipose inflammation and IR were found in mice with B cell-specific IL-10 deletion, while adoptive transference of Breg cells reversed this phenotype [130]. This suggests that Bregs contribute to WAT homeostasis and that their dysfunction promotes inflammation of AT in obesity (Fig. 2 and Table 1).

3.4.4. Dendritic cells

Dendritic cells (DCs) are the link between the innate and adaptive immune response. They can be classified as conventional DCs (cDCs), which are antigen-presenting cells, and plasmocytoid DCs (pDCs), characterized by their IFN-1 secretion when activated [79,131].

The infiltration of both DC subtypes was increased in AT from obese subjects. In this context, HFD-induced obese mice showed increased accumulation of DCs in WAT with higher IL-2, IL-1α, IFN-γ, and IL-1β, but not IL-6 and TNF-α gene expression levels (Table 1). cDCs are characterized by the expression of the surface marker MHC-II [132]. The percentage of cDCs was 2-fold higher in obese mice compared with lean mice, with a higher level of MHC-II on their surface. Similarly, human studies showed that obese patients had more cDCs than lean patients, and that this increment was higher in SAT compared with VAT [132]. Moreover, the increase in WAT DCs was correlated with adiposity and the number of WAT-infiltrating Th17. In addition, these cells drive *ex vivo* Th17 differentiation. [133]. Macdougall *et al.* found that cDC1 triggers the Wnt/β-catenin pathway, while cDC2 stimulates the PPARγ pathway, both responsible for controlling inflammation and lipid accumulation in adipocytes. Additionally, obesity delays the β-catenin and PPARγ pathways and inhibits cDC function. For this reason, the authors suggested that cDCs contribute to WAT homeostasis, delaying the development of metabolic diseases [134].

On the other hand, Ghosh *et al.* found increased infiltration of pDCs ($CLEC4C^+$) in VAT from obese subjects. Additionally, when the gene expression of these infiltrated cells was analyzed, it was found that CLEC4C expression was correlated with the expression of IFN signature genes (ISGs), with a stronger correlation in obese compared with lean individuals. Furthermore, ISG expression was correlated with ADIPO-IR and HOMA2-IR in obese subjects. Therefore, pDCs could act as a source of IFN secretion and M1 polarization, and consequently promote inflammation and IR in obesity [135]. In this context, $IFNAR^{-/-}$ mice fed a HFD showed weight gain resistance compared with the control group, and this was associated with a lower fat mass and infiltration of M1 in VAT. In this context, like $IFNAR^{-/-}$ mice, deletion of pDCs also triggered an improvement in the metabolic response and weight gain compared with HFD control mice [136]. This evidence suggests that DC infiltration and the consequent IFN-1 secretion contribute to a pro-inflammatory phenotype responsible for IR in obesity. The role of DCs in senescence remains to be determined.

4. Metabolic derangement of adipose tissue in obesity and aging

In addition to the differences in AT distribution and their implication in the development of metabolic diseases, other potential mechanisms involved in the metabolic deterioration that occurs in obesity and aging, such as inflammation and AT remodeling, are described below.

4.1. Inflammation

WAT is a highly active organ involved in numerous metabolic, hormonal, and immune processes [137,138]. It has been reported that an increase in adipocyte size (hypertrophy) and number (hyperplasia) causes local and systemic low-grade chronic inflammation that triggers the development of severe metabolic diseases [6,139] (Table 1).

Adipokines are the main molecules secreted by the AT and contribute to structural and functional WAT rearrangement [140]. In obesity, an increase in triglyceride accumulation in the adipocyte causes an enlargement of WAT, and consequently dysregulation in the secretion of adipocytokines [141] (Fig. 2 and Table 1). Adipocytokines are the main factor responsible for immune cell chemoattraction, promoting chronic and self-maintained low-grade inflammation that is associated with several obesity-related pathologies [142]. Similarly, in the senescence process, a large number of inflammatory cytokines and chemokines are secreted and have a direct impact on their microenvironment, promoting senescence in their neighboring cells and recruiting immune cells to the affected tissue, in turn promoting an inflammatory milieu in the affected tissue [143]. In fact, aging, like obesity, is characterized by chronic, low-grade systemic inflammation in several tissues, due to dysregulation of the immune system, the so-called “inflammaging” [125,126] (Table 1). When AT ages, inflammaging contributes to the onset and progression of metabolic diseases in the elderly, affecting their life expectancy [144].

The number of adipocytes in the AT of an individual remains relatively constant throughout life [145]. Therefore, an increase in AT

translates into an increase in the hypertrophy of adipocytes, which activates the ERK and p38 MAPK pathways, resulting in an increase in CCL2 expression in adipocytes [146] (Fig. 2). This contributes to macrophage recruitment, the formation of crown-like structures and adipocyte death. The consequent release of triglycerides activates TLR4 receptors in macrophages, activating the IKK/NF-κB pathway and, consequently TNF-α secretion [146–148]. Both triglycerides and TNF-α are crucial to the development of IR, because they inhibit the IRS-1 signaling cascade, affecting glucose uptake into the AT [54,55,149,150]. AT inflammation directly affects insulin sensitivity, and is associated with the development of T2D and CVD. Thus, an increase in WAT promotes the infiltration of pro-inflammatory immune cells, which secrete cytokines that promote an inflammatory phenotype and worsen the prognosis in related metabolic illnesses [15].

4.2. Adipose tissue remodeling

4.2.1. Adipocyte morphology

In a study of the morphology of adipocytes, Arner *et al.* found that hypertrophy was negatively correlated with the hyperplasia of WAT independently of BMI (18–60 kg/m^2) [151]. They classified subjects as having either hyperplasia or hypertrophy and found that the number of new adipocytes per year was 70% less in hypertrophic compared with hyperplasic classified subjects. In fact, impaired adipogenesis is present in hypertrophic obesity (Fig. 2 and Table 1) and contributes to the development of IR in obesity [152,153].

Obesity-associated metabolic complications are also observed in aging, and they are linked to a decreased lifespan [154]. In this context, metabolic interventions driving weight loss also increases life expectancy [44–46]. Additionally, rapamycin-treated HFD-fed mice, IRS1-null and S6K1-null mice showed limited adipogenesis and an increase in lifespan [155–158]. This suggests that fat accumulation contributes to the reduction in life expectancy during aging.

4.2.2. Role of extracellular matrix in adipose tissue

Seminal studies demonstrated that in late stages of obesity there is an accumulation of extracellular matrix (ECM) proteins, and consequently AT fibrosis, which is associated with the pro-inflammatory phenotype observed in obesity [159–161]. A transcriptomic analysis of AT from obese subjects found that an increase in ECM components (Table 1) (which decreased 3 months after bariatric surgery) was accompanied by the increased expression of some enzymes responsible for ECM degradation [162].

Studies in obese humans and mouse models have shown that WAT collagen gene expression is increased in obese subjects and correlates with insulin resistance, inflammatory markers, the size of fibrotic areas and the number of infiltrated macrophages [163–167]. Moreover, Col6 knockout mice showed less AT fibrosis and inflammation and improved glucose metabolism [167].

Analogous to obesity, studies in aged mice (~30 months of age) demonstrated an increase in WAT collagen staining, indicating more fibrosis in this tissue [168]. The same authors also demonstrated that the size of both VAT and SAT was reduced in aged animals [168]. This suggests that senescence affects lipid handling in AT, promoting ectopic lipid accumulation and thus impairing glucose tolerance and IR [168,169].

4.2.3. Role of apoptosis in adipose tissue

Adipocyte apoptosis and fibrosis are crucial events that promote AT macrophage infiltration and, subsequently the development of obesity-associated metabolic diseases [170,171]. AT from mice fed a HFD showed more hypertrophy and inflammation, events typically associated with a pro-apoptotic phenotype [171]. Moreover, intrinsic pathways of apoptosis were activated in obese mice and humans (Table 1), and inhibition of adipocyte apoptosis in mice protects from macrophage infiltration and the development of fatty liver and IR [171]. In fact, AT macrophage infiltration is characterized by the presence of crown-like structures [172,173] surrounding dead adipocytes and promoting pro-inflammatory signaling, a hallmark of obesity-related diseases [174,175]. However, inducible elimination of adipocytes in a mouse model, through the targeted activation of caspase-8, promoted the influx of alternative activated M2 macrophages [176]. Taken together, this data suggests that adipocyte apoptosis might be the origin of AT macrophage infiltration, thus triggering obesity-related diseases.

To our knowledge there have been no studies associating adipocyte apoptosis with aging and metabolic complications, and it seems that AT turnover remains constant in adulthood [145]. In this context, as mentioned above, the AT is affected by "inflammaging" and changes in distribution, leading to an increase in the VAT/SAT ratio. In aging mouse models, there is an increase in resident immune cells in VAT and a decrease in AT autophagy, promoting inflammation [90,177]. Additionally, dysregulation of the extracellular matrix (ECM) occurs during aging [178,179] (Table 1). In fact, senescent cells induce a state of chronic inflammation, which compromises the integrity of ECM components such as elastin and collagen, and the basement membrane [180–182]. This evidence suggests that AT apoptosis and fibrosis could be higher in the elderly, contributing to the establishment of metabolic diseases.

5. Conclusions and perspectives

Both obesity and aging are associated with a parallel increase in chronic metabolic diseases. Aging promotes WAT redistribution from SAT to VAT, and in obesity VAT accumulation is associated with a worsening of glucose metabolism. VAT contains larger adipocytes than SAT. Thus, visceral adiposity is associated with chronic WAT inflammation, which contributes to the development of cardiovascular disease, T2D and other co-morbidities usually associated with obesity [30,36,37,39,40,42,43]. Moreover, increased WAT fibrosis in old and obese subjects modifies AT lipid metabolism and promotes IR. Importantly, the profile of the immune cells infiltrated into the AT is a main feature of the pro-inflammatory phenotype observed in both obesity and aging. In this review we have summarized current data on common cellular and molecular mechanisms for obesity and age-related WAT inflammation and its role in affecting glucose metabolism and producing insulin resistance. Chronic low-grade WAT inflammation leads to co-morbidities linked to obesity and aging and reduces life expectancy [6,139,142–144].

Thus, a key challenge will be identifying intervention strategies able to reduce adipocyte size, VAT accumulation and WAT inflammation and to modulate the role of AT-infiltrated immune populations. In this context, it will be important to study the mechanisms involved in adipocyte size and expansion of VAT. Tools able to inhibit the increase in VAT would be an effective treatment to prevent the development of obesity- and aging-associated diseases and to increase life expectancy. Pre-adipocytes are found within the adipose tissue, and their proliferative capacity is associated with metabolic status. Therefore, strategies focused on increasing the VAT adipogenesis rate might help change WAT depot distribution and improve metabolic status.

Another point of interest is the WAT-infiltrated immune cell populations. In this context, cell reprogramming therapies favoring regulatory and anti-inflammatory phenotypes could be a therapeutic strategy to modulate immune responses and reduce metabolic diseases associated with obesity and aging. Currently there are several *in vitro* and *in vivo* studies where the reprogramming of immune cells is being used as a treatment against autoimmune diseases and cancer [183–185]. However, there is no evidence about reprogramming AT-resident immune cells into an anti-inflammatory phenotype. For this reason, it will be important to determine whether metabolic interventions leading to weight loss contribute to the reprogramming of WAT-infiltrated immune cells or whether immune cell reprogramming by itself could induce weight loss and improve metabolic status in obesity and aging. An

interesting therapeutic strategy would be to induce the reprogramming of regulatory phenotypes in B- and T-WAT resident cells.

In vitro and *in vivo* intervention studies in humans and animal models are needed to further investigate therapeutic strategies that promote changes in WAT distribution or immune cell reprogramming towards an anti-inflammatory phenotype. This might improve glucose metabolism in obesity and the elderly, thereby providing a novel strategy to fight against chronic low-grade inflammation in obese and aged subjects.

Funding

This study was supported by the Ministry of Spain (MINECO) (SAF2017-83813-C3-1-R to Dolors Serra (DS) and LH cofunded by the ERDF), the Centro de Investigación Biomédica en Red de Fisiopatología de la Obesidad y la Nutrición (CIBEROBN) (Grant CB06/03/0001 to DS), the Government of Catalonia (2017SGR278 to DS), the Fundació La Marató de TV3 (201627-30 to DS), and by the Instituto de Salud Carlos III (PI17/01455). MR is a recipient of a CONICYT-ANID Chile doctoral fellowship.

CRediT authorship contribution statement

Marjorie Reyes-Farias: Conceptualization, Writing - review & editing, Visualization. **Julia Fos-Domenech:** Conceptualization, Writing - review & editing, Visualization. **Dolors Serra:** Conceptualization, Writing - review & editing, Visualization, Supervision, Funding acquisition. **Laura Herrero:** Conceptualization, Writing - review & editing, Visualization, Supervision, Funding acquisition. **David Sánchez-Infantes:** Conceptualization, Writing - review & editing, Visualization, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] A. Abbas, A. Lichtman, S. Pillai, Cellular and Molecular Immunology, 9th ed., 2017.
[2] B.C. Lee, J. Lee, Cellular and molecular players in adipose tissue inflammation in the development of obesity-induced insulin resistance, BBA 1842 (3) (2014) 446–462.
[3] G. Cildir, S.C. Akincilar, V. Tergaonkar, Chronic adipose tissue inflammation: all immune cells on the stage, Trends Mol. Med. 19 (8) (2013) 487–500.
[4] P.C. Calder, N. Ahluwalia, R. Albers, N. Bosco, R. Bourdet-Sicard, D. Haller, S. T. Holgate, L.S. Jonsson, M.E. Latulippe, A. Marcos, J. Moreines, C. M'Rini, M. Muller, G. Pawelec, R.J. van Neerven, B. Watzl, J. Zhao, A consideration of biomarkers to be used for evaluation of inflammation in human nutritional studies, Br. J. Nutr. 109 (Suppl. 1) (2013) S1–S34.
[5] M.A. Sugimoto, L.P. Sousa, V. Pinho, M. Perretti, M.M. Teixeira, Resolution of Inflammation: What Controls Its Onset? Front. Immunol. 7 (2016) 160.
[6] G.S. Hotamisligil, Inflammation and metabolic disorders, Nature 444 (7121) (2006) 860–867.
[7] C.N. Serhan, N. Chiang, T.E. Van Dyke, Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators, Nat. Rev. Immunol. 8 (5) (2008) 349–361.
[8] A. Freund, A.V. Orjalo, P.Y. Desprez, J. Campisi, Inflammatory networks during cellular senescence: causes and consequences, Trends Mol. Med. 16 (5) (2010) 238–246.
[9] T. Mau, R. Yung, Adipose tissue inflammation in aging, Exp. Gerontol. 105 (2018) 27–31.
[10] M. Tremmel, U.G. Gerdtham, P.M. Nilsson, S. Saha, Economic Burden of Obesity: A Systematic Literature Review, Int. J. Environ. Res. Public Health 14 (4) (2017).
[11] C. Centers for Disease, Prevention, Trends in aging–United States and worldwide, MMWR Morb Mortal Wkly Rep 52(6) (2003) 101-4, 106.
[12] H.Y. Chung, D.H. Kim, E.K. Lee, K.W. Chung, S. Chung, B. Lee, A.Y. Seo, J. H. Chung, Y.S. Jung, E. Im, J. Lee, N.D. Kim, Y.J. Choi, D.S. Im, B.P. Yu, Redefining Chronic Inflammation in Aging and Age-Related Diseases: Proposal of the Senoinflammation Concept, Aging Dis 10 (2) (2019) 367–382.
[13] K.S. Krabbe, M. Pedersen, H. Bruunsgaard, Inflammatory mediators in the elderly, Exp. Gerontol. 39 (5) (2004) 687–699.
[14] T.K. Howcroft, J. Campisi, G.B. Louis, M.T. Smith, B. Wise, T. Wyss-Coray, A. D. Augustine, J.E. McElhaney, R. Kohanski, F. Sierra, The role of inflammation in age-related disease, Aging (Albany NY) 5 (1) (2013) 84–93.
[15] F.-I. Corona-Meraz, J.-A. Robles-De Anda, P.-M. Madrigal-Ruiz, G.-I. Díaz-Rubio, J. Castro-Albarrán, R.-E. Navarro-Hernández, Adipose Tissue in Health and Disease, in: H. Çakmur (Ed.), Obesity2020.
[16] L. Szablewski, Introductory Chapter: Adipose Tissue, Adipose Tissue - An Update, Intechopen, 2019.
[17] W. van Marken Lichtenbelt, Brown adipose tissue and the regulation of nonshivering thermogenesis, Curr Opin Clin Nutr Metab Care 15 (6) (2012) 547–552.
[18] G. Fruhbeck, Overview of adipose tissue and its role in obesity and metabolic disorders, Methods Mol. Biol. 456 (2008) 1–22.
[19] J. Salvador, C. Silva, P. Pujante, G. Fruhbeck, Abdominal obesity: an indicator of cardiometabolic risk, Endocrinol. Nutr. 55 (9) (2008) 420–432.
[20] A. Booth, A. Magnuson, M. Foster, Detrimental and protective fat: body fat distribution and its relation to metabolic disease, Horm. Mol. Biol. Clin. Investig. 17 (1) (2014) 13–27.
[21] R.K. Zwick, C.F. Guerrero-Juarez, V. Horsley, M.V. Plikus, Anatomical, Physiological, and Functional Diversity of Adipose Tissue, Cell Metab. 27 (1) (2018) 68–83.
[22] I. Schlecht, W. Gronwald, G. Behrens, S.E. Baumeister, J. Hertel, J. Hochrein, H. U. Zacharias, B. Fischer, P.J. Oefner, M.F. Leitzmann, Visceral adipose tissue but not subcutaneous adipose tissue is associated with urine and serum metabolites, PLoS One 12 (4) (2017), e0175133.
[23] A. Shuster, M. Patlas, J.H. Pinthus, M. Mourtzakis, The clinical importance of visceral adiposity: a critical review of methods for visceral adipose tissue analysis, Br. J. Radiol. 85 (1009) (2012) 1–10.
[24] A. Philipsen, M.E. Jorgensen, D. Vistisen, A. Sandbaek, T.P. Almdal, J. S. Christiansen, T. Lauritzen, D.R. Witte, Associations between ultrasound measures of abdominal fat distribution and indices of glucose metabolism in a population at high risk of type 2 diabetes: the ADDITION-PRO study, PLoS ONE 10 (4) (2015), e0123062.
[25] B.L. Wajchenberg, Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome, Endocr. Rev. 21 (6) (2000) 697–738.
[26] M.J. Lee, Y. Wu, S.K. Fried, Adipose tissue heterogeneity: implication of depot differences in adipose tissue for obesity complications, Mol. Aspects Med. 34 (1) (2013) 1–11.
[27] F. Item, D. Konrad, Visceral fat and metabolic inflammation: the portal theory revisited, Obes. Rev. 13 (Suppl 2) (2012) 30–39.
[28] S. Wueest, F. Item, F.C. Lucchini, T.D. Challa, W. Muller, M. Bluher, D. Konrad, Mesenteric Fat Lipolysis Mediates Obesity-Associated Hepatic Steatosis and Insulin Resistance, Diabetes 65 (1) (2016) 140–148.
[29] S.A. Ritchie, J.M. Connell, The link between abdominal obesity, metabolic syndrome and cardiovascular disease, Nutr Metab Cardiovasc Dis 17 (4) (2007) 319–326.
[30] T. McLaughlin, C. Lamendola, A. Liu, F. Abbasi, Preferential fat deposition in subcutaneous versus visceral depots is associated with insulin sensitivity, J. Clin. Endocrinol. Metab. 96 (11) (2011) E1756–E1760.
[31] S. Virtue, A. Vidal-Puig, Adipose tissue expandability, lipotoxicity and the Metabolic Syndrome–an allostatic perspective, BBA 1801 (3) (2010) 338–349.
[32] G.I. Shulman, Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease, N. Engl. J. Med. 371 (23) (2014) 2237–2238.
[33] S. Gesta, M. Bluher, Y. Yamamoto, A.W. Norris, J. Berndt, S. Kralisch, J. Boucher, C. Lewis, C.R. Kahn, Evidence for a role of developmental genes in the origin of obesity and body fat distribution, Proc. Natl. Acad. Sci. U.S.A 103 (17) (2006) 6676–6681.
[34] A. Vidal-Puig, Adipose tissue expandability, lipotoxicity and the metabolic syndrome, Endocrinol Nutr 60 (Suppl 1) (2013) 39–43.
[35] A. Chait, L.J. den Hartigh, Adipose Tissue Distribution, Inflammation and Its Metabolic Consequences, Including Diabetes and Cardiovascular Disease, Front Cardiovasc. Med. 7 (2020) 22.
[36] K. Indulekha, R.M. Anjana, J. Surendar, V. Mohan, Association of visceral and subcutaneous fat with glucose intolerance, insulin resistance, adipocytokines and inflammatory markers in Asian Indians (CURES-113), Clin. Biochem. 44 (4) (2011) 281–287.
[37] S.R. Preis, J.M. Massaro, S.J. Robins, U. Hoffmann, R.S. Vasan, T. Irlbeck, J. B. Meigs, P. Sutherland, R.B. D'Agostino Sr., C.J. O'Donnell, C.S. Fox, Abdominal subcutaneous and visceral adipose tissue and insulin resistance in the Framingham heart study, Obesity (Silver Spring) 18 (11) (2010) 2191–2198.
[38] I. Gabriely, X.H. Ma, X.M. Yang, G. Atzmon, M.W. Rajala, A.H. Berg, P. Scherer, L. Rossetti, N. Barzilai, Removal of visceral fat prevents insulin resistance and glucose intolerance of aging: an adipokine-mediated process? Diabetes 51 (10) (2002) 2951–2958.
[39] P. Chen, X. Hou, G. Hu, L. Wei, L. Jiao, H. Wang, S. Chen, J. Wu, Y. Bao, W. Jia, Abdominal subcutaneous adipose tissue: a favorable adipose depot for diabetes? Cardiovasc Diabetol 17 (1) (2018) 93.
[40] N. Kloting, M. Fasshauer, A. Dietrich, P. Kovacs, M.R. Schon, M. Kern, M. Stumvoll, M. Bluher, Insulin-sensitive obesity, Am. J. Physiol. Endocrinol. Metab. 299 (3) (2010) E506–E515.
[41] F. Bonomini, L.F. Rodella, R. Rezzani, Metabolic syndrome, aging and involvement of oxidative stress, Aging Dis. 6 (2) (2015) 109–120.
[42] M. Schosserer, J. Grillari, C. Wolfrum, M. Scheideler, Age-Induced Changes in White, Brite, and Brown Adipose Depots: A Mini-Review, Gerontology 64 (3) (2018) 229–236.

[43] A. Coin, G. Sergi, E.M. Inelmen, G. Enzi, Pathophysiology of Body Composition Changes in Elderly People, in: G. Mantovani, S.D. Anker, A. Inui, J.E. Morley, F. R. Fanelli, D. Scevola, M.W. Schuster, S.-.-S. Yeh (Eds.), Cachexia and Wasting: A Modern Approach, Springer, Milano, 2006, pp. 369–375.

[44] N. Barzilai, G. Gupta, Revisiting the role of fat mass in the life extension induced by caloric restriction, J. Gerontol. A Biol. Sci. Med. Sci. 54 (3) (1999) B89–B96, discussion B97-8.

[45] E.J. Masoro, Caloric restriction and aging: controversial issues, J. Gerontol. A Biol. Sci. Med. Sci. 61 (1) (2006) 14–19.

[46] F. Picard, L. Guarente, Molecular links between aging and adipose tissue, Int. J. Obes. (Lond) 29 (Suppl 1) (2005) S36–S39.

[47] M.T. Foster, H. Shi, R.J. Seeley, S.C. Woods, Removal of intra-abdominal visceral adipose tissue improves glucose tolerance in rats: role of hepatic triglyceride storage, Physiol. Behav. 104 (5) (2011) 845–854.

[48] R. Muzumdar, D.B. Allison, D.M. Huffman, X. Ma, G. Atzmon, F.H. Einstein, S. Fishman, A.D. Poduval, T. McVei, S.W. Keith, N. Barzilai, Visceral adipose tissue modulates mammalian longevity, Aging Cell 7 (3) (2008) 438–440.

[49] Y. Sun, S. Chen, X. Zhang, M. Pei, Significance of Cellular Cross-Talk in Stromal Vascular Fraction of Adipose Tissue in Neovascularization, Arterioscler. Thromb. Vasc. Biol. 39 (6) (2019) 1034–1044.

[50] P.-C. Chan, P.-S. Hsieh, The Role of Adipocyte Hypertrophy and Hypoxia in the Development of Obesity-Associated Adipose Tissue Inflammation and Insulin Resistance, in: J. Gordeladze (Ed.), Adiposity - Omics and Molecular Understanding, IntechOpen2017, p. 296.

[51] A. Misra, N.K. Vikram, Clinical and pathophysiological consequences of abdominal adiposity and abdominal adipose tissue depots, Nutrition 19 (5) (2003) 457–466.

[52] F. Liu, J. He, H. Wang, D. Zhu, Y. Bi, Adipose Morphology: a Critical Factor in Regulation of Human Metabolic Diseases and Adipose Tissue Dysfunction, Obes. Surg. 30 (12) (2020) 5086–5100.

[53] L. Vishvanath, R.K. Gupta, Contribution of adipogenesis to healthy adipose tissue expansion in obesity, J. Clin. Invest. 129 (10) (2019) 4022–4031.

[54] M. Longo, F. Zatterale, J. Naderi, L. Parrillo, P. Formisano, G.A. Raciti, F. Beguinot, C. Miele, Adipose Tissue Dysfunction as Determinant of Obesity-Associated Metabolic Complications, Int. J. Mol. Sci. 20 (9) (2019).

[55] K. Verboven, K. Wouters, K. Gaens, D. Hansen, M. Bijnen, S. Wetzels, C. D. Stehouwer, G.H. Goossens, C.G. Schalkwijk, E.E. Blaak, J.W. Jocken, Abdominal subcutaneous and visceral adipocyte size, lipolysis and inflammation relate to insulin resistance in male obese humans, Sci. Rep. 8 (1) (2018) 4677.

[56] P. Mancuso, B. Bouchard, The Impact of Aging on Adipose Function and Adipokine Synthesis, Front. Endocrinol. (Lausanne) 10 (2019) 137.

[57] W.P. Cawthorn, E.L. Scheller, O.A. MacDougald, Adipose tissue stem cells meet preadipocyte commitment: going back to the future, J. Lipid Res. 53 (2) (2012) 227–246.

[58] J. Lessard, S. Laforest, M. Pelletier, M. Leboeuf, L. Blackburn, A. Tchernof, Low abdominal subcutaneous preadipocyte adipogenesis is associated with visceral obesity, visceral adipocyte hypertrophy, and a dysmetabolic state, Adipocyte 3 (3) (2014) 197–205.

[59] L.F. Liu, C.M. Craig, L.L. Tolentino, O. Choi, J. Morton, H. Rivas, S.W. Cushman, E.G. Engleman, T. McLaughlin, Adipose tissue macrophages impair preadipocyte differentiation in humans, PLoS One 12 (2) (2017), e0170728.

[60] Y. Tchoukalova, C. Koutsari, M. Jensen, Committed subcutaneous preadipocytes are reduced in human obesity, Diabetologia 50 (1) (2007) 151–157.

[61] E. Andersen, L.R. Ingerslev, O. Fabre, I. Donkin, A. Altintas, S. Versteyhe, T. Bisgaard, V.B. Kristiansen, D. Simar, R. Barres, Preadipocytes from obese humans with type 2 diabetes are epigenetically reprogrammed at genes controlling adipose tissue function, Int J Obes (Lond) 43 (2) (2019) 306–318.

[62] M.J. Cartwright, K. Schlauch, M.E. Lenburg, T. Tchkonia, T. Pirtskhalava, A. Cartwright, T. Thomou, J.L. Kirkland, Aging, depot origin, and preadipocyte gene expression, J. Gerontol. A Biol. Sci. Med. Sci. 65 (3) (2010) 242–251.

[63] L. Rossmeislová, L. Mališová, J. Kračmerová, M. Tencerová, Z. Kováčová, M. Koc, M. Šiklová-Vítková, N. Viquerie, D. Langin, V. Štich, Weight Loss Improves the Adipogenic Capacity of Human Preadipocytes and Modulates Their Secretory Profile, 62(6) (2013) 1990-1995.

[64] M.A. Mori, P. Raghavan, T. Thomou, J. Boucher, S. Robida-Stubbs, Y. Macotela, S. J. Russell, J.L. Kirkland, T.K. Blackwell, C.R. Kahn, Role of microRNA processing in adipose tissue in stress defense and longevity, Cell Metab. 16 (3) (2012) 336–347.

[65] M. Xu, A.K. Palmer, H. Ding, M.M. Weivoda, T. Pirtskhalava, T.A. White, A. Sepe, K.O. Johnson, M.B. Stout, N. Giorgadze, M.D. Jensen, N.K. LeBrasseur, T. Tchkonia, J.L. Kirkland, Targeting senescent cells enhances adipogenesis and metabolic function in old age, Elife 4 (2015), e12997.

[66] R. Berry, E. Jeffery, M.S. Rodeheffer, Weighing in on adipocyte precursors, Cell Metab. 19 (1) (2014) 8–20.

[67] K.R. Silva, I. Cortes, S. Liechocki, J.R. Carneiro, A.A. Souza, R. Borojevic, C. M. Maya-Monteiro, L.S. Baptista, Characterization of stromal vascular fraction and adipose stem cells from subcutaneous, preperitoneal and visceral morbidly obese human adipose tissue depots, PLoS One 12 (3) (2017), e0174115.

[68] M. Roldan, M. Macias-Gonzalez, R. Garcia, F.J. Tinahones, M. Martin, Obesity short-circuits stemness gene network in human adipose multipotent stem cells, FASEB J. 25 (12) (2011) 4111–4126.

[69] J.A. Fafian-Labora, M. Morente-Lopez, M.C. Arufe, Effect of aging on behaviour of mesenchymal stem cells, World J Stem Cells 11 (6) (2019) 337–346.

[70] Y.K. Yang, Aging of mesenchymal stem cells: Implication in regenerative medicine, Regen Ther 9 (2018) 120–122.

[71] J.S. Jung, C. Volk, C. Marga, A. Navarrete Santos, M. Jung, D. Rujescu, A. Navarrete Santos, Adipose-Derived Stem/Stromal Cells Recapitulate Aging Biomarkers and Show Reduced Stem Cell Plasticity Affecting Their Adipogenic Differentiation Capacity, Cell Reprogram 21 (4) (2019) 187–199.

[72] M. Alicka, K. Kornicka-Garbowska, K. Kucharczyk, M. Kepska, M. Rcken, K. Marycz, Age-dependent impairment of adipose-derived stem cells isolated from horses, Stem Cell Res. Ther. 11 (1) (2020) 4.

[73] M. Maredziak, K. Marycz, K.A. Tomaszewski, K. Kornicka, B.M. Henry, The Influence of Aging on the Regenerative Potential of Human Adipose Derived Mesenchymal Stem Cells, Stem Cells Int. 2016 (2016) 2152435.

[74] M. Liu, H. Lei, P. Dong, X. Fu, Z. Yang, Y. Yang, J. Ma, X. Liu, Y. Cao, R. Xiao, Adipose-Derived Mesenchymal Stem Cells from the Elderly Exhibit Decreased Migration and Differentiation Abilities with Senescent Properties, Cell Transp. 26 (9) (2017) 1505–1519.

[75] A.A. Hill, W. Reid Bolus, A.H. Hasty, A decade of progress in adipose tissue macrophage biology, Immunol. Rev. 262 (1) (2014) 134–152.

[76] L. Orliaguet, E. Dalmas, K. Drareni, N. Venteclef, F. Alzaid, Mechanisms of Macrophage Polarization in Insulin Signaling and Sensitivity, Front. Endocrinol. (Lausanne) 11 (2020) 62.

[77] F. Tourniaire, B. Romier-Crouzet, J.H. Lee, J. Marcotorchino, E. Gouranton, J. Salles, C. Malezet, J. Astier, P. Darmon, E. Blouin, S. Walrand, J. Ye, J. F. Landrier, Chemokine Expression in Inflamed Adipose Tissue Is Mainly Mediated by NF-kappaB, PLoS One 8 (6) (2013), e66515.

[78] Aging and Health: A Systems Biology Perspective, Karger, Germany, 2015.

[79] S. Khan, Y.T. Chan, X.S. Revelo, D.A. Winer, The Immune Landscape of Visceral Adipose Tissue During Obesity and Aging, Front. Endocrinol. (Lausanne) 11 (2020) 267.

[80] S.P. Weisberg, D. McCann, M. Desai, M. Rosenbaum, R.L. Leibel, A. W. Ferrante Jr., Obesity is associated with macrophage accumulation in adipose tissue, J. Clin. Invest. 112 (12) (2003) 1796–1808.

[81] S.U. Amano, J.L. Cohen, P. Vangala, M. Tencerova, S.M. Nicoloro, J.C. Yawe, Y. Shen, M.P. Czech, M. Aouadi, Local proliferation of macrophages contributes to obesity-associated adipose tissue inflammation, Cell Metab. 19 (1) (2014) 162–171.

[82] I.K. Lesna, S. Cejkova, A. Kralova, J. Fronek, M. Petras, A. Sekerkova, F. Thieme, L. Janousek, R. Poledne, Human adipose tissue accumulation is associated with pro-inflammatory changes in subcutaneous rather than visceral adipose tissue, Nutr. Diabetes 7 (4) (2017), e264.

[83] I. Kralova Lesna, A. Kralova, S. Cejkova, J. Fronek, M. Petras, A. Sekerkova, F. Thieme, L. Janousek, R. Poledne, Characterisation and comparison of adipose tissue macrophages from human subcutaneous, visceral and perivascular adipose tissue, J. Transl. Med. 14 (1) (2016) 208.

[84] J. Aron-Wisnewsky, J. Tordjman, C. Poitou, F. Darakhshan, D. Hugol, A. Basdevant, A. Aissat, M. Guerre-Millo, K. Clement, Human adipose tissue macrophages: m1 and m2 cell surface markers in subcutaneous and omental depots and after weight loss, J. Clin. Endocrinol. Metab. 94 (11) (2009) 4619–4623.

[85] A.M. Blaszczak, A. Jalilvand, J. Liu, V.P. Wright, A. Suzo, B. Needleman, S. Noria, W. Lafuse, W.A. Hsueh, D. Bradley, Human Visceral Adipose Tissue Macrophages Are Not Adequately Defined by Standard Methods of Characterization, J. Diabetes Res. 2019 (2019) 8124563.

[86] C.A. Curat, V. Wegner, C. Sengenes, A. Miranville, C. Tonus, R. Busse, A. Bouloumie, Macrophages in human visceral adipose tissue: increased accumulation in obesity and a source of resistin and visfatin, Diabetologia 49 (4) (2006) 744–747.

[87] J.M. Wentworth, G. Naselli, W.A. Brown, L. Doyle, B. Phipson, G.K. Smyth, M. Wabitsch, P.E. O'Brien, L.C. Harrison, Pro-inflammatory CD11c+CD206+ adipose tissue macrophages are associated with insulin resistance in human obesity, Diabetes 59 (7) (2010) 1648–1656.

[88] L. Liu, K.E. Inouye, W.R. Allman, A.S. Coleman, S. Siddiqui, G.S. Hotamisligil, M. Akkoyunlu, TACI-Deficient Macrophages Protect Mice Against Metaflammation and Obesity-Induced Dysregulation of Glucose Homeostasis, Diabetes 67 (8) (2018) 1589–1603.

[89] E. Ortega Martinez de Victoria, X. Xu, J. Koska, A.M. Francisco, M. Scalise, A. W. Ferrante Jr., J. Krakoff, Macrophage content in subcutaneous adipose tissue: associations with adiposity, age, inflammatory markers, and whole-body insulin action in healthy Pima Indians, Diabetes 58 (2) (2009) 385–393.

[90] C.N. Lumeng, J. Liu, L. Geletka, C. Delaney, J. Delproposto, A. Desai, K. Oatmen, G. Martinez-Santibanez, A. Julius, S. Garg, R.L. Yung, Aging is associated with an increase in T cells and inflammatory macrophages in visceral adipose tissue, J. Immunol. 187 (12) (2011) 6208–6216.

[91] C.D. Camell, J. Sander, O. Spadaro, A. Lee, K.Y. Nguyen, A. Wing, E.L. Goldberg, Y.H. Youm, C.W. Brown, J. Elsworth, M.S. Rodeheffer, J.L. Schultze, V.D. Dixit, Inflammasome-driven catecholamine catabolism in macrophages blunts lipolysis during ageing, Nature 550 (7674) (2017) 119–123.

[92] A. Kosteli, E. Sugaru, G. Haemmerle, J.F. Martin, J. Lei, R. Zechner, A. W. Ferrante Jr., Weight loss and lipolysis promote a dynamic immune response in murine adipose tissue, J. Clin. Invest. 120 (10) (2010) 3466–3479.

[93] H. Frikke-Schmidt, B.F. Zamarron, R.W. O'Rourke, D.A. Sandoval, C.N. Lumeng, R.J. Seeley, Weight loss independent changes in adipose tissue macrophage and T cell populations after sleeve gastrectomy in mice, Mol. Metab. 6 (4) (2017) 317–326.

[94] B. Zamarron, T. Mergian, G. Martinez-Santibanez, C. Lumeng, Impact of weight loss on obese adipose tissue immune cell function (CAM1P.154), J. Immunol. 194 (1) (2015).

[95] P. Auerbach, P. Nordby, L.Q. Bendtsen, J.L. Mehlsen, S.K. Basnet, H. Vestergaard, T. Ploug, B. Stallknecht, Differential effects of endurance training and weight loss on plasma adiponectin multimers and adipose tissue macrophages in younger, moderately overweight men, Am. J. Physiol. Regul. Integr. Comp. Physiol. 305 (5) (2013) R490–R498.

[96] J.O. Aleman, N.M. Iyengar, J.M. Walker, G.L. Milne, J.C. Da Rosa, Y. Liang, D. D. Giri, X.K. Zhou, M.N. Pollak, C.A. Hudis, J.L. Breslow, P.R. Holt, A. J. Dannenberg, Effects of Rapid Weight Loss on Systemic and Adipose Tissue Inflammation and Metabolism in Obese Postmenopausal Women, J. Endocr. Soc. 1 (6) (2017) 625–637.

[97] D.A. Hill, H.W. Lim, Y.H. Kim, W.Y. Ho, Y.H. Foong, V.L. Nelson, H.C.B. Nguyen, K. Chegireddy, J. Kim, A. Habertheuer, P. Vallabhajosyula, T. Kambayashi, K. J. Won, M.A. Lazar, Distinct macrophage populations direct inflammatory versus physiological changes in adipose tissue, Proc. Natl. Acad. Sci. U.S.A 115 (22) (2018) E5096–E5105.

[98] M. Morgan-Bathke, D. Harteneck, P. Jaeger, E. Sondergaard, R. Karwoski, A. Espinosa De Ycaza, B.G. Carranza-Leon, W.A. Faubion Jr., A.M. Oliveira, M. D. Jensen, Comparison of Methods for Analyzing Human Adipose Tissue Macrophage Content, Obesity (Silver Spring) 25 (12) (2017) 2100–2107.

[99] P. Isakson, A. Hammarstedt, B. Gustafson, U. Smith, Impaired preadipocyte differentiation in human abdominal obesity: role of Wnt, tumor necrosis factor-alpha, and inflammation, Diabetes 58 (7) (2009) 1550–1557.

[100] Q. Wang, H. Wu, T Cells in Adipose Tissue: Critical Players in Immunometabolism, Front. Immunol. 9 (2018) 2509.

[101] K.J. Strissel, J. DeFuria, M.E. Shaul, G. Bennett, A.S. Greenberg, M.S. Obin, T-cell recruitment and Th1 polarization in adipose tissue during diet-induced obesity in C57BL/6 mice, Obesity (Silver Spring) 18 (10) (2010) 1918–1925.

[102] T. Deng, C.J. Lyon, L.J. Minze, J. Lin, J. Zou, J.Z. Liu, Y. Ren, Z. Yin, D. J. Hamilton, P.R. Reardon, V. Sherman, H.Y. Wang, K.J. Phillips, P. Webb, S. T. Wong, R.F. Wang, W.A. Hsueh, Class II major histocompatibility complex plays an essential role in obesity-induced adipose inflammation, Cell Metab. 17 (3) (2013) 411–422.

[103] I.M. Khan, X.Y. Dai Perrard, J.L. Perrard, A. Mansoori, C. Wayne Smith, H. Wu, C. M. Ballantyne, Attenuated adipose tissue and skeletal muscle inflammation in obese mice with combined CD4+ and CD8+ T cell deficiency, Atherosclerosis 233 (2) (2014) 419–428.

[104] S. Winer, Y. Chan, G. Paltser, D. Truong, H. Tsui, J. Bahrami, R. Dorfman, Y. Wang, J. Zielenski, F. Mastronardi, Y. Maezawa, D.J. Drucker, E. Engleman, D. Winer, H.M. Dosch, Normalization of obesity-associated insulin resistance through immunotherapy, Nat. Med. 15 (8) (2009) 921–929.

[105] V.Z. Rocha, E.J. Folco, G. Sukhova, K. Shimizu, I. Gotsman, A.H. Vernon, P. Libby, Interferon-gamma, a Th1 cytokine, regulates fat inflammation: a role for adaptive immunity in obesity, Circ. Res. 103 (5) (2008) 467–476.

[106] P. Uciechowski, L. Kahmann, B. Plumakers, M. Malavolta, E. Mocchegiani, G. Dedoussis, G. Herbein, J. Jajte, T. Fulop, L. Rink, TH1 and TH2 cell polarization increases with aging and is modulated by zinc supplementation, Exp. Gerontol. 43 (5) (2008) 493–498.

[107] W. Paul, J. Zhu, How are TH2-type immune responses initiated and amplified? Nat. Rev. Immunol. 10 (2010) 225–235.

[108] Y.H. Lee, A.P. Petkova, E.P. Mottillo, J.G. Granneman, In vivo identification of bipotential adipocyte progenitors recruited by beta3-adrenoceptor activation and high-fat feeding, Cell Metab. 15 (4) (2012) 480–491.

[109] T. McLaughlin, L.F. Liu, C. Lamendola, L. Shen, J. Morton, H. Rivas, D. Winer, L. Tolentino, O. Choi, H. Zhang, M. Hui Yen Chng, E. Engleman, T-cell profile in adipose tissue is associated with insulin resistance and systemic inflammation in humans, Arterioscler Thromb. Vasc. Biol. 34 (12) (2014) 2637–2643.

[110] A.S. Mansfield, W.K. Nevala, R.S. Dronca, A.A. Leontovich, L. Shuster, S. N. Markovic, Normal ageing is associated with an increase in Th2 cells, MCP-1 (CCL1) and RANTES (CCL5), with differences in sCD40L and PDGF-AA between sexes, Clin. Exp. Immunol. 170 (2) (2012) 186–193.

[111] S. Sakata-Kaneko, Y. Wakatsuki, Y. Matsunaga, T. Usui, T. Kita, Altered Th1/Th2 commitment in human CD4+ T cells with ageing, Clin. Exp. Immunol. 120 (2) (2000) 267–273.

[112] M. Feuerer, L. Herrero, D. Cipolletta, A. Naaz, J. Wong, A. Nayer, J. Lee, A. B. Goldfine, C. Benoist, S. Shoelson, D. Mathis, Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters, Nat. Med. 15 (8) (2009) 930–939.

[113] S.P. Bapat, J. Myoung Suh, S. Fang, S. Liu, Y. Zhang, A. Cheng, C. Zhou, Y. Liang, M. LeBlanc, C. Liddle, A.R. Atkins, R.T. Yu, M. Downes, R.M. Evans, Y. Zheng, Depletion of fat-resident Treg cells prevents age-associated insulin resistance, Nature 528 (7580) (2015) 137–141.

[114] R.L. Travers, A.C. Motta, J.A. Betts, A. Bouloumie, D. Thompson, The impact of adiposity on adipose tissue-resident lymphocyte activation in humans, Int. J. Obes. (Lond) 39 (5) (2015) 762–769.

[115] S. Nishimura, I. Manabe, M. Nagasaki, K. Eto, H. Yamashita, M. Ohsugi, M. Otsu, K. Hara, K. Ueki, S. Sugiura, K. Yoshimura, T. Kadowaki, R. Nagai, CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity, Nat. Med. 15 (8) (2009) 914–920.

[116] E. Jiang, X.D. Perrard, D. Yang, I.M. Khan, J.L. Perrard, C.W. Smith, C. M. Ballantyne, H. Wu, Essential role of CD11a in CD8+ T-cell accumulation and activation in adipose tissue, Arterioscler. Thromb. Vasc. Biol. 34 (1) (2014) 34–43.

[117] M.E. Rausch, S. Weisberg, P. Vardhana, D.V. Tortoriello, Obesity in C57BL/6J mice is characterized by adipose tissue hypoxia and cytotoxic T-cell infiltration, Int. J. Obes. (Lond) 32 (3) (2008) 451–463.

[118] C. Lee-Chang, M. Bodogai, K. Moritoh, P.B. Olkhanud, A.C. Chan, M. Croft, J. A. Mattison, P.J. Holst, R.E. Gress, L. Ferrucci, F. Hakim, A. Biragyn, Accumulation of 4–1BBL+ B cells in the elderly induces the generation of granzyme-B+ CD8+ T cells with potential antitumor activity, Blood 124 (9) (2014) 1450–1459.

[119] H. Ahnstedt, M. Roy-O'Reilly, M.S. Spychala, A.S. Mobley, J. Bravo-Alegria, A. Chauhan, J. Aronowski, S.P. Marrelli, L.D. McCullough, Sex Differences in Adipose Tissue CD8(+) T Cells and Regulatory T Cells in Middle-Aged Mice, Front. Immunol. 9 (2018) 659.

[120] D.A. Winer, S. Winer, L. Shen, P.P. Wadia, J. Yantha, G. Paltser, H. Tsui, P. Wu, M. G. Davidson, M.N. Alonso, H.X. Leong, A. Glassford, M. Caimol, J.A. Kenkel, T. F. Tedder, T. McLaughlin, D.B. Miklos, H.M. Dosch, E.G. Engleman, B cells promote insulin resistance through modulation of T cells and production of pathogenic IgG antibodies, Nat. Med. 17 (5) (2011) 610–617.

[121] D. Frasca, A. Diaz, M. Romero, T. Vazquez, B.B. Blomberg, Obesity induces pro-inflammatory B cells and impairs B cell function in old mice, Mech. Ageing Dev. 162 (2017) 91–99.

[122] L. Shen, M.H. Chng, M.N. Alonso, R. Yuan, D.A. Winer, E.G. Engleman, B-1a lymphocytes attenuate insulin resistance, Diabetes 64 (2) (2015) 593–603.

[123] K. Minton, B1 B cells link gut dysbiosis and insulin resistance, Nat. Rev. Immunol. 19 (1) (2019) 1.

[124] W. Ying, J. Wollam, J.M. Ofrecio, G. Bandyopadhyay, D. El Ouarrat, Y.S. Lee, D. Y. Oh, P. Li, O. Osborn, J.M. Olefsky, Adipose tissue B2 cells promote insulin resistance through leukotriene LTB4/LTB4R1 signaling, J. Clin. Invest. 127 (3) (2017) 1019–1030.

[125] L. Muller, S. Di Benedetto, G. Pawelec, The Immune System and Its Dysregulation with Aging, Subcell. Biochem. 91 (2019) 21–43.

[126] C. Franceschi, J. Campisi, Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases, J. Gerontol. A Biol. Sci. Med. Sci. 69 (Suppl 1) (2014) S4–S9.

[127] C. Lee-Chang, M. Bodogai, K. Moritoh, X. Chen, R. Wersto, R. Sen, H.A. Young, M. Croft, L. Ferrucci, A. Biragyn, Aging Converts Innate B1a Cells into Potent CD8 + T Cell Inducers, J. Immunol. 196 (8) (2016) 3385–3397.

[128] M. Bodogai, J. O'Connell, K. Kim, Y. Kim, K. Moritoh, C. Chen, F. Gusev, K. Vaughan, N. Shulzhenko, J.A. Mattison, C. Lee-Chang, W. Chen, O. Carlson, K. G. Becker, M. Gurung, A. Morgun, J. White, T. Meade, K. Perdue, M. Mack, L. Ferrucci, G. Trinchieri, R. de Cabo, E. Rogaev, J. Egan, J. Wu, A. Biragyn, Commensal bacteria contribute to insulin resistance in aging by activating innate B1a cells, Sci. Transl. Med. 10 (467) (2018).

[129] S. Carter, S. Miard, A. Caron, S. Salle-Lefort, P. St-Pierre, F.F. Anhe, E. Lavoie-Charland, P. Blais-Lecours, M.C. Drolet, J.S. Lefebvre, J. Lacombe, Y. Deshaies, J. Couet, M. Laplante, M. Ferron, Y. Bosse, A. Marette, D. Richard, D. Marsolais, F. Picard, Loss of OcaB Prevents Age-Induced Fat Accretion and Insulin Resistance by Altering B-Lymphocyte Transition and Promoting Energy Expenditure, Diabetes 67 (7) (2018) 1285–1296.

[130] S. Nishimura, I. Manabe, S. Takaki, M. Nagasaki, M. Otsu, H. Yamashita, J. Sugita, K. Yoshimura, K. Eto, I. Komuro, T. Kadowaki, R. Nagai, Adipose Natural Regulatory B Cells Negatively Control Adipose Tissue Inflammation, Cell Metab. 18 (5) (2013) 759–766.

[131] M. Merad, P. Sathe, J. Helft, J. Miller, A. Mortha, The dendritic cell lineage: ontogeny and function of dendritic cells and their subsets in the steady state and the inflamed setting, Annu. Rev. Immunol. 31 (2013) 563–604.

[132] K.W. Cho, B.F. Zamarron, L.A. Muir, K. Singer, C.E. Porsche, J.B. DelProposto, L. Geletka, K.A. Meyer, R.W. O'Rourke, C.N. Lumeng, Adipose Tissue Dendritic Cells Are Independent Contributors to Obesity-Induced Inflammation and Insulin Resistance, J. Immunol. 197 (9) (2016) 3650–3661.

[133] A. Bertola, T. Ciucci, D. Rousseau, V. Bourlier, C. Duffaut, S. Bonnafous, C. Blin-Wakkach, R. Anty, A. Iannelli, J. Gugenheim, A. Tran, A. Bouloumie, P. Gual, A. Wakkach, Identification of adipose tissue dendritic cells correlated with obesity-associated insulin-resistance and inducing Th17 responses in mice and patients, Diabetes 61 (9) (2012) 2238–2247.

[134] C.E. Macdougall, E.G. Wood, J. Loschko, V. Scagliotti, F.C. Cassidy, M. E. Robinson, N. Feldhahn, L. Castellano, M.B. Voisin, F. Marelli-Berg, C. Gaston-Massuet, M. Charalambous, M.P. Longhi, Visceral Adipose Tissue Immune Homeostasis Is Regulated by the Crosstalk between Adipocytes and Dendritic Cell Subsets, Cell Metab. 27 (3) (2018), 588-601 e4.

[135] A.R. Ghosh, R. Bhattacharya, S. Bhattacharya, T. Nargis, O. Rahaman, P. Duttagupta, D. Raychaudhuri, C.S. Liu, S. Roy, P. Ghosh, S. Khanna, T. Chaudhuri, O. Tantia, S. Haak, S. Bandyopadhyay, S. Mukhopadhyay, P. Chakrabarti, D. Ganguly, Adipose Recruitment and Activation of Plasmacytoid Dendritic Cells Fuel Metaflammation, Diabetes 65 (11) (2016) 3440–3452.

[136] T.D. Hannibal, A. Schmidt-Christensen, J. Nilsson, N. Fransen-Pettersson, L. Hansen, D. Holmberg, Deficiency in plasmacytoid dendritic cells and type I interferon signalling prevents diet-induced obesity and insulin resistance in mice, Diabetologia 60 (10) (2017) 2033–2041.

[137] E.E. Kershaw, J.S. Flier, Adipose tissue as an endocrine organ, J. Clin. Endocrinol. Metab. 89 (6) (2004) 2548–2556.

[138] R.W. Grant, V.D. Dixit, Adipose tissue as an immunological organ, Obesity (Silver Spring) 23 (3) (2015) 512–518.

[139] J.I. Leon-Pedroza, L.A. Gonzalez-Tapia, E. del Olmo-Gil, D. Castellanos-Rodriguez, G. Escobedo, A. Gonzalez-Chavez, Low-grade systemic inflammation and the development of metabolic diseases: from the molecular evidence to the clinical practice, Cir. Cir. 83 (6) (2015) 543–551.

[140] X. Unamuno, J. Gomez-Ambrosi, A. Rodriguez, S. Becerril, G. Fruhbeck, V. Catalan, Adipokine dysregulation and adipose tissue inflammation in human obesity, Eur. J. Clin. Invest. 48 (9) (2018), e12997.

[141] I. Barchetta, F.A. Cimini, G. Ciccarelli, M.G. Baroni, M.G. Cavallo, Sick fat: the good and the bad of old and new circulating markers of adipose tissue inflammation, J. Endocrinol. Invest. 42 (11) (2019) 1257–1272.
[142] H. Kwon, J.E. Pessin, Adipokines mediate inflammation and insulin resistance, Front. Endocrinol. (Lausanne) 4 (2013) 71.
[143] A. Lasry, Y. Ben-Neriah, Senescence-associated inflammatory responses: aging and cancer perspectives, Trends Immunol. 36 (4) (2015) 217–228.
[144] C. Franceschi, P. Garagnani, G. Vitale, M. Capri, S. Salvioli, Inflammaging and 'Garb-aging', Trends Endocrinol. Metab. 28 (3) (2017) 199–212.
[145] K.L. Spalding, E. Arner, P.O. Westermark, S. Bernard, B.A. Buchholz, O. Bergmann, L. Blomqvist, J. Hoffstedt, E. Naslund, T. Britton, H. Concha, M. Hassan, M. Ryden, J. Frisen, P. Arner, Dynamics of fat cell turnover in humans, Nature 453 (7196) (2008) 783–787.
[146] A. Ito, T. Suganami, Y. Miyamoto, Y. Yoshimasa, M. Takeya, Y. Kamei, Y. Ogawa, Role of MAPK phosphatase-1 in the induction of monocyte chemoattractant protein-1 during the course of adipocyte hypertrophy, J. Biol. Chem. 282 (35) (2007) 25445–25452.
[147] S.E. Shoelson, J. Lee, M. Yuan, Inflammation and the IKK beta/I kappa B/NF-kappa B axis in obesity- and diet-induced insulin resistance, Int. J. Obes. Relat. Metab. Disord. 27 (Suppl 3) (2003) S49–S52.
[148] I. Nieto-Vazquez, S. Fernandez-Veledo, D.K. Kramer, R. Vila-Bedmar, L. Garcia-Guerra, M. Lorenzo, Insulin resistance associated to obesity: the link TNF-alpha, Arch. Physiol. Biochem. 114 (3) (2008) 183–194.
[149] A.S. Greenberg, M.S. Obin, Obesity and the role of adipose tissue in inflammation and metabolism, Am. J. Clin. Nutr. 83 (2) (2006) 461S–465S.
[150] S.E. Shoelson, J. Lee, A.B. Goldfine, Inflammation and insulin resistance, J Clin Invest 116 (7) (2006) 1793–1801.
[151] E. Arner, P.O. Westermark, K.L. Spalding, T. Britton, M. Ryden, J. Frisen, S. Bernard, P. Arner, Adipocyte turnover: relevance to human adipose tissue morphology, Diabetes 59 (1) (2010) 105–109.
[152] B. Gustafson, A. Hammarstedt, S. Hedjazifar, U. Smith, Restricted adipogenesis in hypertrophic obesity: the role of WISP2, WNT, and BMP4, Diabetes 62 (9) (2013) 2997–3004.
[153] B. Gustafson, S. Gogg, S. Hedjazifar, L. Jenndahl, A. Hammarstedt, U. Smith, Inflammation and impaired adipogenesis in hypertrophic obesity in man, Am. J. Physiol. Endocrinol. Metab. 297 (5) (2009) E999–E1003.
[154] R.S. Ahima, Connecting obesity, aging and diabetes, Nat. Med. 15 (9) (2009) 996–997.
[155] G.R. Chang, Y.S. Chiu, Y.Y. Wu, W.Y. Chen, J.W. Liao, T.H. Chao, F.C. Mao, Rapamycin protects against high fat diet-induced obesity in C57BL/6J mice, J. Pharmacol. Sci. 109 (4) (2009) 496–503.
[156] C. Selman, J.M. Tullet, D. Wieser, E. Irvine, S.J. Lingard, A.I. Choudhury, M. Claret, H. Al-Qassab, D. Carmignac, F. Ramadani, A. Woods, I.C. Robinson, E. Schuster, R.L. Batterham, S.C. Kozma, G. Thomas, D. Carling, K. Okkenhaug, J. M. Thornton, L. Partridge, D. Gems, D.J. Withers, Ribosomal protein S6 kinase 1 signaling regulates mammalian life span, Science 326 (5949) (2009) 140–144.
[157] C. Selman, S. Lingard, A.I. Choudhury, R.L. Batterham, M. Claret, M. Clements, F. Ramadani, K. Okkenhaug, E. Schuster, E. Blanc, M.D. Piper, H. Al-Qassab, J. R. Speakman, D. Carmignac, I.C. Robinson, J.M. Thornton, D. Gems, L. Partridge, D.J. Withers, Evidence for lifespan extension and delayed age-related biomarkers in insulin receptor substrate 1 null mice, FASEB J. 22 (3) (2008) 807–818.
[158] D.E. Berryman, J.S. Christiansen, G. Johannsson, M.O. Thorner, J.J. Kopchick, Role of the GH/IGF-1 axis in lifespan and healthspan: lessons from animal models, Growth Horm IGF Res 18 (6) (2008) 455–471.
[159] A. Divoux, J. Tordjman, D. Lacasa, N. Veyrie, D. Hugol, A. Aissat, A. Basdevant, M. Guerre-Millo, C. Poitou, J.D. Zucker, P. Bedossa, K. Clement, Fibrosis in human adipose tissue: composition, distribution, and link with lipid metabolism and fat mass loss, Diabetes 59 (11) (2010) 2817–2825.
[160] K. Sun, J. Tordjman, K. Clement, P.E. Scherer, Fibrosis and adipose tissue dysfunction, Cell Metab. 18 (4) (2013) 470–477.
[161] R. Datta, M.J. Podolsky, K. Atabai, Fat fibrosis: friend or foe? JCI Insight 3 (19) (2018).
[162] C. Henegar, J. Tordjman, V. Achard, D. Lacasa, I. Cremer, M. Guerre-Millo, C. Poitou, A. Basdevant, V. Stich, N. Viguerie, D. Langin, P. Bedossa, J.D. Zucker, K. Clement, Adipose tissue transcriptomic signature highlights the pathological relevance of extracellular matrix in human obesity, Genome Biol. 9 (1) (2008) R14.
[163] S. Reggio, C. Rouault, C. Poitou, J.C. Bichet, E. Prifti, J.L. Bouillot, S. Rizkalla, D. Lacasa, J. Tordjman, K. Clement, Increased Basement Membrane Components in Adipose Tissue During Obesity: Links With TGFbeta and Metabolic Phenotypes, J. Clin. Endocrinol. Metab. 101 (6) (2016) 2578–2587.
[164] M. Pasarica, B. Gowronska-Kozak, D. Burk, I. Remedios, D. Hymel, J. Gimble, E. Ravussin, G.A. Bray, S.R. Smith, Adipose tissue collagen VI in obesity, J. Clin. Endocrinol. Metab. 94 (12) (2009) 5155–5162.
[165] S.N. Dankel, J. Svard, S. Mattha, M. Claussnitzer, N. Kloting, V. Glunk, Z. Fandalyuk, E. Grytten, M.H. Solsvik, H.J. Nielsen, C. Busch, H. Hauner, M. Bluher, T. Skurk, J.V. Sagen, G. Mellgren, COL6A3 expression in adipocytes associates with insulin resistance and depends on PPARgamma and adipocyte size, Obesity (Silver Spring) 22 (8) (2014) 1807–1813.
[166] M. Spencer, A. Yao-Borengasser, R. Unal, N. Rasouli, C.M. Gurley, B. Zhu, C. A. Peterson, P.A. Kern, Adipose tissue macrophages in insulin-resistant subjects are associated with collagen VI and fibrosis and demonstrate alternative activation, Am. J. Physiol. Endocrinol. Metab. 299 (6) (2010) E1016–E1027.
[167] T. Khan, E.S. Muise, P. Iyengar, Z.V. Wang, M. Chandalia, N. Abate, B.B. Zhang, P. Bonaldo, S. Chua, P.E. Scherer, Metabolic dysregulation and adipose tissue fibrosis: role of collagen VI, Mol. Cell. Biol. 29 (6) (2009) 1575–1591.
[168] A.J. Donato, G.D. Henson, C.R. Hart, G. Layec, J.D. Trinity, R.C. Bramwell, R. A. Enz, R.G. Morgan, K.D. Reihl, S. Hazra, A.E. Walker, R.S. Richardson, L. A. Lesniewski, The impact of ageing on adipose structure, function and vasculature in the B6D2F1 mouse: evidence of significant multisystem dysfunction, J. Physiol. 592 (18) (2014) 4083–4096.
[169] A.A. Johnson, A. Stolzing, The role of lipid metabolism in aging, lifespan regulation, and age-related disease, Aging Cell 18 (6) (2019), e13048.
[170] A. Sorisky, R. Magun, A.M. Gagnon, Adipose cell apoptosis: death in the energy depot, Int. J. Obes. Relat. Metab. Disord. 24 (Suppl 4) (2000) S3–S7.
[171] N. Alkhouri, A. Gornicka, M.P. Berk, S. Thapaliya, L.J. Dixon, S. Kashyap, P. R. Schauer, A.E. Feldstein, Adipocyte apoptosis, a link between obesity, insulin resistance, and hepatic steatosis, J. Biol. Chem. 285 (5) (2010) 3428–3438.
[172] S. Cinti, G. Mitchell, G. Barbatelli, I. Murano, E. Ceresi, E. Faloia, S. Wang, M. Fortier, A.S. Greenberg, M.S. Obin, Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans, J. Lipid Res. 46 (11) (2005) 2347–2355.
[173] I. Murano, G. Barbatelli, V. Parisani, C. Latini, G. Muzzonigro, M. Castellucci, S. Cinti, Dead adipocytes, detected as crown-like structures, are prevalent in visceral fat depots of genetically obese mice, J. Lipid Res. 49 (7) (2008) 1562–1568.
[174] C.N. Lumeng, J.L. Bodzin, A.R. Saltiel, Obesity induces a phenotypic switch in adipose tissue macrophage polarization, J Clin Invest 117 (1) (2007) 175–184.
[175] C.N. Lumeng, J.B. DelProposto, D.J. Westcott, A.R. Saltiel, Phenotypic switching of adipose tissue macrophages with obesity is generated by spatiotemporal differences in macrophage subtypes, Diabetes 57 (12) (2008) 3239–3246.
[176] P. Fischer-Posovszky, Q.A. Wang, I.W. Asterholm, J.M. Rutkowski, P.E. Scherer, Targeted deletion of adipocytes by apoptosis leads to adipose tissue recruitment of alternatively activated M2 macrophages, Endocrinology 152 (8) (2011) 3074–3081.
[177] A.K. Ghosh, T. Mau, M. O'Brien, S. Garg, R. Yung, Impaired autophagy activity is linked to elevated ER-stress and inflammation in aging adipose tissue, Aging (Albany NY) 8 (10) (2016) 2525–2537.
[178] S. Hibbert, Extracellular matrix is an influential force in ageing, Br. J. Dermatol. 177 (5) (2017) 1160–1161.
[179] H.L. Birch, Extracellular Matrix and Ageing, Subcell. Biochem. 90 (2018) 169–190.
[180] T.M. Callaghan, K.P. Wilhelm, A review of ageing and an examination of clinical methods in the assessment of ageing skin. Part I: Cellular and molecular perspectives of skin ageing, Int. J. Cosmet. Sci. 30 (5) (2008) 313–322.
[181] J.M. Phillip, I. Aifuwa, J. Walston, D. Wirtz, The Mechanobiology of Aging, Annu. Rev. Biomed. Eng. 17 (2015) 113–141.
[182] S. Freitas-Rodriguez, A.R. Folgueras, C. Lopez-Otin, The role of matrix metalloproteinases in aging: Tissue remodeling and beyond, Biochim. Biophys. Acta Mol. Cell Res. 1864 (11 Pt A) (2017) 2015–2025.
[183] S.K. Biswas, Metabolic Reprogramming of Immune Cells in Cancer Progression, Immunity 43 (3) (2015) 435–449.
[184] P. Garcia-Gonzalez, G. Ubilla-Olguin, D. Catalan, K. Schinnerling, J.C. Aguillon, Tolerogenic dendritic cells for reprogramming of lymphocyte responses in autoimmune diseases, Autoimmun. Rev. 15 (11) (2016) 1071–1080.
[185] C. Jing, T. Castro-Dopico, N. Richoz, Z.K. Tuong, J.R. Ferdinand, L.S.C. Lok, K. W. Loudon, G.D. Banham, R.J. Mathews, Z. Cader, S. Fitzpatrick, K.R. Bashant, M. J. Kaplan, A. Kaser, R.S. Johnson, M.P. Murphy, R.M. Siegel, M.R. Clatworthy, Macrophage metabolic reprogramming presents a therapeutic target in lupus nephritis, Proc. Natl. Acad. Sci. U.S.A 117 (26) (2020) 15160–15171.
[186] V. Guarner-Lans, M.E. Rubio-Ruiz, I. Perez-Torres, G. Banos de MacCarthy, Relation of aging and sex hormones to metabolic syndrome and cardiovascular disease, Exp. Gerontol. 46 (7) (2011) 517–523.
[187] G. Veronica, R.R. Esther, Aging, metabolic syndrome and the heart, Aging Dis. 3 (3) (2012) 269–279.
[188] M. Bechtold, J. Palmer, J. Valtos, C. Iasiello, J. Sowers, Metabolic syndrome in the elderly, Curr. Diab. Rep. 6 (1) (2006) 64–71.
[189] P. Arner, P. Petrus, D. Esteve, A. Boulomie, E. Naslund, A. Thorell, H. Gao, I. Dahlman, M. Ryden, Screening of potential adipokines identifies S100A4 as a marker of pernicious adipose tissue and insulin resistance, Int. J. Obes. 42 (12) (2018) 2047–2056.