Published in final edited form as:

Semin Immunopathol. 2020 October ; 42(5): 573–587. doi:10.1007/s00281-020-00812-1.

Adipose tissue, immune aging and cellular senescence

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Abstract

Obesity represents a serious health problem as it is rapidly increasing worldwide. Obesity is associated with reduced healthspan and lifespan, decreased responses to infections and vaccination and increased frequency of inflammatory conditions typical of old age. Obesity is characterized by increased fat mass and remodeling of the adipose tissue (AT). In this review we summarize published data on the different types of AT present in mice and humans, and their roles as fat storage as well as endocrine and immune tissues. We review the age-induced changes, including those in the distribution of fat in the body, in abundance and function of adipocytes and their precursors, and in the infiltration of immune cells from the peripheral blood. We also show that cells with a senescent-associated secretory phenotype accumulate in the AT of mice and humans with age, where they secrete several factors involved in the establishment and maintenance of local inflammation, oxidative stress, cell death, tissue remodeling and infiltration of proinflammatory immune cells. Not only adipocytes and preadipocytes, but also immune cells, show a senescent phenotype in the AT. With the increase in human lifespan, it is crucial to identify strategies of intervention and target senescent cells in the AT to reduce local and systemic inflammation and the development of age-associated diseases. Several studies have indeed shown that senescent cells can be effectively targeted in the AT by selectively removing them or by inhibiting the pathways that lead to the secretion of pro-inflammatory factors.

Keywords

Adipose tissue; Adipocytes; Aging; Cell senescence; Immune cells

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Conflict of Interest

The authors declare that they have no conflict of interest.

Introduction

Obesity, defined as a body-mass index (BMI) ≥ 30 kg/m², has reached epidemic proportions worldwide. Obesity has been defined by the American Medical Association a complex chronic disease, characterized by accumulation of body fat [1], responsible for the development of chronic diseases of old age such as cardiovascular disease [2]. Type-2 Diabetes Mellitus (T2DM) [3–5], cancer [6], psoriasis [7], atherosclerosis [8], and Inflammatory Bowel Disease [9]. The obesity pandemic affects children [10] and adults [11]. In a recent study in which BMI data from 68 million people living in 195 countries were analyzed, it was found that obesity prevalence has doubled since 1980 in more than 70 countries and continuously increased in most other countries [11].

Obesity decreases healthspan and lifespan, increases premature mortality and significantly increases global healthcare costs. BMI is negatively correlated with protective immune responses to viral, bacterial and fungal infections [12–14] and to vaccination [15–17]. Obesity increases the risk of musculoskeletal disorders and chronic back/lower limb pain [18]; increases the risk of Alzheimer's disease and dementia [19,20]; induces infertility [21] and increases the risk of miscarriage, gestational diabetes and preeclampsia, complicated labor and delivery [22]; reduces respiratory function and lung expansion by narrowing airways in the lung [23], leading to asthma [24] and obstructive sleep apnea [25], through changes in lung function likely due to higher weight load on the thorax. Obesity is a well-known risk factor for insulin resistance (IR) and progression to T2DM. Aging, independently from obesity, also increases the risk of IR and other metabolic conditions through adipose tissue (AT) dysfunction and associated changes such as activation of pro-inflammatory pathways, increased infiltration of immune cells and accumulation of senescent cells. Epidemiological studies have shown that elderly individuals with subclinical but elevated circulating levels of pro-inflammatory mediators (CRP, IL-6, and IL-1 β) increase the risk of developing IR and T2DM [26–28].

Obesity is associated with an increase in fat mass and remodeling of the AT, which is characterized by the expansion of adipocyte size and accumulation of extracellular matrix components (collagens, elastins) which occurs concomitantly with increased secretion of pro-inflammatory cytokines and chemokines. Failure to undergo appropriate remodeling in response to over-nutrition is detrimental to metabolic homeostasis. Moreover, excess nutrients promote “metaflammation”, the chronic inflammation orchestrated by metabolic cells (adipocytes) in response to excess nutrients and energy, whose metabolic hallmarks are high levels of glucose, lipids, free fatty acids (FFAs) and reactive oxygen species (ROS) [29].

Characterization of the AT

Types of AT

There are two major types of AT in mammals, the white AT (WAT) and the brown AT (BAT), which differ in morphology, metabolic activity and function, all of which affect the adipocytes [30,31]. WAT is involved in lipid storage and immuno-endocrine responses, whereas BAT regulates thermogenesis which indicates the generation of heat through

uncoupling of mitochondrial respiration. Thermogenesis is finely regulated by catecholamines released by activated macrophages [32], by eosinophils [33] and by sympathetic neuron-associated macrophages [34]. Catecholamines stimulate the expression of the thermogenic genes PPAR- γ coactivator 1a (Ppargc1a), uncoupling protein 1 (Ucp1) and acyl-CoA synthase long-chain family member 1.

The WAT includes several anatomical depots with different structural organization, cellular size, and biological function. The accumulation of fat between these depots is more important than the amount of total fat in the body for the risk of developing obesity-associated conditions. The WAT consists of subcutaneous AT (SAT) and visceral AT (VAT). The SAT is generally located in lower parts of the body, and is measured by hip, thigh and leg circumference, but can also accumulate in the area around the neck. The VAT surrounds internal organs and includes omental, mesenteric, epididymal, perirenal, retroperitoneal, epicardial [35]. The SAT accounts for almost 80% of human AT, but the VAT is more metabolically active, and VAT accumulation is a greater predictor of obesity-associated mortality. SAT and VAT are biologically distinct AT depots and secrete different pro-inflammatory cytokines, chemokines and adipokines, all of which contribute to IR and age-associated chronic diseases [36–38].

The BAT also consists of SAT and VAT. BAT is the main AT in fetuses and newborns. Experiments conducted in mice have shown that BAT is characterized by adipocytes with many small lipid droplets, abundant mitochondria that express high levels of Ucp1 needed for FA oxidation and heat production [39]. The BAT also contains different immune cell types (macrophages, neutrophils and lymphocytes) [40,41] and it has been postulated that, although BAT seems to be more resistant to macrophage infiltration than WAT, infiltrated immune cells in BAT contribute to local inflammation and BAT dysfunction [42]. Several regions of functionally active BAT in humans have been identified [43], but their role is not well understood.

Browning of WAT represents the adaptive and reversible response to stimuli. This reaction includes a step in which “beige” adipocytes are detected. These adipocytes contain many lipid droplets in the cytoplasm, numerous mitochondria and are characterized by several features that are intermediate between WAT and BAT adipocytes. Beige adipocytes, similar to BAT adipocytes, have the capacity to burn glucose and fat to produce heat, a function mediated by Ucp1.

Functions of the AT

The main function of the AT is to store FFAs in the form of triglycerides that are then released during starvation or physical activity. In conditions of hyper-nutrition, the storage of extra fat leads to the development of obesity, followed by IR. Mechanisms proposed to explain the development of IR involve metabolic stress-driven activation of NF- κ B signaling pathways in insulin sensitive tissues (AT, liver, muscle) [44], release of TNF- α and local inflammation [45,46]. It has been shown that neutralization of TNF- α with a soluble TNF receptor [(TNFR)-IgG fusion protein] leads to significantly increased signaling through the insulin receptor in the AT and insulin-stimulated glucose uptake [47]. Although these pre-clinical studies have clearly shown a significant association between IR and inflammation

(TNF- α), more recent studies have failed to show decreased IR in individuals with obesity and associated conditions treated with TNF- α -blockers [48–50].

The AT is a major endocrine organ [51,52] that regulates body metabolism and represents the largest endocrine tissue of humans [35,53]. The AT secretes several adipocyte-derived proteins with endocrine functions that act locally and systemically, such as adipokines (leptin, adiponectin, resistin), cytokines (TNF- α , IL-6), complement components, proteins involved in lipid (lipoprotein lipase, apolipoprotein E) and steroid (Cytochrome P450-dependent aromatase) metabolism, plasminogen activator inhibitor-1, and proteins of the renin-angiotensin system such as resistin. Leptin and adiponectin have been studied extensively. Leptin has been shown to have a crucial role in the regulation of whole-body metabolism as it stimulates energy expenditure, inhibits food intake and restores normal levels of glycemia. In cases of obesity and super-obesity, however, leptin resistance limits its biological efficacy. In contrast to leptin, adiponectin secretion is often decreased in obesity. Adiponectin increases energy expenditure, insulin sensitivity (IS) and FA oxidation, and decreases the production of glucose by the liver.

The AT is also an immunological organ, composed of adipocytes and a mixture of mesenchymal, endothelial and immune cells, known as Stromal Vascular Fraction (SVF) [54,55]. The AT is the largest organ in individuals that are overweight/obese. The lean AT of mice and humans contains M2 macrophages, Th2 CD4+ T cells, T regulatory cells (Treg), B cells, iNKT, group 2 innate lymphoid cells (ILC2) and eosinophils, all localized around crown-like structures and perivascular spaces. Macrophages in the AT are tissue-resident cells, established during embryonic development and maintained throughout life independently of monocyte infiltration [56]. In the obese AT of mice and humans, crown-like structures increase in number and size as compared to lean AT, primarily due to the heavy infiltration of immune pro-inflammatory cells such as Th1, Th17, T γ δ , IFN- γ -producing CD8+ T cells, B cells and ILC1 s, all of which contribute to the secretion of pro-inflammatory cytokines and adipokines and to IR [57]. M2 macrophages exposed to AT Danger- and Pathogen-Associated Molecular Patterns, acquire the pro-inflammatory M1 phenotype [55]. In the obese AT, the supply of oxygen becomes inadequate, due to the expansion of AT without concomitant expansion of the vasculature, and areas of hypoxia are generated, leading to the activation of the transcription factor hypoxia-inducible factor-1 α (HIF-1 α) and further release of pro-inflammatory cytokines [58–60]. TNF- α , secreted by the adipocytes and the immune cells in the obese AT, also contributes to local and systemic inflammation [61,45,62]. TNF- α is a tonic stimulator of lipolysis, the process of hydrolysis of triglycerides that generates FFAs, glycerol and lipids, all inducing NF-kB activation and activation of M1 macrophages [63]. FFAs also directly inhibit B cell cytokine secretion in vitro [64]. Excessive lipolysis in the obese AT leads to increased oxidative stress that promotes DNA damage and AT inflammation [65,66].

The WAT is innervated by the sympathetic nervous system, whose activation is necessary for lipolysis, for lipid metabolism and for adipocyte differentiation [67]. There is a lack of evidence supporting the parasympathetic innervation of WAT. It has been postulated that VAT is innervated to a greater extent than SAT, leading to several well known adverse health consequences including high blood pressure, T2D and also cancer.

The BAT is also innervated by the sympathetic nervous system, and this regulates thermogenesis [68]. Pathways involve the release of norepinephrine (NE), followed by the stimulation of β 3-adrenoceptors and activation of Ucp1. BAT innervation may also function to monitor BAT lipolysis, a response necessary for activation of Ucp1 by FAs.

Sympathetic innervation is necessary for the generation of beige adipocyte as well [69].

Changes in the WAT with aging

The large majority of studies on the effects of aging on the AT have been done on WAT. It has recently been shown, using proteome-wide measurements with two-dimensional multiplexing technology, that the WAT of mice is the most affected tissue by aging, suggesting that the WAT is crucial for the organism's adaptation and response to aging [70]. Age-induced changes in WAT include changes in distribution of fat mass, in protein expression, in metabolic pathways, in immune cell infiltration, in inflammation. These will be described in detail below.

Very little is known on the effects of aging on BAT. The amount of detectable BAT significantly decreases with age [43]. Moreover, the proliferative capacity of BAT adipocytes and Ucp1 expression in response to cold are both completely abolished during aging [71,72]. Aging also induces a decrease in the number of beige adipocytes, likely caused by changes in the trophic factors present in the microenvironment which are involved in the differentiation of beige adipocytes from WAT precursors [73]. After exposure to cold, beige adipocytes from young mice express Ucp1 [74]. However, beige adipocytes from old mice have a WAT morphology and lose their thermogenic capacity [75].

Aging has been shown to be associated with alterations in sympathetic nerve activity, and changes in the output and balance of sympathetic and parasympathetic outflow to visceral tissues, including the WAT, have been reported [76]. One example is the effect of aging on NE-induced lipolysis in VAT macrophages, due to the NLRP3 inflammasome-dependent increase in NE degradation, limiting its bioavailability [77]. No data are available on the effects of aging on sympathetic innervation of the BAT.

Changes in distribution of fat mass

The AT undergoes significant changes during aging, such as abundance, distribution and cellular composition. These changes accelerate the onset of age-associated disease [78,79]. Studies in mice have shown that obesity, similar to aging, leads to reduced lifespan [80], while caloric restriction increases lifespan, due to reduction in the amount of VAT depots [81].

Fat mass increases with age in mice [28] and humans [28,82]. Computational tomography scans have shown that SAT mass decreases and VAT mass increases with age [82], with VAT being more inflammatory. An age-associated increase in the accumulation of triglycerides outside fat depots (liver, muscle, heart, pancreas, kidney) [83,66,84–86] and in blood vessels [87] has been reported. A mechanism proposed is the differentiation of multipotent mesenchymal progenitor cells into adipocyte-like cells. This process, called

“dysdifferentiation of mesenchymal progenitors into mesenchymal adipocyte-like cells” could result from the activation of age-associated stress responses [88]. The increase in VAT depots in internal organs has been associated with higher low-grade chronic inflammation, inflammaging [89], which contributes to metabolic dysfunction and development of IR which also increases with age [90]. Epidemiological studies have shown that the VAT is responsible more than the SAT for the establishment of IR [91,92]. Moreover, insulin action is significantly impaired in individuals with visceral adiposity [93,94].

An age-related increase in fat accumulation also occurs in the bone marrow, and accounts for decreased numbers of hematopoietic stem cells and decreased levels of stromal-derived factor and insulin-like growth factor [95], both involved in bone maintenance. Moreover, studies in mice have shown decreased B lymphopoiesis in the bone marrow of old mice, due to adipocyte activation of the NLRP3 inflammasome, a major regulator of age-related inflammation and metabolic disorders, leading to IL-1 β secretion [96]. IL-1 β inhibits lymphopoiesis and favors myelopoiesis [97].

The thymus involutes with age [98,99]. Thymic involution plays a crucial role in T cell immunosenescence [98] and is responsible for reduced circulating naive T cells, reduced T cell receptor (TCR) excision circles, markers of thymic output, and reduced TCR diversity in individuals >60 years [100]. Morphologically, thymic involution is characterized by decreased cortical and medullary areas and increased accumulation of unilocular adipocytes and fat-storing multilocular adipocytes in parenchymal regions. These adipocytes may differentiate from mesenchymal stem cells that immigrate and differentiate in the aging thymus, or from immigrating pre-adipocytes, as suggested by the fact that they express the chemokine receptor CCR5 [101].

The redistribution of fat mass that occurs with aging has also esthetic consequences on the face and in the body. Facial aging has been associated with loss of soft tissue fullness in some areas such as periorbital, forehead, mandibular, perioral and parallel hypertrophy of fat in other areas such as submental, nasolabial and labiomental. These changes lead to a senile face and increased amount of wrinkles [102]. SAT mass loss has been shown to be responsible for sunken cheeks as well as thinning of epidermis and dermis over the hands, arms and legs [103].

Changes in pre-adipocytes

Several age-related changes in pre-adipocytes, also known as AT-derived stem cells, have been reported. These include the number, replicative potential and capacity to differentiate. Studies conducted in rats have shown that pre-adipocyte numbers increase or remain constant with aging in different AT depots, whereas replication and differentiation decline at different rates in different AT depots [104–106]. The decline in pre-adipocyte proliferation and differentiation, together with the decline in lipogenic capacity, may contribute to changes in AT distribution and function, including the slow turnover of fat cells, observed in elderly individuals. It may also contribute to increased systemic exposure to lipotoxic FFAs that induce and support inflammaging. Decreased differentiation of pre-adipocytes with aging has been associated with the decreased expression of the transcription factors involved in adipogenesis CCAAT/enhancer binding protein α, β, δ (C/EBP) and PPAR- γ [106], in part

due to the increased secretion of TNF- α in different AT depots. TNF- α inhibits early induction of both C/EBP proteins and PPAR- γ and induces the transcription factor T cell factor 4 that activates the anti-adipogenesis factor Wnt/ β -catenin [107]. Genes downstream of PPAR- γ (Ppargcla, aP2, carnitine palmitoyl transferase-1) regulate the pathways of FA handling and mitochondrial function [108].

Pre-adipocytes can acquire the secretory phenotype of activated macrophages, becoming phagocytic and expressing markers of macrophages such as F4/80, Mac-1, CD80, CD86, and CD45 [109], suggesting the existence of a link between the AT and the innate immune system. Conversion of preadipocytes into macrophages is exacerbated by aging in both animals [110] and humans [111], likely due to stress responses in the AT such as hypoxia and lipotoxicity.

Changes in adipocytes

Aging changes the profile of pro- and anti-inflammatory mediators secreted by the adipocytes. The VAT of old versus young mice is enriched in RNA for the pro-inflammatory cytokines IL-1 β , IL-6 and TNF- α and for COX-2 [112], clearly showing that obesity accelerates aging by inducing inflammaging [89]. Conversely, the expression of PPAR- γ , whose activation increases IS and enhances glucose metabolism [113] is decreased. Also, sphingolipid ceramide levels are higher in old versus young adipocytes, these high levels being responsible for ceramide-induced activation of NF- κ B and pro-inflammatory cytokine secretion, suggesting a role for ceramides in AT inflammation. Ceramides have already been proposed as molecules linking excess of lipids with pro-inflammatory cytokines and IR [114].

Aging also changes the amounts of circulating adipokines such as leptin and adiponectin. Leptin is a pro-inflammatory adipokine that regulates appetite, satiety and energy expenditure. Serum levels of leptin increase with age and have been associated with increased fat mass in the elderly [115]. Adiponectin is an anti-inflammatory adipokine that promotes adipogenesis and reduces AT inflammation maintaining insulin responsiveness and glucose metabolism [116]. Obesity decreases serum levels of adiponectin [117]. Aging, however, increases circulating adiponectin, as shown in individuals 95 years in which these levels were inversely correlated with BMI, waist circumference and amount of body fat [118]. The high levels of adiponectin in centenarians represents a possible compensatory response to maintain metabolic homeostasis [119].

Both adipocytes and immune cells in the mouse and human AT are responsible for the secretion of TNF- α [61,120]. AT TNF- α secretion increases with aging [45]. TNF- α released in the obese AT is a tonic regulator of lipolysis, and contributes to local and systemic inflammation and IR [121]. Paradoxically, and in apparent contrast with the above results, catecholamine-stimulated lipolysis in the lean AT decreases with age in mice [77] and humans [122], although catecholamine signaling in adipocytes is normal during aging [123]. The mechanism proposed is that AT macrophages regulate age-related reduction in adipocyte lipolysis by reducing the bioavailability of NE due to the upregulation of genes controlling catecholamine degradation in an NLRP3 inflammasome-dependent manner. Deletion of NLRP3 in aging restored catecholamine-induced lipolysis through

downregulation of growth differentiation factor-3 and monoamine oxidase-a that is known to degrade NE [77].

Changes in immune cell infiltration

Aging increases the infiltration of immune cells into the AT, the majority of which are inflammatory, responsible for the secretion of pro-inflammatory cytokines and chemokines, and for the release of glycerol and FFAs. FFAs that are not packaged into lipid droplets are present in blood at high concentrations, and become toxic (“Npotoxic”) within non-adipose tissues. Immune cells infiltrating the AT are localized around crown-like clusters and in perivascular spaces and include macrophages, T cells, B cells, NK cells, ILCs, neutrophils. The cellular composition of AT is dynamic and is regulated by acute and chronic stimuli that include diet, body weight, fasting. Under obesity conditions, neutrophils are the first cells recruited to the AT, followed by monocytes/macrophages and then by B, T, NK cells as shown in studies conducted in mice [124]. Only a few studies in mice, however, have investigated how aging affects the infiltration of immune cells, in particular macrophages, T and B cells. To our knowledge, there are no reports on the infiltration of the AT of aging mice by NK cells, ILCs, neutrophils. The function of the different immune cells infiltrating the AT of aging mice are shown in Table 1.

Aging induces qualitative changes in AT macrophages, with a decrease in resident M2 (antiinflammatory) and an increase in M1 (pro-inflammatory) macrophages [125]. The age-induced shift in the phenotypic profile of AT macrophages has been associated with decreased expression of PPAR- δ , known to lead to increased expression of chemokine/chemokine receptors leading to their recruitment to the AT.

Aging also induces a significant increase in the frequencies of AT T cells, including CD4+ (Th1/Th17) and CD8+ T cells that are inflammatory and secrete large amounts of pro-inflammatory cytokines [125], and of T regulatory (Treg) cells that are Foxp3+CD4+ and account for 50% of total CD4+T cells in the AT [126,125]. Treg in the AT of old mice are involved in the maintenance of tissue homeostasis, and are characterized by high levels of transcripts for PPAR- γ , Gata-3, CCR2, crucial for their adaptation to the lipophilic, hypoxic AT microenvironment [127]. They also express ST2, the receptor for IL-33, crucial for the accumulation and expansion of these cells in the AT [126,128]. A subset of T $\gamma\delta$, PLZF+, has recently been shown to induce the accumulation of Treg in the AT of old mice through IL-17A-driven IL-33 secretion [129].

We have identified molecular mechanisms through which the AT leads to impaired B cell function in aging mice. These include increased size of the AT, production of pro-inflammatory cytokines and chemokines by the adipocytes, increased inflammatory B cells and systemic inflammation [130]. The adipocytes promote migration of B cells to the VAT through secretion of pro-inflammatory chemokines. The adipocytes from the VAT of both young and old mice express RNA for the chemokines CXCL10, CCL2, CCL5, with higher levels found in old mice. The corresponding receptors are expressed by VAT B cells. When we analyzed B cells infiltrating the VAT of young and old mice, we found reduced frequencies of Follicular (FO) B cells in the spleen of old mice as compared to young mice and concomitant increased percentages of the pro-inflammatory (Age-associated B Cells,

ABCs) B cell subset as previously shown by different groups [131,132] as well as by us [133,134]. No effects on MZ were observed. Frequencies of FO B cells were reduced (and percentages of ABCs were increased) even more in VAT versus spleen, suggesting that obesity exacerbated age-associated defects in B cells. Numbers of cells showed similar differences. We also found that VAT B cells express higher pro-adipogenic and inflammatory markers, including NF- κ B, as compared to splenic B cells, and also secrete autoimmune antibodies (IgG2c), known to be pathogenic [124]. Moreover, in the presence of an adipocyte-conditioned medium FO B cells differentiated into ABCs, showing for the first time a direct effect of adipocytes on the generation of pro-inflammatory B cells.

Aging induces the expansion of a population of mouse AT-resident B cells that are highly inflammatory, and their expansion is dependent on the activation of the NLRP3 inflammasome, likely due to AT-associated metabolic and mitochondria dysfunction and increased production of mitochondrial ROS [135,136]. Inhibition of NLRP3 activation by blocking IL-1 signaling, or intra-AT removal of B cells with anti-CD20 antibodies, inhibits the NLRP3-dependent B cell accumulation and rescues the metabolic dysfunction of the aging AT [137]. These results demonstrate that the NLRP3 inflammasome may be effectively targeted to reduce AT inflammation and associated complications.

Accumulation of senescent cells in the AT during aging

Cellular senescence indicates the irreversible arrest of cell proliferation that is induced by a variety of stressors, such as DNA damage, telomere shortening, radiation, ROS and other reactive metabolites, mitogenic and metabolic stressors. Proliferative arrest is mediated by the inhibition of cell cycle progression through p16^{INK4} and/or the activation of cell cycle arrest through p53/p21. Once a cell becomes senescent, it shows changes in chromatin organization and gene expression, although it remains metabolically active [138,139]. Senescent cells accumulate in the body during aging and promote tissue degeneration and malignant transformation, mainly due to impaired immune surveillance and impaired cytotoxicity by NK cells, and lead to the development of age-associated diseases [140].

Senescent cells accumulate in the AT with aging in all mammalian species and secrete multiple factors that constitute the senescence-associated secretory phenotype (SASP) [28]. The SASP is responsible for the secretion of soluble pro-inflammatory factors (cytokines, chemokines, micro-RNAs), soluble receptors (TNF receptors), non-protein soluble factors (nitric oxide), growth factors (EGF, VEGF, NGF) and extracellular matrix (ECM) macromolecules (Fibronectin, Collagens, Laminin) [141]. Secretion of SASP markers leads to ROS production, cell death, tissue remodeling and infiltration of proinflammatory immune cells in tissues [142,143]. The age-dependent accumulation of senescent cells represents a favorable environment for the development of inflammatory-based age-associated diseases. It is not known how the SASP is acquired. It has been postulated that intrinsic (telomeric and non-telomeric DNA damage, oxidative stress, genomic and epigenomic damage) and extrinsic (chronic viral infections, gut dysbiosis, pollution and industrial toxicants) factors are involved [144]. Secretion of SASP products by adipose cells has been shown to inhibit adipogenesis, recruit immune cells and induce IR.

Pre-adipocyte differentiation is affected by immunosenescence as pre-adipocytes acquire several SASP markers with aging. It has recently been shown that human senescent pre-adipocytes secrete the anti-adipogenic factor activin A, a member of the transforming growth factor superfamily. The inhibition of activin A partially restores lipid accumulation and expression of key adipogenic markers in differentiating progenitors exposed to senescent cells [145]. Moreover, human senescent pre-adipocytes undergoing poor differentiation are restrained by increased activation of the SASP markers p53 and p16^{INK4}, and this phenotype is associated with reduced levels of the zinc finger protein ZNF521, involved in early steps of adipogenesis, leading to the hypertrophic expansion of adipose cells [146]. Human senescent preadipocytes also secrete several pro-inflammatory cytokines, with increased secretion being associated with increased p53 and DNA damage inducible transcript 4 (DDIT4), a marker of p53 activation [146]. Increased senescence of pre-adipocytes is also associated with reduced adipose cell replacement and consequent increased cell size with aging. It has been shown that the small GTPase, GTP-binding RAS-like 3 (DIRAS3), a negative regulator of adipogenesis, is key in inducing cellular senescence in human pre-adipocytes, leading to the secretion of several SASP markers including pro-inflammatory cytokines (IL-6, IL-8, IL-1 β , TNF- α) and chemokines (CXCR2) [147]. Senescent adipocyte progenitors from the AT of elderly individuals express reduced levels of adipogenic transcription factors PPAR- γ and C/EBP α and reduced adipogenic capacity of pre-adipocytes in culture [148,145].

One of the biomarkers of senescence is senescence-associated β -galactosidase (SA β -gal), the enzyme that catalyzes the hydrolysis of β -galactosides into monosaccharides. SA β -gal detected at pH 6.0 allows the identification of senescent cells in culture and in tissues. Increased SA β -gal activity, together with increased expression of cyclin-dependent kinase inhibitor-1 A (Cdkn1a) and of p53, and increased production of pro-inflammatory cytokines and chemokines, have been associated with the development of IR in diabetic mice [149]. Inhibition of p53 has been shown to increase IS and glucose tolerance. SA β -gal^H-pre-adipocytes significantly increase in the AT of super-obese individuals and these senescent cells and their SASP have been suggested to promote immune cell infiltration into the AT, leading to increased local and systemic inflammation [28]. In support of this hypothesis, it has been shown that the co-culture of 3T3-L1 pre-adipocytes with a macrophage cell line induces TNF- α secretion by the pre-adipocytes, suggesting the establishment of a loop between pre-adipocytes and macrophages leading to TNF- α secretion and to a vicious cycle that exacerbates AT inflammation [150].

The VAT of obese mice is enriched in T cells with characteristics of cellular senescence. A unique subset of CD4⁺ T cells has been identified. Like T cells from old mice, these cells have the CD44^{hi}CD62L^{lo} phenotype and also constitutively express PD-1 and CD153, an age-associated marker that identifies senescent T cells [151]. Upon T cell receptor stimulation, they secrete large amounts of osteopontin [152], a pro-inflammatory cytokine responsible for chronic VAT inflammation and establishment of IR and metabolic disease in obese T2DM patients [153]. They also express the senescence markers SA β -gal, δ -H2AX (marker of DNA damage following exposure to genotoxic stress) and Cdkn1a, and they induce VAT inflammation and IR upon adoptive transfer.

The VAT of old mice is also enriched in the pro-inflammatory ABCs, exhibiting characteristics of cellular senescence [130]. These B cells express high levels of pro-inflammatory cytokines and chemokines, as well as high levels of Hormone-Sensitive Lipase, the enzyme responsible for the hydrolysis of triglycerides and production of FFAs and glycerol [154,155]. ABCs express low levels of the anti-oxidant enzyme superoxide dismutase-1, which is anti-inflammatory and decreases ROS production and oxidative stress [156]. ABCs from the VAT of old mice secrete IgG2c antibodies which have been shown to be autoimmune and pathogenic [131,132].

Also in humans, the AT contributes to the increased production of autoimmune antibodies [61,124]. It has been shown that the serum of IR obese individuals contains autoantibodies specific for intracellular proteins, ubiquitously expressed in immune cells as well in tissues including, pancreas, liver, muscle or AT, suggesting the release of “self” antigens in insulin target tissues. These IgG autoantibodies are present in the serum of IR individuals at a significantly higher extent as compared to insulin sensitive individuals. This result was obtained using a protein array in which more than 9000 selected “self” antigens were probed with serum from IR and IS individuals, overweight to obese, age- and BMI-matched [124]. The majority of “self” antigens are intracellular proteins (Golgi and endoplasmic reticulum proteins, RNA polymerase, glutathione transferase, signaling proteins) with variable tissue expression. We have recently shown that the B cells that make adipocyte-specific IgG antibodies in the AT are the pro-inflammatory Double Negative (DN) B cells, also called late/exhausted memory or tissue-like memory B cells. DN B cells are similar to mouse ABCs. They represent the most pro-inflammatory B cell subset, shown to be increased in the blood of patients with autoimmune [157–159] and chronic infectious diseases [160–162], suggesting that these cells may expand in vivo in the presence of autoantigens or pathogen-derived antigens, in the context of a favorable inflammatory microenvironment, leading to the production of autoimmune or protective antibodies, respectively. DN B cells are also significantly increased in the blood of elderly [163,164] and obese [15] individuals. In the AT, DN frequencies are even higher and in some individuals reach 50% of the B cell pool [165]. DN B cells are transcriptionally and metabolically active and secrete several pro-inflammatory cytokines (TNF- α , IL-6), chemokines (IL-8), micro-RNAs (miRs) (miR-16, miR-155, miR-93), all of which are SASP components, including the senescence markers p16 and p21 [163]. DN B cells are therefore able to sustain and propagate systemic inflammation [163]. DN B cells from the AT have high metabolic requirements, they consume high amounts of glucose and they activate oxidative phosphorylation (OXPHOS), glycolysis and FFAs oxidation. The increased glucose uptake and the activation of the pathways of glucose metabolism (OXPHOS, glycolysis, FFAs oxidation) in AT DN cells is needed to support their function, i.e. the production of autoimmune antibodies. It is not known if DN B cells further increase in frequency in the AT of elderly individuals.

Strategies to target cell senescence in the AT

Although senescent cells are present in tissues in relatively small numbers, they have been associated with multiple age-associated conditions and diseases. Senescent cells are emerging as the cells to target and several therapeutic strategies of intervention have shown promising results in many age-associated diseases (cardiovascular disease, T2DM,

neurodegeneration, osteoporosis). Pharmacological compounds able to reduce the accumulation of senescent cells in the AT and/or to suppress the SASP (senolytics) have recently been identified and their function has been characterized. These compounds have been shown to promote pre-adipocyte differentiation, reduce immune cell infiltration in the AT, increase IS and health span, and alleviate metabolic dysfunction [145,166]. Senolytics are not able to prevent the generation of senescent cells but have shown therapeutic effects in chronologically old and progeroid mice [167], as well as in inflammatory diseases such as T2DM [168], osteoarthritis [169] and atherosclerosis [170].

The first senolytics identified were compounds designed to target anti-apoptotic pathways such as BCL-2 and BCL-X_L [171]. Subsequently, dasatinib, quercetin [172,167] and navitoclax (ABT263) [171] were also identified and characterized as drugs that transiently target these survival pathways to induce apoptosis preferentially in senescent cells. Unfortunately, the clinical application of these compounds for age-associated diseases are limited because of the toxicity of BCL-2 and BCL-X_L inhibitors.

Studies in obese mice have demonstrated that AT dysfunction may also be reduced by the activation of drug-inducible “suicide” genes driven by the p16^{INK4} promoter [172]. These interventions were shown to increase glucose tolerance, reduce IR and circulating pro-inflammatory factors, and promote adipogenesis. Elimination of senescent cells also reduced the number of AT macrophages that were highly correlated with p16^{INK4}-expressing senescent cells in the AT. The expression of the macrophage marker F4/80 significantly decreased in the AT after 3 months of treatment to remove senescent cells. In these experiments, pre-adipocytes, rather than endothelial cells, macrophages, or T cells, were shown to be the main cell type targeted. It was also shown that the use of neutralizing antibodies against the SASP chemokines MCP-1 and MIP-1 β significantly decreased immune cell infiltration in the AT and in turn macrophage burden in the AT and alleviate local inflammation.

Exercise may prevent accumulation of senescent cells and systemic metabolic dysfunction in the AT of mice fed high-fat diet [173]. Using transgenic mice that express EGFP in response to activation of the p16^{INK4} promoter, it was shown that high-fat diet induces deleterious changes in body weight and composition and reduces physical, cardiac, and metabolic health. This is due to the dramatic increase in several markers of the SASP, including p16^{INK4} and SA β -gal, in the AT. Exercise was able to prevent the accumulation of senescent cells and the expression of SASP markers as well as to almost abolish the negative effects of the high-fat diet on parameters of health.

With the increase in human lifespan and the aging population, the increased accumulation of senescent cells in aged tissues promotes inflammaging and leads to the development of age-associated diseases. Therefore, therapeutic strategies to selectively remove senescent cells and/or to control/suppress the SASP represent a promising approach to prevent the negative effects of senescence. This could be achieved by targeting SASP regulatory systems such as NF- κ B [174] and mTOR, the mammalian target of rapamycin [175]. This strategy is supported by the evidence that rapamycin, a specific mTOR inhibitor, decreases the secretion of pro-inflammatory cytokines in senescent cells [175,176], suggesting that mTOR

inhibitors may be promising drugs for the prevention of the deleterious effects of cellular senescence. Both the pharmacological inhibition of mTOR in senescent human pre-adipocytes, as well as weight reduction intervention, have been shown to be positively associated with the expression of the inhibitor of adipogenesis DIRAS3, and with increased proliferation of pre-adipocytes and increased differentiation of adipocytes [147]. In the HEK-293T cell line a mechanism through which mTOR controls the SASP involves the mitogen-activated protein kinase activated 2 (MAPKAPK2 or MK2) [175]. MK2 enhances inflammatory processes through the phosphorylation of several RNA-binding proteins involved in the degradation of the mRNA for proinflammatory cytokines and chemokines. Once phosphorylated, these proteins are unable to bind the mRNA and induce its degradation. As a consequence, inflammation is maintained. A similar mechanism may also be occurring in the AT, and MK2-deficient mice, even if fed a high-fat diet, show decreased AT inflammation and IR [177]. However, MK2 inhibitors have shown potential metabolic adverse effects, limiting their possibility to be used in human studies.

In conclusion, efforts to reduce AT accumulation of senescent cells, that represent a fundamental mechanism of aging and age-related disease, are increasing and therapies have already shown feasibility in mouse models, suggesting that the possibility to block, slow or reverse age-associated conditions is concrete and the final goal of improving healthspan closer.

Conclusions

The AT is the most affected tissue by the aging process, as shown by recent studies conducted in mice, suggesting its crucial role in the organism's adaptation to aging. The AT undergoes profound changes during aging, such as abundance, distribution and cellular composition. Senescent cells accumulate in the AT of aging mice and humans, and contribute to age-associated diseases. Several experimental findings have clearly shown that the removal of senescent cells delays the onset of age-associated diseases and extends healthy lifespan, suggesting that drugs that target senescent cells may be effective anti-aging drugs. Future work is needed to explore ways to selectively target senescent cells in tissues, including the AT, without losing the benefits that senescent cells provide, for example in the clearance of tumor cells.

Acknowledgements

Work supported by NIH R56 AG32576 (DF/BBB), R56 AG059719 (DF) and R01 AG023717 (BBB).

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Table 1.

Immune cells infiltrating the AT during aging

CELL TYPE	FUNCTION
M1 Macrophages	↑ secretion of pro-inflammatory cytokines (TNF- α , IL-6) ↑ secretion of pro-inflammatory chemokines
CD4+ Th1 cells	↑ secretion of pro-inflammatory cytokines (IFN- γ , TNF- α)
CD4+ Th17 cells	↑ secretion of pro-inflammatory cytokines (IL-17)
CD4+ Treg	Maintenance of tissue homeostasis
CD8+ T cells	↑ secretion of pro-inflammatory cytokines (IFN- γ) Regulation of insulin resistance
T $\gamma\delta$	↑ secretion of pro-inflammatory cytokines (IFN- γ , IL-17)
Age-associated B Cells	↑ secretion of autoimmune antibodies ↑ expression of inflammatory markers (NF- κ B)