



The role of adipose tissue aging in organismal aging

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Abstract

Aging, a complex process marked by the progressive decline in cellular and systemic functions, increases vulnerability to metabolic and age-associated disorders. Adipose tissue, being the largest energy reservoir in the body, plays a crucial role in regulating metabolism and maintaining energy balance. Adipose tissue exhibit early onset of age-associated dysfunctions, which ultimately contribute to organismal aging. For instance, the secretion of adipokines and batokines from adipose tissue becomes dysregulated with aging, not only facilitating metabolic disturbances but also hindering proper communication between different tissue and organs by disrupting both paracrine and endocrine signaling mechanisms. This dysregulation leads to the decline in physiological function in remote organs and tissues such as the liver, heart, and skeletal muscles, thus promoting the onset of age-related pathologies, such as obesity, insulin resistance, diabetes and cardiovascular conditions, and accelerating organismal aging. The interconnection between adipose tissue aging and obesity, with both sharing molecular and physiological characteristics, such as increased oxidative stress, senescent cell accumulation, and chronic inflammation, amplify systemic metabolic dysfunctions and predispose to plethora of diseases. Moreover, pro-inflammatory cytokines, excessively produced in aging adipose tissue, worsens immune system dysfunction and fosters chronic inflammation throughout the body, aiding in disease onset and progression. Hence, in-depth understanding of the role of adipose tissue aging in organismal aging is instrumental, targeting which by lifestyle modulation and therapeutic interventions, such as calorie restriction, and pharmacological agents like metformin and senolytics, offer promising strategies to delay organismal aging, enhance metabolic health, and extend lifespan.

Key words adipose aging, systemic aging, adipokines, batokines, inflammation, calorie restriction, senolytics

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Introduction

Aging, characterized by progressive decline in physiological function over time, leads to compromised cellular and organ function, reflecting the gradual breakdown of regenerative and protective processes in most living organisms [1]. Aging-related changes often increase susceptibility to major pathologies, including cancer, diabetes, cardiovascular diseases, autoimmune conditions, and neurodegenerative disorders, ultimately heightening mortality risk [2, 3]. Although it is a continuous process, beginning at birth and continuing throughout life, onset of aging varies across tissues, and the rate of aging differs in a tissue-specific manner over time. Furthermore, cells and/or cell types within a tissue also often exhibit varying aging patterns [4]. Adipose tissue, the body's largest energy reservoir and a key endocrine organ essential for maintaining metabolic balance [5], is among the first organ to undergo aging-related changes [6]. Adipose tissue plays a critical role in regulating various physiological functions, including appetite, glucose metabolism, insulin sensitivity, inflammation, and tissue repair [7, 8]. In addition, adipose tissue interacts with other organs by releasing endocrine factors called adipokines and batokines. Aging disrupts the regulation of these molecules, impairing the tissue's capacity to effectively manage nutrient excess, which increases the risk of obesity, a significant driver of accelerated aging [9]. Moreover, adipose tissue secretes inflammatory cytokines, and aging-related disturbances in its secretory profile contribute to chronic inflammation which is linked to a variety of age-associated disorders [10]. Gaining a deeper understanding of the underlying mechanisms of adipose tissue aging is crucial for achieving the broader objective of identifying pharmacological interventions to target adipose tissue aging, and enhance human health by counteracting organismal aging. Such advancements could help combat aging-related challenges and metabolic disorders, including obesity, insulin resistance, and diabetes. Here, we explore the role of adipose tissue aging in influencing organismal aging by discussing the impact of aging-related changes in adipokines and batokines secretion, the interplay between adipose tissue aging and obesity, and aging adipose tissue-driven inflammatory signaling on organismal aging. Furthermore, we present ongoing research efforts aimed at targeting adipose tissue therapeutically to promote healthy aging.

Adipose tissue aging: a trigger for organismal aging

Nearly all tissue types experience age-associated shifts in the expression of critical molecular pathways and biological processes, including extracellular matrix remodeling, the unfolded protein stress response, mitochondrial activity, immune cell infiltration, and inflammation. However, the timing and extent of these expression changes vary significantly between tissues, resulting in an asynchronous pattern of aging across different tissue types [11, 12]. Evidence from a comprehensive RNA-sequencing study, which analyzed 17 organs alongside plasma proteomics across 10 stages of the murine lifespan, reveals that aging-related changes in adipose tissue commence earlier than in other tissues. Given the central function of adipose tissue in maintaining energy homeostasis and its systemic interactions with other tissues and organs through its secreted factors, such as adipokines and batokines, this early onset may hasten the aging process throughout the organism by precipitating in physiological decline in other tissues [11]. Supporting this observation, a proteomic analysis targeting young and old murine tissues has highlighted that adipose tissue shows pronounced age-related disruptions in lipid metabolism, central carbon metabolism, electron transport chain activity, and inflammatory processes [12]. In addition, early

aging in adipose tissue is also evident from the observation that scapular brown adipose tissue which is present during infancy, is gradually lost overtime [6]. White adipose tissue, in particular, is a major source of pro-aging plasma proteins, which may drive accelerated aging throughout the body [11, 13]. These early abnormalities in adipose tissue metabolism are linked to reduced fat storage capacity in mature adipocytes. This impairment exposes other tissues to harmful free fatty acids, which can lead to complications such as fat accumulation in the liver, exacerbating non-alcoholic fatty liver disease during aging and contributing to the overall aging process [14, 15]. Hence, early onset of adipose tissue aging serves trigger for organismal aging (**Figure 1**).

Aging adipose tissue-driven dysregulated adipokines drive organismal aging

Adipose tissue communicates with other tissues by releasing signaling molecules, such as adipokines (leptin, adiponectin, resistin etc) into circulation, which modulate metabolic and functional activities of target organs [16]. For instance, both leptin and adiponectin are vital in preventing β -cell dysfunction by shielding insulin-producing cells from apoptosis induced by cytokines and fatty acids, thereby indirectly supporting glucose regulation [17]. Circulating leptin levels are proportional to body fat mass and are sensed by the hypothalamus to regulate appetite by increasing anorexigenic peptides and decreasing orexigenic peptides, thereby maintaining energy balance [18]. However, with aging, structural and functional decline in white adipose tissue disrupts leptin signaling, leading to hypothalamic dysfunction and leptin resistance. This condition persists even in the presence of high circulating leptin levels, contributing to obesity [16]. Leptin plays a significant role in liver dysfunction as elevated leptin levels in the bloodstream are linked to the development of hepatic steatosis and cirrhosis and contribute to hepatic insulin resistance [19, 20]. In contrast, adiponectin, known for its insulin-sensitizing properties, is considered protective against metabolic syndrome. Decreased levels of adiponectin are often observed in metabolic conditions like obesity, diabetes, hypertension, and atherosclerosis. However, elevated plasma adiponectin concentrations are associated with diseases such as Alzheimer's disease, chronic heart failure, and chronic kidney disease [21]. Unlike these adipokines, resistin, primarily secreted by inflammatory cells within adipose tissue, is involved in various physiological processes, including glucose and lipid metabolism, insulin resistance, inflammation, angiogenesis, cardiac dysfunction, and bone remodeling [22]. Resistin derived from adipose tissue hinders insulin signaling while reducing glucose uptake in adipocytes and muscle cells. Additionally, resistin activates NF- κ B signaling, promoting the expression of pro-inflammatory cytokines and chemokines, leading to vascular smooth muscle cell proliferation, endothelial damage, and accelerated cardiovascular disease onset [23]. Adipose tissue also produces numerous other adipokines, such as vaspin, omentin and apelin, dysregulations in which are also implicated in organ dysfunction and related diseases [16]. Hence, adipokines from aging adipose tissue contribute to organismal aging (**Figure 1**).

Aging adipose tissue-driven dysregulated batokines drive organismal aging

Similar to white adipose tissue, a decline in brown adipose tissue function adversely impacts the metabolism of other organs, particularly the liver, heart, and skeletal muscles, by disrupting the secretion of brown adipose tissue-specific regulatory factors, called batokines [24]. Brown adipose tissue mitigates insulin resistance and hepatic steatosis by releasing neuregulin 4

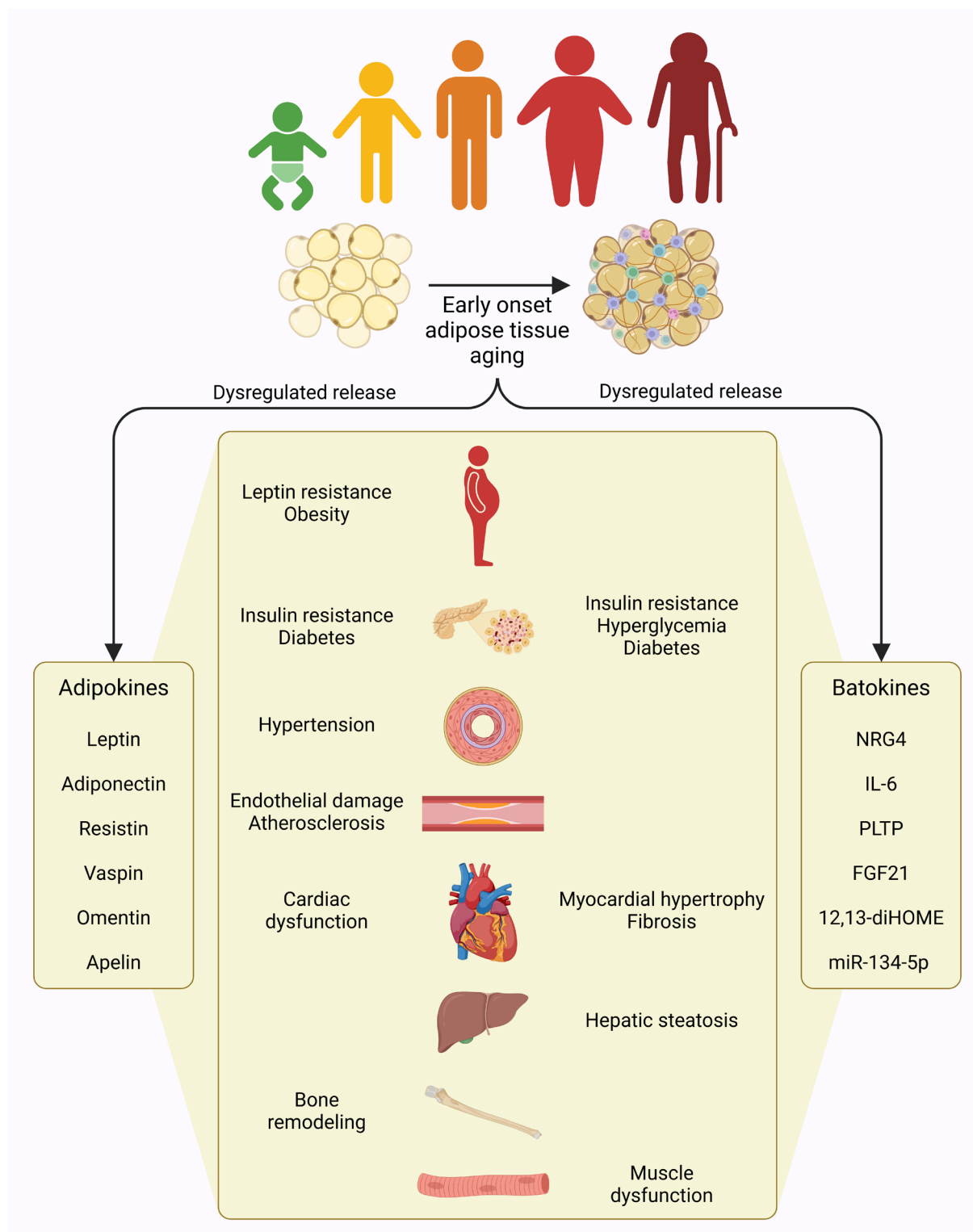


Figure 1. Adipose tissue aging. The distribution of fat mass undergoes significant changes with aging, characterized by reduced subcutaneous and brown fat, and an increased visceral fat, particularly in the lower body regions.

(NRG4), an endocrine factor, which limits hepatic lipogenesis via activation of the ErbB signaling pathway in liver cells [25]. Additionally, the secretory profile of brown adipose tissue may offer protection to hepatocytes, shielding them from apoptosis triggered by lipotoxicity. Interestingly, alcohol consumption has been associated with increased brown adipose tissue activity, and

specific batokines, including interleukin 6 (IL-6) and adiponectin, are implicated in mitigating liver injury and steatosis resulting from alcohol intake [26]. Additionally, the brown adipose tissue-specific upregulation of phospholipid transfer protein (PLTP) enhances bile acid production in the liver, improves insulin sensitivity, and supports glucose uptake and thermogenesis in

brown adipose tissue [27]. While the secretion of IL-6 driven by brown adipose tissue enhances the thermogenic capacity of adipose tissue by promoting browning within white adipose tissue, IL-6 released from brown adipose tissue through β 3AR signaling can exacerbate hyperglycemia by stimulating hepatic gluconeogenesis under acute physiological stress conditions [28]. During periods of hyperactivation, brown adipose tissue may become a major source of fibroblast growth factor 21 (FGF21) that regulates obesity, hyperglycemia, and insulin resistance through autocrine and paracrine signaling in liver and adipose tissue. In addition, FGF21 may provide liver protection against steatosis and non-alcoholic liver disease [29, 30]. Furthermore, brown adipose tissue-derived microRNA-99b (miR-99b) influences liver metabolism by targeting FGF21 expression in the liver, highlighting brown adipose tissue's crucial role in systemic FGF21 regulation [31]. The cardio-protective functions of brown adipose tissue are partly attributed to its release of factors such as FGF21 and 12,13-diHOME. Specifically, FGF21 from brown adipose tissue contributes to regulating cardiac remodeling and helps prevent hypertension [32], while 12,13-diHOME improves heart function by modulating calcium signaling pathways [33]. Epicardial adipose tissue, a brown adipose tissue-like adipose tissue located near the myocardium, release factors that promote myocardial hypertrophy and fibrosis by upregulating miR-134-5p expression in cardiomyocytes, which subsequently increases reactive oxygen species production [34]. Brown adipose tissue and muscle perform complementary functions in thermogenesis, with muscle contributing to shivering thermogenesis and brown adipose tissue facilitating non-shivering heat production. This interplay ensures a balance between energy expenditure and heat generation during physical activity [35]. Brown adipose tissue activation enhances skeletal muscle development and functionality by secreting lower levels of myostatin compared to inactive brown adipose tissue, which produces higher myostatin levels associated with diminished exercise performance [36]. Brown adipose tissue also contributes to energy balance by releasing 12,13-diHOME, a paracrine factor that promotes fatty acid uptake and β -oxidation in skeletal muscle. However, aging reduces brown adipose tissue's release of 12,13-diHOME, which in turn limits energy expenditure during cold exposure and exercise [37]. Hence, batokines from aging adipose tissue are critical determining factors in organismal aging (Figure 1).

Aging adipose tissue-obesity link drives organismal aging

Obesity is weight gain due to a prolonged imbalance between energy intake and expenditure, resulting in accumulation of visceral fat. A positive energy balance prompts hypertrophy in adipocytes to address the imbalance, resulting in generation of new adipocytes from precursor cells to compensate for the excess nutrition, ultimately leading to obesity [38, 39]. Obesity shares notable similarities with adipose tissue aging at the molecular, morphological, and physiological levels. For instance, obese adipose tissue is marked by a heightened presence of senescent cells and low-grade inflammation, accompanied by increased oxidative stress, as well as elevated levels of adipokines and cytokines in the bloodstream [40, 41]. In addition, both aging and obesity contribute to a decline in brown adipose tissue mass and functionality. Individuals who are older or obese show a significant reduction in brown adipose tissue-specific uncoupling protein 1 (UCP1) expression and decreased brown adipose tissue activity [42]. Furthermore, a significant reduction in telomere length in subcutaneous adipose tissue, as compared to visceral adipose tissue, is a key factor in the redistribution of fat that occurs with aging. Similarly, subcutaneous adipose tissue in obese individuals also shows shorter telomeres, which further links the obesity

to aging process in adipose tissue [43]. Moreover, excessive hyperplastic growth following hypertrophic saturation in the visceral white adipose tissue during obesity plays a key role in the age-related redistribution of adipose tissue [44]. Obesity is strongly associated with the onset of systemic insulin resistance, where the body fails to respond appropriately to circulating insulin in key tissues like the liver, muscle, and adipose tissue, resulting in disrupted glucose metabolism [45, 46]. Obesity is also associated with the onset of other age-related conditions, such as diabetes, fatty liver disease, cardiovascular issues, arthritis, and cancer [47, 48]. The molecular processes that connect obesity to these metabolic disorders are primarily characterized by an imbalance in adipokine secretion and the chronic elevation of oxidative stress, which worsens with age [49]. In this line, three primary hypotheses have been proposed to explain how obesity negatively affects various tissues and organs, leading to diseases associated with accelerated aging. 1) Obesity-associated chronic inflammation, coupled with the release of inflammatory mediators from adipose tissue during obesity, causes pathological alterations in distant organs. 2) Obesity-related inability of adipose tissue to properly store fat results in ectopic fat accumulation in organs such as the liver, muscles, and pancreas. 3) Obesity triggers dysfunctional secretion of endocrine factors, such as adipokines and hormones, from white adipose tissue, which leads to metabolic disruptions in various target tissues and organs [50]. Notably, obesity is now linked to shorter lifespans in both animal models and human populations, as well as an elevated mortality rate in obese individuals [51]. Hence, interconnection between adipose tissue aging and obesity plays a critical role in organismal aging (Figure 2).

Aging adipose tissue-driven insulin resistance drives organismal aging

Age-associated epigenetic modifications in adipose tissue are evident in genes linked to insulin signaling pathways, which subsequently contribute to the development of insulin resistance [52]. In addition, changes in the subcellular distribution of the insulin receptor and its substrate, IRS-1, as well as diminished insulin receptor activation in response to insulin happens with aging. Collectively, these alterations contribute to the development of insulin resistance in adipose tissue [53]. Cellular senescence, marked by increased adipocyte size, exacerbates metabolic dysfunction by activating p53 signaling pathways and releasing pro-inflammatory cytokines [54]. Notably, inhibiting p53 activity has been shown to improve insulin sensitivity in adipose tissue by mitigating senescence-like characteristics [55], as suppressing senescent adipose-derived stem/progenitor cells enhances their regenerative potential, adipogenic differentiation, and metabolic functions [56]. Elevated circulation of retinol-binding protein-4 (RBP4) in obese individuals impairs PI3K signaling in muscles and stimulates gluconeogenesis in the liver, ultimately promoting the development of insulin resistance [57]. While the hypertrophic enlargement of adipocytes with aging enhances lipid storage capacity, it simultaneously reduces the surface area-to-volume ratio, impairing nutrient transport and intracellular signaling in these cells. This aligns with findings that associate hypertrophic white adipose tissue with insulin resistance and diabetes in obese individuals [58]. Additionally, hypertrophic growth restricts vascular development and oxygen delivery while fostering inflammation [59]. Aging adipocytes may exhibit heightened oxygen consumption, which can initiate hypoxic signaling pathways that contribute to inflammation and insulin resistance [60]. Chronic hypoxia, accompanied by reduced vascularization and diminished expression of the angiogenic factor, vascular endothelial growth factor (VEGF), is a hallmark of aging adipose

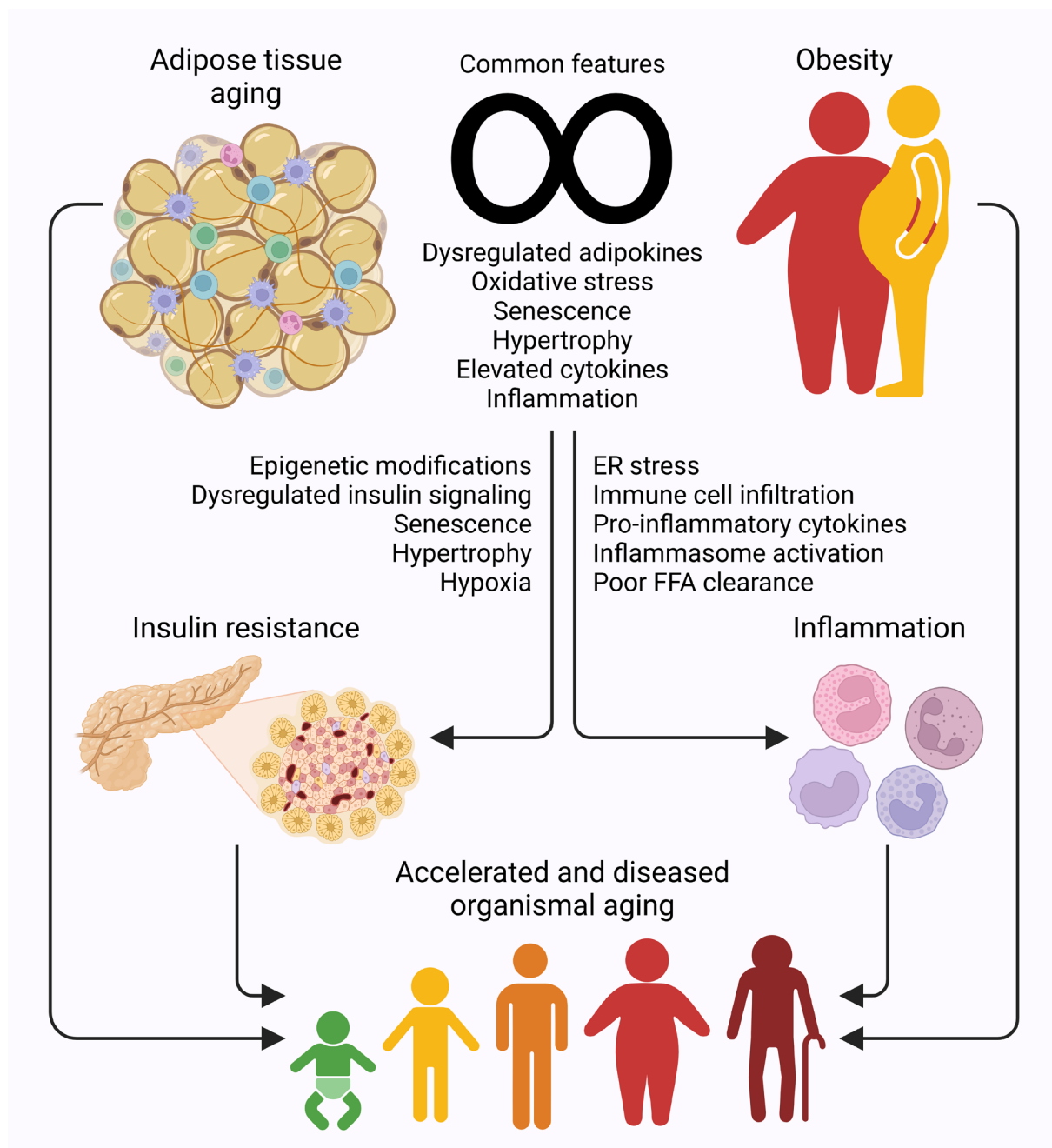


Figure 2. Aging adipose tissue-obesity link drives insulin resistance and inflammation in organismal aging. Adipose tissue shares molecular, morphological, and physiological similarities with obesity, with both contributing to onset of insulin resistance and systemic inflammation, dysregulations that lead to metabolic and pathological conditions, and result in accelerated and diseased organismal aging.

tissue and significantly contributes to its metabolic dysfunction [61]. Hypoxia-inducible factor-1 α (HIF-1 α) plays a crucial role in the age-associated decline of mitochondrial activity in adipocytes by regulating the expression of various transcripts essential for mitochondrial complex VI assembly [62]. The interplay between hypertrophic growth and hypoxia also influences extracellular matrix remodeling, primarily through increased collagen deposition, which can lead to tissue fibrosis [63]. Lower expression of periostin, a non-structural extracellular matrix component, in aged adipose tissue has been linked to reduced β -adrenergic responsiveness and impaired lipid utilization [64]. If left unchecked, insulin resistance can progress to metabolic syndrome, a cluster of conditions that may include diabetes, hypertension,

liver and kidney diseases, atherosclerosis, and cardiovascular problems [45]. Modulating hypoxia signaling pathways has shown promise in reducing adipocyte size in middle-aged mice [62] and mitigating insulin resistance in obese mice [65]. Hence, adipose tissue-driven insulin resistance fosters organismal aging (Figure 2).

Aging adipose tissue-driven inflammation drives organismal aging

Adipose tissue is susceptible to age-related inflammation, with significant immune cell activation becoming evident in white adipose tissue as early as middle age [11, 12]. Endoplasmic

reticulum stress, which becomes more pronounced with aging, disrupts the normal function of adipose tissue. Heightened ER stress responses in adipose tissue lead to an increased release of pro-inflammatory cytokines, thereby contributing to organismal aging [66]. The infiltration of immune cells and the presence of chronic inflammation within aging adipose tissue are key contributors to metabolic dysfunction [67]. Increased macrophage infiltration during aging is accompanied by heightened activation of the NLRP3 inflammasome, which stimulates the production of pro-inflammatory cytokines and worsens insulin resistance in adipose tissue [68]. NLRP3 inflammasome in aging adipose tissue collaborates with activated T cells within the microenvironment, promoting the release of pro-inflammatory cytokines, intensifying inflammation in both adipose tissue and the liver, ultimately leading to insulin resistance [68]. Excessive secretion of IL-1 family cytokines within adipose tissue disrupts insulin signaling pathways, thereby aggravating insulin resistance [69]. The interplay between IL-1 β and tumor necrosis factor- α (TNF- α) synergistically enhances IL-6 expression during states of obesity and insulin resistance by facilitating CREB binding to the IL-6 promoter [70]. Approximately 30% of circulating pro-inflammatory IL-6 during age-associated systemic inflammation is secreted by white adipose tissue [71]. This situation is further exacerbated by age-related redistribution of adipose tissue, as visceral adipose tissue produces higher levels of IL-6 compared to subcutaneous adipose tissue [72]. Hypertrophic adipocytes are characterized by increased production of pro-inflammatory mediators, including leptin, IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1), alongside a diminished secretion of anti-inflammatory agents such as adiponectin and IL-10 [16]. This imbalance contributes significantly to adipose tissue dysfunction. Additionally, elevated levels of circulating TNF- α further accelerate organismal aging by impairing hematopoietic stem cell functionality, driving these cells toward a myeloid lineage bias by inducing the expression of IL-27 receptor alpha (IL-27Ra) through the ERK-ETS1 signaling pathway in hematopoietic stem cells [73]. Furthermore, aging adipose tissue demonstrates reduced efficiency in clearing free fatty acids, resulting in an increased release of lipids and fatty acids into the bloodstream, which may further aggravate systemic inflammation. For instance, the presence of excessive non-esterified fatty acids in circulation has been shown to enhance CD11b expression in monocytes, facilitating their adhesion to endothelial cells and contributing to the development of atherosclerosis [74]. Notably, the process of immune cell infiltration, crucial for clearing senescent cells, is often delayed in other organs due to the age-associated accumulation of these cells in adipose tissue. This delay allows senescent cells to act as reservoirs of pro-inflammatory cytokines, which are released as part of the senescence-associated secretory phenotype, thereby sustaining systemic inflammation over time [75]. Interestingly, thermogenic activation of brown adipose tissue stimulates the release of C-X-C Motif Chemokine Ligand 4 (CXCL14) and growth differentiation factor-15 (GDF15), which may collectively reduce inflammation and metabolic dysfunction by modulating macrophage infiltration and suppressing the pro-inflammatory activity of macrophages [76, 77]. Hence, adipose tissue-driven inflammation accelerates organismal aging (Figure 2).

Targeting adipose tissue aging to counteract organismal aging

Calorie restriction prevents the accumulation of fat associated with aging and mitigates its harmful impact on nearby tissues and distant organs. On a molecular level, calorie restriction rejuvenates adipose tissue function by restoring the white adipose tissue-specific expression of PPAR- γ , a key regulator of adipogenesis and lipid metabolism, in older animals [78]. Sirtuins (SIRT6)

are essential enzymes that play a pivotal role in the epigenetic regulation of gene expression. Both calorie restriction and the SIRT1-mediated deacetylation of PPAR- γ have been independently linked to reduced fat accumulation through the induction of browning in white adipose tissue [79, 80]. SIRT6 requires specific cofactors, such as nicotinamide adenine dinucleotide (NAD⁺) and Zinc, to perform their functions. However, with advancing age, the expression of SIRT6 and the availability of NAD⁺ and Zn decline across the body, impairing their proper functioning [81, 82]. For instance, SIRT6 expression decreases in subcutaneous adipose tissue with age [83]. SIRT6 regulates adipose tissue homeostasis and fat accumulation by promoting PPAR- γ -driven lipogenesis and by indirectly inhibiting SIRT1 activity [84]. Certain dietary components, such as biotin, act as negative regulators of SIRT1 activity. Notably, calorie restriction lowers biotin levels, which helps limit fat accumulation and stimulates lipolysis by enhancing SIRT1 activity in adipose tissue [85]. Calorie restriction can also restore the healthy activity of SIRT6, either by directly increasing SIRT6 expression or indirectly by boosting NAD⁺ levels [79, 80]. Calorie restriction may also promote health and lifespan extension by triggering AMP-activated protein kinase signaling, which stimulates autophagy [86]. Furthermore, calorie restriction is considered to be five times more effective in extending lifespan than the surgical removal of visceral adipose tissue [87]. A recent study has revealed that adipose tissue retains an epigenetic memory of fat accumulation and obesity even after weight loss [88], reinforcing the need for sustained healthy lifestyles and dietary practices to prevent harmful fat accumulation and enhance healthspan during aging.

At the therapeutic front, senolytic therapies have garnered significant attention as potential anti-aging treatments. A senolytic cocktail, D+Q, has been shown to reduce physical dysfunction in older individuals by eliminating senescent cells and decreasing the pro-inflammatory senescence-associated secretory phenotype released from adipose tissue, thus enhancing survival in animal models during late life [89]. Furthermore, research demonstrates that a specific senolytic treatment, utilizing a targeted cocktail, effectively removes senescent cells expressing p16 and p21, particularly in adipose tissues. This intervention helps combat aging by reducing circulating levels of pro-inflammatory factors, including IL-1 α , IL-6, and MMPs, in subjects with diabetic kidney disease [90]. Metformin, an anti-diabetic and anti-aging drug, mimics the effects of calorie restriction and improves fatty acid metabolism by modulating adipogenic signaling, mitochondrial fatty acid oxidation, and extracellular matrix remodeling [91]. Moreover, metformin increases the expression of FGF21, which helps reduce the accumulation of white adipocytes and promotes browning in white adipose tissue [92]. Additionally, the PPAR- γ agonist, rosiglitazone, has been shown to prolong the lifespan of animals. This effect is attributed to the drug's ability to enhance insulin sensitivity, preserve adipose tissue integrity, and counteract mitochondrial dysfunction, inflammation, fibrosis, and tissue degeneration. It also helps mitigate symptoms related to anxiety and depression [93]. An increase in the expression of nuclear receptor-interaction protein 1 (NRIP1) is believed to be linked to the expansion of visceral adipose tissue with age. Targeting NRIP1 in animal models has been shown to extend lifespan by enhancing autophagy and reducing cellular senescence and inflammation in white adipose tissue [94]. Heterochronic parabiosis, which involves linking the circulatory systems of young and older animals, alleviates signs of cellular senescence in the visceral adipose tissue of the aged by downregulating the expression of p16 and p21, while also lowering levels of inflammatory molecules in circulation [95]. Despite these promising findings, the clinical application of above-discussed therapies remains obscure, highlighting the urgent need for more research to develop therapeutic strategies to target

adipose tissue aging in a hope to alleviate organismal aging.

Conclusion

Aging adipose tissue fosters organismal aging due to its multifaceted roles in metabolic regulation, energy storage, and endocrine signaling. Adipose tissue influences systemic health through its dynamic interactions with other tissues via adipokines, batokines, and inflammatory mediators. Aging-related structural and functional impairments in adipose tissue, such as altered adipokine profiles and chronic inflammation, disrupt metabolic equilibrium and contribute to the onset of age-associated disorders, like obesity, insulin resistance, diabetes, cardiovascular diseases. Notably, obesity exacerbates these effects by amplifying adipose tissue dysfunction, fostering a state of persistent oxidative stress and inflammation. Current therapeutic approaches, including calorie restriction, and pharmacological agents like metformin, and senolytic therapies, have shown promise in mitigating the detrimental effects of adipose tissue aging. These interventions target pathways, such as inflammation, oxidative stress, and insulin resistance, while promoting beneficial processes like autophagy and mitochondrial function. Moreover, strategies aimed at enhancing brown adipose tissue activity hold potential for improving systemic metabolism and energy expenditure. However, clinical translation of these preclinical findings related to targeting adipose tissue is far from reach. The heterogeneity of aging across different adipose depots and individual variability in response to therapies underscore the need for personalized approaches in managing adipose tissue aging. Future research on unraveling the precise molecular mechanisms driving adipose tissue aging and its impact on organismal aging, with an emphasis on developing targeted interventions, will help in addressing the metabolic challenges associated with aging, and pave the way for innovative strategies to enhance healthspan and lifespan in aging populations.

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Ethics approval

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Data availability

The data will be available upon request.

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Authors' contribution

AI Maskari Raya contributed to the design and writing of this review article. Nomier Yousra collected data and drew figures for the manuscript.

Competing interests

The authors declare no competing interests.

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