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Molecular bases of adipose tissue aging

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Abstract

Aging impacts each and every living organism. In higher organisms, it is an asynchronous process with its onset and pace varying among tissue types as well as among different cell types within a tissue. Adipose tissue is the largest energy depot in the body and is an endocrine organ responsible for metabolic homeostasis. Adipose tissue aging is marked by fat redistribution, with increased visceral and reduced subcutaneous fat observed as we age. At molecular level, aging in adipose tissue is a multifaceted process driven by diverse mechanisms, involving dysregulated adipogenic pathways, impaired thermogenesis, reduced regeneration, onset of senescence, and emergence of inflammation. Dysregulated adipogenic pathways introduce metabolic dysfunction by compromising lipid metabolism, leading to complications such as insulin resistance and diabetes. In addition, beige and brown adipose tissue dysfunction further aggravates the scenario by impacting thermogenesis. Moreover, a decline in regenerative potential due to loss of function in APSCs limits adipogenesis. Onset of senescence within adipose tissue disrupts local tissue homeostasis by impairing cellular function and increasing metabolic stress. Chronic inflammation in adipose tissue extends its effects beyond local disruption, contributing to systemic metabolic imbalances. Here, we discuss our current understanding of molecular mechanisms driving adipose tissue aging, highlighting their implications in metabolic health. Interventions, such as, senolytics, pharmacological modulators, and adipose tissue-specific approaches offer promising avenues for mitigating aging-related dysfunction in adipose tissue. Identifying potential therapeutic targets and their clinical translation for preserving adipose function is crucial for mitigating the metabolic complications associated with aging.

Key words adipose tissue, aging, adipogenesis, thermogenesis, senescence, inflammation

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Introduction

Aging, defined as the progressive physiological deterioration occurring with the passage of time, represents a chronic yet natural phenomenon caused by the gradual loss of specific regenerative and protective mechanisms across most living organisms [1]. Adipose tissue is recognized as the body's largest energy reservoir that serves as a vital endocrine organ, playing a pivotal role in regulating numerous physiological processes, such as appetite control, glucose metabolism, insulin sensitivity, inflammation, and tissue repair, which are essential for maintaining overall health [2, 3]. Adipose tissue is functionally categorized into white adipose tissue (WAT) and brown adipose tissue (BAT). WAT primarily stores energy in lipid form, whereas BAT facilitates non-shivering thermogenesis, an energy-intensive process triggered by cold exposure. Additionally, beige fat derived from WAT exhibits structural and functional similarities to BAT. Anatomically, adipose tissue is further classified into subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) based on its location within the body [4]. Notably, fat mass tends to increase with age across individuals, with the exception of a decline observed in those who reach very advanced ages. In addition, this fat it redistributed during the process of aging [5].

At molecular level, aging in adipose tissue is a multifaceted process driven by diverse mechanisms, involving dysregulated adipogenic pathways, impaired thermogenesis, reduced regeneration, onset of senescence, and emergence of inflammation [6]. Morphological alterations in WAT appear to be age-dependent, as older individuals exhibit significantly larger white adipocytes compared to younger counterparts. This observation aligns with the presence of a prominent central lipid droplet and smaller, displaced nuclei in aged adipocytes [7]. Despite an overall increase in fat mass with aging, there is a progressive reduction in brown and beige fat stores over time, leading to poor thermogenesis [8]. The capacity for proliferation and differentiation in adipose progenitor and stem cells (APSCs) declines with age, becoming notably impaired in older adults [9, 10]. Cellular senescence contributes to adipose tissue dysfunction in several ways, including compromised adipogenesis, heightened inflammation, altered adipocytokine production, and insulin resistance [11, 12]. Aging cells frequently exhibit the senescence-associated secretory phenotype (SASP), characterized by the secretion of a combination of cytokines, chemokines, proteases, and growth factors. This phenomenon serves as a signal of aging to neighboring cells [11, 13]. During middle age, abnormal immune cell activation begins to emerge in response to endogenous and exogenous stressors, including hypoxia, fatty acids associated with excessive nutrient intake, cellular debris, and endoplasmic reticulum stress. These stressors can provoke varying levels of inflammation within adipose tissue [14]. Despite advances in our understanding of adipose tissue aging, targeting these mechanisms therapeutically is still in preliminary stages. This review delves into the molecular mechanisms underpinning adipose tissue aging, offering insights that are crucial for identifying potential pharmacological targets to enhance human health. These advancements may support efforts to combat aging and associated metabolic disorders.

Adipose tissue aging

The distribution of fat mass undergoes significant changes with aging, characterized by an increase in visceral fat and a reduction in subcutaneous fat, particularly in the lower body regions (**Figure 1**) [15]. These distinct fat depots influence metabolic processes differently; subcutaneous fat is generally considered beneficial for metabolism, whereas visceral fat is often implicated as detrimental to metabolic stability. Consequently, this shift in fat distribution significantly affects systemic aging, elevating the likelihood of metabolic disorders and conditions such as insulin resistance, diabetes, and cardiovascular diseases [5, 16]. Shorter telomere length observed in SAT compared to VAT represent a plausible mechanism behind age-related decline in subcutaneous fat [17]. Considering the critical role of SAT in maintaining systemic metabolism, it has been hypothesized that SAT deficiency may underlie metabolic dysfunction associated with aging. Apart from the redistribution of fat during aging, notable differences in fat distribution between males and females also emerge with age, often linked to varying disease risks between sexes. In premenopausal women, higher estrogen levels contribute to fat accumulation around the hips and thighs [18]. This hormonal influence explains why women in middle age are less susceptible to metabolic disorders compared to men. However, during menopause, a decline in estrogen levels leads to increased VAT storage, heightening the risk of developing metabolic syndrome [18]. Overall, fat redistribution is phenotypic marker of adipose and organismal aging, showing sex-specific pattern over the course of aging process.

Molecular mechanisms governing adipose tissue aging

At the molecular level, dysregulated adipogenic pathways, impaired thermogenesis, senescence, reduced regeneration and emergence of inflammation contribute to aging in adipose tissue (**Figure 2, Table 1**). Here, we provide a comprehensive overview of these molecular mechanisms and their association with aging in adipose tissue.

Dysregulated adipogenic pathways

Aging is associated with a decline in the expression of adipogenic factors and a diminished release of adipokines from WAT, leading to dysfunction within the adipose tissue [19, 20]. One of the most critical changes during WAT aging is the decline in the expression of key adipogenic regulators, including C/EBP-α and PPAR-γ [13]. The decline in PPAR-γ levels is closely associated with a reduction in the adipogenic potential of white adipocytes in SAT, contributing to the redistribution of fat tissue observed with aging [21]. Furthermore, hypermethylation of the PPAR-γ promoter region in WAT suppresses its expression, which may result in metabolic complications as individuals age [22]. WAT also plays a critical role in producing and secreting key adipokines, such as leptin and adiponectin, which are essential for regulating overall metabolic functions. Leptin facilitates communication between adipose tissue and the brain, directly influencing food intake and body weight regulation. However, with age, leptin resistance often develops, and the age-related decline in WAT functionality contributes to reduced leptin production and secretion into the bloodstream. This decline is commonly linked to metabolic disorders in older adults [23]. Unlike leptin, adiponectin is an anti-inflammatory adipokine that promotes insulin sensitivity and is involved in extending longevity by participating in multiple signaling pathways, including AMPK signaling [24]. Circulating levels of adiponectin inversely correlate with fat mass, and the age-associated reduction of this adipokine is linked to a shorter healthspan and lifespan, as well as the early onset of glucose intolerance and hyperlipidemia [25]. Importantly, the genes for leptin and adiponectin are subject to selective DNA methylation during aging, which may impair their synthesis in WAT, hinder adipogenesis, and increase susceptibility to metabolic disorders and aging processes [7]. Additionally, factors associated with aging, such as hypoxia and inflammation, along with lifestyle factors like high-fat diets and sedentary behavior, further influence the expression of these adipokines [26, 27]. Lastly, suppression of

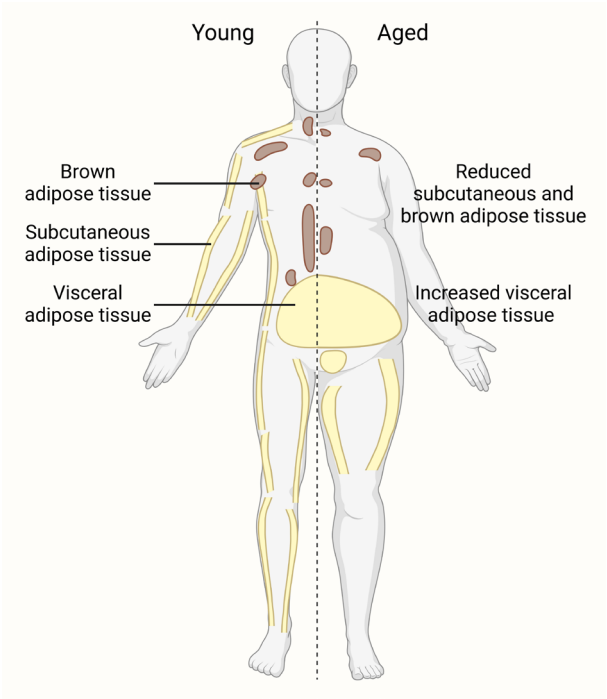

Figure 1. Adipose tissue aging. The distribution of fat mass undergoes significant changes with aging, characterized by reduced subcutaneous and brown fat, and an increased visceral fat, particularly in the lower body regions.

β3-adrenergic receptor (β3AR) signaling has been shown to impair the functionality of brown and beige fat, indirectly contributing to increased fat accumulation in visceral regions [28]. Overall, these findings underscore the role of dysregulated adipogenic pathways in adipose tissue aging.

Impaired thermogenesis

Formation of thermogenic beige adipocytes also decreases with age. While SIRT1 promotes the browning of WAT by deacetylating PPAR-γ, which activates the BAT-specific genetic program, the age-related reduction in SIRT1 levels may reverse this process, leading to the accumulation of visceral WAT [29]. On the other hand, an increase in the winged helix factor forkhead box protein (FOXA3) in aging adipose tissue suppresses browning by limiting cAMP-mediated transcriptional regulation of PGC1α [30]. In case of BAT, decrease in BAT-specific uncoupling protein 1 (UCP1) expression, the accumulation of mitochondrial DNA mutations, and a reduction in oxidative phosphorylation contribute to mitochondrial dysfunction, which is linked to impaired BAT function and thermogenesis during aging [31, 32]. Numerous molecular processes control the expression of UCP1 in BAT as individuals age. One example is the role of the receptor-interacting protein of 140 kDa (RIP140), which attracts DNA methyltransferases to UCP1 enhancer regions, thereby silencing UCP1 expression by promoting DNA methylation during aging [33]. In contrast, the demethylation of UCP1 enhancer regions supports its expression in brown adipose tissue [34]. A key transcription factor involved in brown adipose tissue development and thermogenesis is PR domain containing 16 (PRDM16). The age-related reduction in SIRT5 expression leads to a drop in α-ketoglutarate levels, which, in turn, promotes H3K9 methylation at the PRDM16 promoter, reducing browning and impairing cold tolerance [35]. Furthermore, TET-mediated DNA demethylation of CpG islands within the PRDM16 promoter plays a crucial role in brown adipogenesis, though the aging-related decrease in α-ketoglutarate availability makes PRDM16 activation more challenging over time [36]. Additionally, PRDM16 influences UCP1 expression by inducing PPAR-γ-mediated phosphorylation of JMJD1A, an H3K9 demethylase, which enhances UCP1 expression and thermogenesis [37]. Thermogenesis in both BAT and beige fat is stimulated by β-adrenergic receptors, which facilitate UCP1 expression. One pathway for this regulation involves the recruitment of ubiquitously transcribed tetratricopeptide repeat on chromosome X (UTX) to the UCP1 promoter, where it demethylates H3K27me3 marks, leading to improved UCP1 transcription through enhanced histone acetylation by CBP at the promoter [38]. Furthermore, β-adrenergic signaling has been shown to inhibit HDAC3, thereby promoting thermogenesis by increasing H3K27 acetylation at the UCP1 promoter [39]. However, some contradictory evidence suggests that UCP1 expression is almost absent in HDAC3-deficient brown adipose tissue, indicating that HDAC3 may act as a coactivator for estrogen-related receptor α (ERRα), thereby supporting UCP1 expression and thermogenic function [40]. Glucocorticoids, on the other hand, suppress adrenergic-stimulated UCP1 expression, potentially contributing to reduced BAT activity with age [41]. Additionally, the increased presence of proinflammatory cytokines during aging can inhibit the thermogenic capacity of BAT by downregulating UCP1 gene expression [42]. Lastly, the sympathetic nervous system plays a key role in regulating thermogenesis under cold conditions by activating BAT. Lower sympathetic activity in older individuals may be a factor in the reduced BAT activity seen in aging [43]. Furthermore, age-related reductions in the production of growth hormones, such as estrogen and androgen, may negatively impact BAT activity in older adults [44]. In contrast, inhibition of circulating Ghrelin hormone has been shown to enhance the thermogenic capacity of BAT in mouse models [45]. Notably, changes in thyroid hormone levels associated with aging may contribute to BAT dysfunction, leading to the conversion of BAT into white-like adipocytes and impairing thermogenesis [44]. Overall, these findings underscore the role of impaired thermogenesis in adipose tissue aging.

Reduced regeneration

Impaired proliferation and differentiation of adipose-derived precursor cells (APSCs), alterations in the levels of adipogenic factors, both pro- and anti-adipogenic, and an increase in cellular senescence may accumulate overtime [46, 47]. Research indicates that APSC proliferation begins to decline around the age of 30, with a more pronounced reduction observed by the age of 50. This impairment in APSC functionality leads to diminished adipose tissue plasticity, potentially contributing to the development of insulin resistance in older individuals [48]. Reduced regeneration in adipose tissue is also evident from the findings that APSCs derived from older donors demonstrate reduced osteogenic potential compared to those from younger individuals, making them less effective for applications in regenerative medicine [49]. Key transcription factors, such as C/EBPs and PPARγ, serve as primary regulators of adiposity. They control the differentiation of pre-adipocytes by activating adipogenic genes [50]. Regrettably, studies have shown that the expression of certain factors in adipose tissue declines with age, particularly in older individuals compared to their younger counterparts, which contributes to impaired adipogenesis as people age [51, 52]. Inadequate differentiation of pre-adipocytes is also closely associated with a reduction in lipid storage within mature adipocytes, thereby exposing other tissues to lipotoxic free fatty acids, which can lead to metabolic

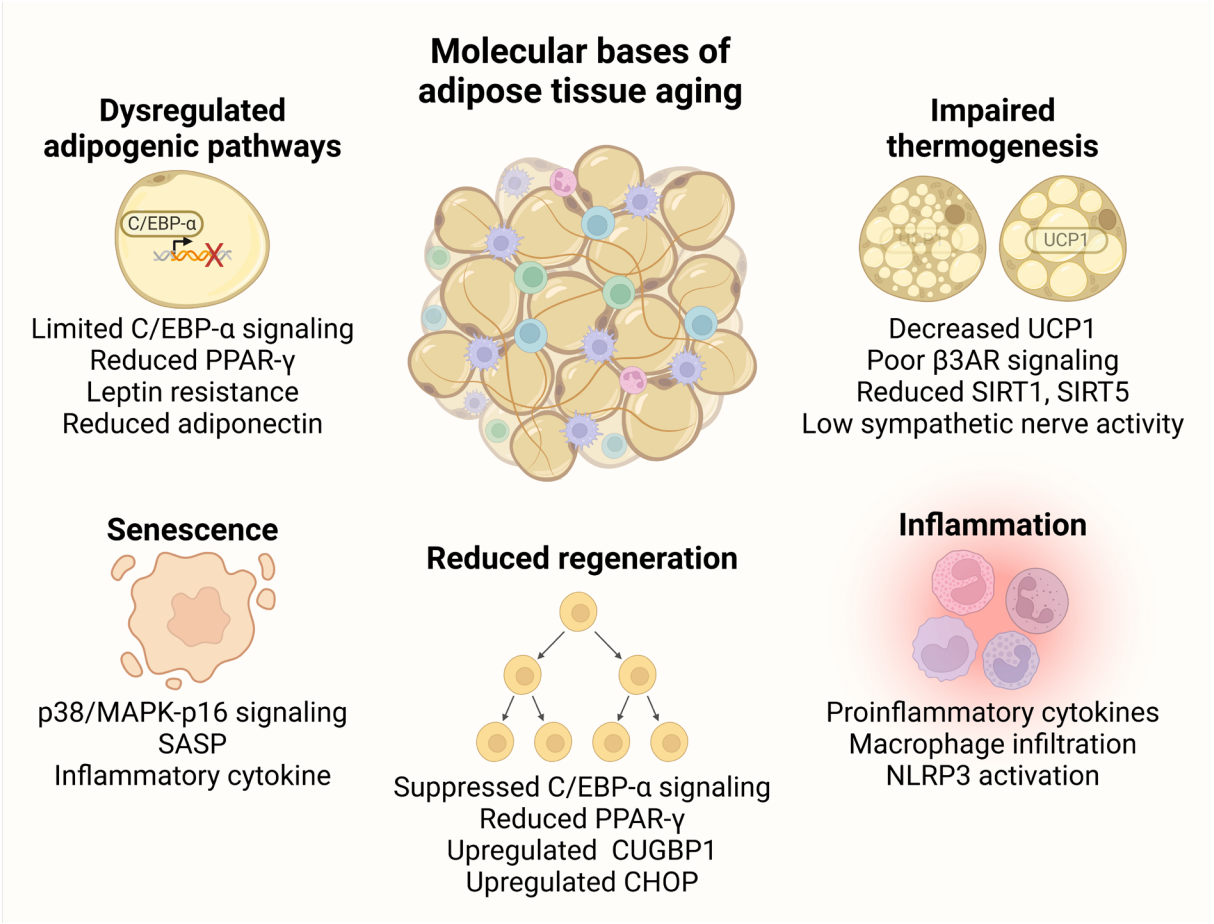

Figure 2. Molecular bases of adipose tissue aging. At molecular level, aging in adipose tissue is a multifaceted process driven by diverse mechanisms, involving dysregulated adipogenic pathways, impaired thermogenesis, reduced regeneration, onset of senescence, and emergence of inflammation.

syndrome in older individuals [53]. Moreover, an increase in DNA methylation has been observed in aging APSCs, which is linked to oxidative stress and mitochondrial dysfunction [54]. There is an age-associated increase in the CUG triplet repeat binding protein 1 (CUGBP1) in fat tissue and pre-adipocytes. CUGBP1 promotes the transcription of a truncated form of C/EBPβ, known as C/EBPβ liver-inhibitory protein (C/EBPβ-LIP), which competes with adipogenic factors and obstructs adipogenesis [55]. Furthermore, the expression of CCAT/enhancer binding protein homologous protein (CHOP), an anti-adipogenic factor, is notably higher in pre-adipocytes from older individuals compared to younger ones. CHOP-induced release of TNFα from aging pre-adipocytes disrupts the adipocyte differentiation process [56]. Thus, targeting CUGBP1 and CHOP in pre-adipocytes of older individuals may help enhance adipogenesis. The accumulation of senescent cells in the stem cell pool further hinders the differentiation potential of these cells [57]. The presence of senescent cells within the APSC population serves as a critical indicator of the overall adipogenic potential of these cells [21]. Overall, these findings underscore the role of declined regeneration capacity in adipose tissue aging.

Senescence

Cellular senescence, marked by the cessation of cell division, is a defining feature of aging across nearly all tissue types and contributes significantly to the functional decline of tissues [58]. Throughout the aging process, adipose tissue faces various internal and external stressors, including those from cellular replication, inflammation, and metabolic disturbances. These stresses contribute to the accumulation of senescent cells within the adipose tissue [59, 60]. In older individuals, both WAT and BAT exhibit hypertrophy, with enlarged adipocytes that store large lipid droplets, a condition often linked to tissue dysfunction, negatively impacting WAT's endocrine functionality and diminishing fatty acid β-oxidation [7]. These cells display the SASP, where they secrete a variety of molecules including cytokines, chemokines, proteases, miRNAs, and growth factors, which collectively act as signals of aging to neighboring cells [11, 13]. For example, senescent p16-positive adipocytes from mouse inguinal fat show elevated levels of the pro-inflammatory cytokine interleukin 6 (IL-6), which contributes to reduced insulin sensitivity in the adipose tissue. This also plays a role in the reduced stemness and adipogenic potential of aging APSCs, as senescent progenitors inhibit the adipogenesis of surrounding non-senescent progenitors via paracrine signaling. This is evidenced by the observation that the differentiation ability of APSCs declines markedly when cultured alongside senescent cells compared to non-senescent ones [13]. The buildup of senescent cells in adipose tissue also disrupts the tissue's ability to undergo beiging. However, inhibiting the senescence-related p38/MAPK-p16 signaling pathway has been shown to restore this capacity, improving insulin sensitivity in mouse models and elderly humans. Conversely, activating

Table 1. Molecular bases of adipose tissue aging.

Molecular bases	Mechanism	Impact on aging	Ref.
Dysregulated adipogenic pathways	Decline in PPAR-γ and C/EBP-α expression; DNA methylation of PPAR-γ promoter; Reduced adipokines (leptin, adiponectin)	Impaired adipogenesis; Fat redistribution (reduced SAT, increased VAT); Metabolic dysfunction; Insulin resistance	[7, 13, 19-28]
Impaired thermogenesis	Reduced UCP1 expression in BAT; Mitochondrial dysfunction; Decrease in SIRT1, SIRT5 and PRDM16 expression	Declined BAT and beige fat activity; Poor thermogenesis; Cold intolerance; Increased VAT storage	[29-45]
Reduced regeneration	Decline in APSC proliferation and differentiation; Accumulation of senescent cells; Altered expression of adipogenic factor	Reduced plasticity and regenerative potential; Lipotoxicity; Insulin resistance; Metabolic syndrome	[21, 46-57]
Senescence	Accumulation of senescent cells with SASP; IL-6 secretion; p38/MAPK-p16 axis activation; Altered beiging of WAT	Impaired adipogenesis and metabolic functions; Increased inflammation; Reduced insulin sensitivity	[7, 11, 13, 59-62]
Inflammation	M1 macrophage infiltration; NF-κB hyperactivation; Dysregulated cytokine production (TNF-α, IL-6)	Chronic inflammation; Impaired lipolysis; Diminished thermogenic and metabolic efficiency	[14, 64-77]

this same pathway in younger individuals leads to an increase in senescent cell accumulation within adipose tissue, thereby impairing the beiging process [61]. Additionally, miR-146a has been recognized as a key component of the SASP, released in VAT, and it fosters both senescence and inflammation. While miR-146a expression naturally increases during aging in animals, mice with a long lifespan, such as Ames dwarf mice, maintain youthful levels of this miRNA even at advanced ages, which is associated with prolonged health and longevity [62]. Overall, these findings underscore the role of senescence in adipose tissue aging.

Inflammation

Aging-related increase in inflammation within subcutaneous fat has been proposed as a key factor behind redistributed fat during aging. Adipose tissue is home to a variety of immune cells, including macrophages, lymphocytes, and eosinophils. Both internal and external stressors, such as hypoxia, excess fatty acids, byproducts of cell death, and endoplasmic reticulum stress, can activate these immune cells inappropriately, leading to varying degrees of inflammation within adipose tissue [14, 63]. Aging diminishes the differentiation and replication capabilities of adipocytes, triggering heightened inflammation through the release of certain pro-inflammatory molecules [64]. Macrophages residing in adipose tissue (ATMs) are the primary contributors to inflammation, and they are classified into two types: M1 (CD11c+, CD206-) and M2 (CD11c-, CD206+) macrophages. In young adipose tissue, M2-type ATMs predominate, releasing anti-inflammatory cytokines that mitigate excessive immune responses and collaborate with Th2 helper cells to promote tissue repair. However, as aging progresses, M1-type ATMs become more abundant, disrupting the homeostasis of adipose tissue [65]. M1-type ATMs typically cluster around dying adipocytes, forming crown-like structures, a hallmark of inflammation in adipose tissue [66]. As individuals age, there is a notable increase in the accumulation of M1 macrophages, which subsequently leads to a heightened release of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α within adipose tissue [67]. Interestingly, a mouse study reveals that while the total number of adipose tissue macrophages (ATMs) remains relatively stable with age, there is a significant shift in the balance between the pro-inflammatory M1 type ATMs and the anti-inflammatory M2 type ATMs, with the former increasing in proportion. This shift at the molecular level is linked to a decline in PPARγ expression in ATMs as a result of aging [65]. These age-associated alterations in adipose tissue-resident ATMs also have functional implications for the tissue. For example, aged ATMs are involved in promoting resistance to lipolysis in a manner dependent on the NLRP3 inflammasome. Mechanistically, NLRP3 activation leads to the upregulation of growth differentiation factor-3 (GDF3) and monoamine oxidase-A (MAOA), which collectively degrade norepinephrine, a key neuromodulator involved in lipolysis [68]. Additionally, the specific expression of V-set immunoglobulin-domain-containing 4 (VSIG4) in ATMs has been shown to correlate with aging and may serve as a potential biomarker for adipose tissue aging [14]. Beyond macrophages, other immune cells such as natural killer cells, neutrophils, eosinophils, mast cells, dendritic cells, and lymphocytes may also infiltrate adipose tissue and contribute to the establishment of low-grade inflammation during the aging process [69]. For instance, age-related increases in fat-resident regulatory T-cells have been linked to the induction of insulin resistance, and their depletion has been shown to restore insulin sensitivity [70]. Additionally, fat-resident B-cells that express high levels of TNF-α have been found to contribute to a diminished vaccine response, particularly to the influenza vaccine, in the elderly [71]. Age-related susceptibility to cold is partially attributed to a compromised ability of adipose tissue-specific Group 2 innate lymphoid cells (ILC2) to respond to pro-inflammatory stimuli and

adopt a senescent-like state, which is associated with dysregulated IL-33 expression [72]. Furthermore, eosinophils in adipose tissue play a crucial role in tissue homeostasis, but exhibit significant age-related changes in both distribution and function, primarily due to a reduction in IL-4 secretion in older individuals [73].

Aging triggers various immunological responses in adipose tissue, including the heightened release of pro-inflammatory cytokines. Specifically, adipose tissue in aged mice demonstrates hyperactive NF-kB signaling, a phenomenon that contrasts with the signaling observed in younger mice. This signaling activation correlates with an increase in inflammatory cytokines like IL-1, IL-6, TNF-α, COX2, and a reduction in the anti-inflammatory molecule PPARγ [74]. Additionally, the dysfunction of autophagy that accompanies aging, along with the accumulation of autophagy substrates such as LC3-II and p62, leads to endoplasmic reticulum stress. This stress is linked to elevated production of pro-inflammatory cytokines such as IL-6 and MCP1 in adipose tissue [75]. The endoplasmic reticulum stress marker CHOP further regulates TNF-α secretion from pre-adipocytes, hinders adipogenesis, and contributes to the age-related deterioration of adipose tissue function [56]. Furthermore, the reduced expression of SIRT1 in adipocytes with age promotes the infiltration of macrophages into adipose tissue, as well as their polarization into the M1 phenotype. This is due to the hyperacetylation-driven upregulation of a set of pro-inflammatory genes [76]. Mature adipocytes release the anti-inflammatory cytokine IL-10, which suppresses the production of pro-inflammatory factors such as TNF-α, IL-2, IL-3, and IL-6 within the adipose tissue. However, with aging and during pathologic aging conditions, the expression of IL-10 in VAT declines. This reduction in IL-10 expression is linked to age-related changes in DNA methylation patterns, as well as modifications to key histone marks, such as H3K4me and H3K9/14ac [77]. Overall, these findings underscore the role of inflammation in adipose tissue aging.

Advancements in targeting adipose tissue aging

Despite exponential growth in understanding the molecular mechanisms behind adipose tissue aging and its systemic consequences in recent years, targeting aging pathways in adipose tissue is still in preliminary stages. For instance, L-carnitine supplementation has been shown to aid in the removal of senescent cells from APSC. This effect occurs through a mechanism where L-carnitine enhances the expression of human telomerase reverse transcriptase (hTERT) by altering the methylation of its promoter, ultimately boosting telomerase activity [78]. Senolytics, a class of compounds specifically designed to target and eliminate senescent cells, are currently under intensive investigation for their potential anti-aging benefits. Among these, a combination of Dasatinib and Quercetin (D+Q) has demonstrated significant effectiveness in targeting and removing senescent cells that express p16 and p21, particularly within adipose tissues. This treatment has been shown to reduce the levels of circulating SASP factors such as IL-1α, IL-6, and matrix metalloproteinases (MMPs), thus alleviating age-related deterioration [79]. Senescent APSCs can inhibit the adipogenesis of adjacent, non-senescent APSCs by secreting activin A, which in turn hampers the lipogenic activity and induces glucose intolerance in the newly formed adipocytes. Therefore, inhibiting activin A production via blocking JAK-mediated signaling pathways has been shown to enhance the adipogenic potential of APSCs [13]. Fat grafting presents a promising therapeutic approach to counteract the diminished adipogenic capacity of APSCs in the elderly [80]. Researchers are actively exploring strategies to clinically modulate aging pathways circulating leptin and adiponectin levels as a means to combat obesity and age-related metabolic disorders. Although recombinant leptin therapy has been developed to address metabolic dysfunction and obesity, its efficacy remains limited, likely due to the onset of central leptin resistance, even in the presence of elevated circulating leptin levels [81]. Improving BAT function presents a promising approach to combat age-related thermogenic impairments. In this context, knocking out the regulator of G protein signaling 14 (RGS14) in mice has been shown to increase BAT mass, promoting healthy aging through improved cold tolerance and protection against obesity. Similar benefits can also be achieved through BAT transplantation [82]. Overall, developing targeted pharmacological strategies to eliminate senescent cells and rejuvenate APSCs present promising approaches for promoting healthy aging in adipose tissue.

Conclusion

As aging is an asynchronous process, the initiation and rate of aging can differ across various tissues and even among the distinct cell types within a given tissue. Aging adipose tissue plays a pivotal role in driving organismal aging, and is phenotypically marked by fat redistribution during aging. At molecular level, dysregulated adipogenic pathways, impaired thermogenesis, reduced regeneration, onset of senescence, and emergence of inflammation contribute to aging in adipose tissue. These age-related changes not only cause local disturbances in adipose tissue but also propagate physiological decline in distant tissues and organs through both paracrine and endocrine signaling pathways, thereby accelerating systemic aging. Regrettably, research on the aging of adipose tissue remains in its early stages, with much still left to discover and comprehend. The diverse anatomical distribution of adipose tissue across various regions, coupled with its heterogeneous nature, adds layers of complexity to studying it comprehensively. Additionally, the molecular mechanisms responsible for the earlier onset of aging in adipose tissue compared to other body parts, as well as the specific contributions of different cell types within adipose tissue to both local and systemic aging, remain largely unexplored. However, recent advancements in single-cell transcriptomics, three-dimensional cell models of adipose tissue, and adipose tissue-specific gene knockout animal models linked to aging [83, 84] offer promising avenues for a deeper understanding of adipose tissue's role in health, disease, and the aging process.

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Ethics approval

No applicable.

Data availability

The data will be available upon request.

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Authors' contribution

Aakeel Ahmad arouse the conception and devoted to writing of this review article. Manlio Fusciello cellected data for the table and drew figures for the manuscript.

Competing interests

The authors declare no competing interests.

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