

Review Article

Sarcopenic obesity: prospects of mitochondrial transplantation to combat metabolic deterioration in aging

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ABSTRACT

Aging impairs adipose tissue function and contributes to metabolic disorders, such as obesity and insulin resistance. Chronic inflammation is mediated by cytokines, including IL-6, IL-1 β , and TNF- α , is a pivotal factor in aging that links mitochondrial dysfunction to activation of the NLRP3 inflammasome in aged adipose tissue. Moreover, distinct adipose tissue and adipose tissue depots exhibit complex molecular and cellular functions related to the deterioration of conventional metabolic regulation pathways. Unraveling these mechanisms is crucial for developing therapeutic strategies to enhance metabolic health and promote longevity. This review elucidates the current understanding of lipid metabolism, insulin resistance, cellular senescence, and mitochondrial dysfunction. Moreover, strategies to improve mitochondrial quality control in aging adipose tissue, such as mitochondrial transplantation, hold promise for addressing mitochondrial dysfunction. Finally, a novel therapeutic approach for mitochondrial transplantation is proposed using exosome cargo to sustain healthy metabolism and thermogenesis in aging populations. These findings lay the groundwork for innovative therapies and preventive strategies to mitigate the impact of obesity and aging.

Keywords: Adipose tissue, Aging, Inflammation, Insulin Resistance, Cellular Senescence, Mitochondrial transplantation

1. INTRODUCTION

Obesity and aging are significant global public health concerns [1]. The modern world provides us with sufficient nutrient sources and public welfare, yet may promise us a prolonged lifespan rather than a healthspan. Obesity occurs when energy intake outweighs energy expenditure, which is a particular issue for individuals >50 years of age. The obesity pandemic has been difficult to control since 1990. Indeed, it has been estimated that approximately one-half of the world's population will be obese by 2030 [2]. Obese individuals have increased susceptibility to a high content of visceral adipose tissue (VAT). Therefore, the viscerosomatic fat index (VSI), which is calculated as the VAT weight-to-total body weight, has been recently proposed to replace the body mass index (BMI) as a

comprehensive marker of obesity [3]. Like obesity, aging individuals often accumulate VAT, which in turn might worsen co-existing health conditions [4]. Aging is normally attributed to cellular and molecular damage, and is characterized by progressive body composition changes and decreased physiologic integrity [5]. Thus, a relatively new concept (sarcopenic obesity) has emerged by combining the characteristics of these two prevalent health issues. Sarcopenic obesity is defined as a gradual loss of muscle mass and functionality with an excess of adipose tissue (AT) [mainly VAT] in an aging population. A meta-analysis showed that 11% of individuals > 60 years of age struggle with sarcopenic obesity [6]. This finding further results in a series of more severe aging-related burdens, including type 2 diabetes, cancer, cardiovascular and neurodegenerative diseases, and all-cause mortality [7, 8].

AT represents a multifaceted and active organ system that encompasses a diverse array of cellular components, such as adipocytes, immune cells, endothelial cells, blood cells, all of which collectively have a crucial role in sustaining metabolic homeostasis. Consensus has been achieved on the role of AT in inflammaging and metaflammation in sarcopenic obesity. Inflammaging occurs in age-related diseases (e.g., sarcopenic obesity and cerebral small vessel diseases) resulting from the long-term stimulation of the immune system due to various cellular and molecular mechanisms, such as metaflammation, cellular senescence, and mitochondrial dysfunction. Under such conditions, resident immune cells are activated and immune cell infiltration is increased in AT, which triggers activation of the nucleotide-binding oligomerization domain-like receptor (NLR) family pyrin domain containing 3 (NLRP3) inflammasome and release of bioactive peptides and proteins. These adipokines and adipocytokines are secreted by white adipose tissue (WAT) and include adiponectin, leptin, and interleukins, as well as batokines that are secreted by brown adipose tissue (BAT) [9]. In addition, AT energy expenditure, lipid regulation, inflammatory responses, and mitochondrial function jointly affect insulin levels in obese-aged models [10]. This phenomenon is termed metaflammation and refers to nutritional imbalance-induced inflammaging, which might exacerbate the innate redox state and inflammatory status and lead to insulin resistance in insulin-sensitive tissues, including fat and muscle [11]. Hence, inflammaging and metaflammation are central to sarcopenic obesity [12, 13]. AT is classified by type (WAT, BAT, and beige adipose tissue) or anatomic location (subcutaneous adipose tissue [SAT] and visceral adipose tissue [VAT]). Generally, WAT and VAT accumulation are detrimental to inflammaging, whereas BAT and SAT are protective to danger signals. Plasticity is one of the most distinguished AT characteristics. AT plasticity helps AT sense and adapt to the physiologic and pathogenic environment within the body [14]. Aging disturbs AT plasticity by altering the size and distribution of AT, affecting adipogenesis and adipokine secretion, and increasing lipotoxicity. These disturbances may contribute to pathologic progression, including alterations in fat depot location, reduction in brown and beige fat, accumulation of senescent cells (adipose-derived stem cells [ADSCs]), and dysregulation of immune cells [10].

According to Mitchell's chemiosmotic theory, substrate oxidation metabolism activated by the mitochondrial respiration chain facilitates mitochondrial inner membrane carrier protein-uncoupling protein 1 (UCP1) to allow proton leak and dissipation of heat in mammalian cells, indicating the essential role of mitochondria. However, dysregulation of AT function in aging is intimately related to a poor-functioning mitochondrial pool [15]. Mitochondrial functions are crucial for preserving the ability of adipose stem cells to differentiate into Schwann cell-like, adipocytes, osteoblasts,

chondrocytes [16, 17]. Mitochondrial function, or more precisely mitochondrial metabolism, in AT declines with age. Impaired mitochondrial metabolism is usually accompanied by dysregulated inflammatory responses, oxidative stress generation, and fatty acid and energy metabolism, ultimately prompting metabolic disorders [18]. Mitochondria have the potential to activate adipose tissue macrophages (ATMs), which elicit autocrine or paracrine inflammaging [19]. A novel therapeutic approach has been proposed to treat age-dependent metabolic disorders, such as metabolic syndrome, as obesity with mitochondria transplantation (MT), which ultimately leads to metabolic reprogramming.

The focus of this review is AT dysfunction in the progression of sarcopenic obesity under conditions of lipid metabolism, fatty acid metabolism, inflammation, cellular senescence, and mitochondrial dysfunction. In addition, a novel therapeutic approach is advanced involving MT with exosome cargo to accelerate mitochondrial function and thermogenesis, and reduce oxidative stress by targeting dysfunctional AT in this populations for a healthy life with endurance and in hope of providing insights into discovering new relevant drugs.

2. ADIPOSE TISSUE FUNCTION IN METABOLISM

AT is a metabolically active endocrine organ that controls whole-body energy, lipid levels, and glucose homeostasis [20, 21]. Energy homeostasis in the host is delicately balanced by energy intake and consumption, which involves an interaction between the brain and peripheral tissues. Those tissues transmit information regarding real-time energy storage levels to the hypothalamus [22]. Among these peripheral tissues, AT functions as an energy reservoir and the melanocortin-4 receptor in the hypothalamus links AT to hypothalamic neurons in metabolic syndrome [23]. This finding suggests the active involvement of neuron communication in AT metabolism. The sympathetic nervous system (SNS) is considered to be a pivotal element. Beyond a primary role in energy storage and adaptive heat generation, AT acts as a central coordinator of insulin action. Insulin facilitates glucose transport into cells to enable the synthesis of fatty acids and lipoproteins and suppress adipose triglyceride lipase (ATGL)-dependent lipolysis to provide energy for the host. AT can mediate insulin sensitivity via the endocrine secretion of adipokines, especially adiponectin, and ectopic fat deposition prevention in insulin-sensitive tissues, such as the liver and skeletal muscles [24].

WAT constitutes the majority of AT mass, accounting for approximately 95% of the total mass. WAT contains large adipocytes filled with single lipid droplets. Therefore, WAT is especially predominant in storing and releasing lipids. These lipids are stored as triglycerides (TGs) by forming a single lipid droplet in mature WAT or multiple lipid droplets in BAT and most other cells, which acts as a burning furnace for body energy [20, 25]. The large TG-filled central vacuole in adipocytes

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is to take charge of uptake, store, and turn over TGs into free fatty acids (FFAs) with the help of lipases in lysosomes, such as hormone-sensitive lipase (HSL), ATGL, and HSL and ATGL co-activators [26]. Because WAT has fewer mitochondria, WAT has limited ability in generating heat (energy). However, through browning, a special process that turns white (pre)adipocytes into beige cells with increased UCP1 levels, special “WAT” is prone to facilitate energy expenditure [27]. Beige adipocytes refer to a subset of cells within WAT that have the ability to differentiate into brown adipocytes. Browning could be triggered by the sympathetic nervous system (SNS)-controlled “fight-or-flight” response, which is affected by cold exposure (Figure 1) [28]. Intriguingly, WAT-generated TG-rich lipoproteins and FFAs promote hepatic carnitilation so that the production of acylcarnitines serves as a fuel source for BAT thermogenesis, which demonstrates a mechanistic link between WAT and BAT [29].

BAT comprises < 2% of AT mass in adults, albeit with abundant mitochondria expressing UCP1, and is largely in charge of heat (energy) mobilization [30]. BAT activity is regulated through UCP1, which uncouples respiration from TG-derived ATP synthesis to generate non-shivering thermogenesis (especially β -adrenergic receptor [β -AR] signaling) or through a UCP1-independent mechanism [31–33]. β -ARs act as stimuli in activation of the adipocyte

lipolytic cascade through crosstalking with G protein in adipocytes [34], then proton leak respiration increases UCP1, which is dependent on energy expenditure. β -ARs mainly consist of three distinct subtypes, including β 1-AR, β 2-AR, and β 3-AR. BAT thermogenesis is driven by β -AR in humans and rodents [35]. In addition, stimulation of β -ARs in brown adipocytes induces UCP1 expression by enhancing inner mitochondrial membrane (IMM) conductance [36, 37]. Beige adipocytes not only express UCP1 but have also been shown to use UCP1-independent thermogenic pathways, including futile creatine and Ca^{2+} cycling, that are especially activated when exposed to a cold and oil-rich (high fat or calorie) environment [38]. Additionally, UCP1 often interplays with peroxisome proliferator-activated receptor (PPAR)- γ coactivator-1 α (PGC-1 α), fibroblast growth factor 21 (FGF21), and innate immunity during AT metabolism [39, 40]. The correlation between UCP1 and mitochondria function is comprehensively reviewed in Section 6. Enhanced thermogenic AT activity confers protection against metabolic dysfunction and serves as a crucial mechanism for maintaining metabolic health.

Lastly, adipokines (leptin and adiponectin) are important adiposity signals acting on the neurons in the arcuate nucleus of the hypothalamus to regulate whole-body energy homeostasis [41]. Leptin exhibits a strong positive correlation with AT mass and is modulated by

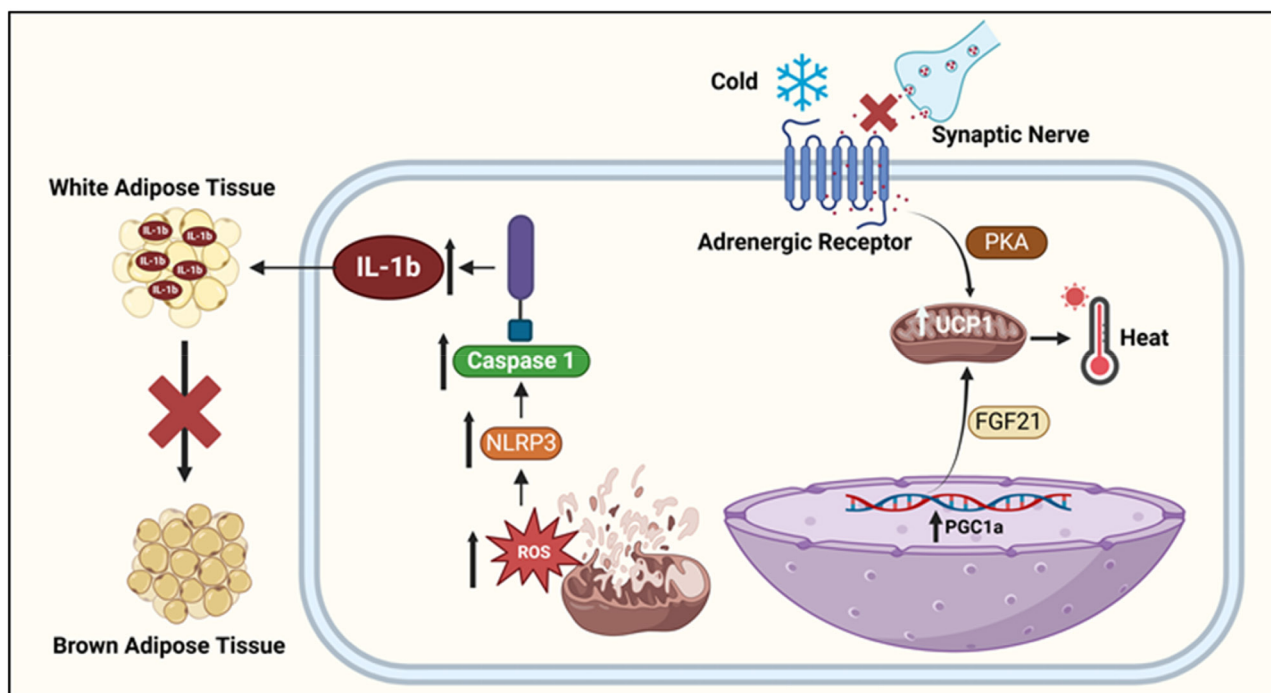


Figure 1 | Thermogenesis in BAT in the context of aging.

Mitochondrial dysfunction induces ROS and activates NLRP3/caspase-1/IL-1b, resulting in impaired browning adipose tissue. In addition, cold triggered β -adrenergic activity increases UCP1 expression in mitochondria, producing BAT thermogenesis via factors, including PKA and FGF21. Created in BioRender. Hdinhg, D. (2025). <https://BioRender.com/gwcqwci>.

dietary intake. Leptin exerts anorexigenic effects while simultaneously inducing energy expenditure. However, adiponectin acts on adiponectin receptors 1,2 to improve energy metabolism through the AMP-activated phosphate kinase (AMPK) signaling pathway [42]. In addition, adipokines, such as $\text{TNF}\alpha$, IL-6, and resistin, may lead to low-grade inflammation and insulin resistance stimulated by nutritional factors, including glucose and lipids [43].

Therefore, the intricate regulatory networks controlling fuel storage and oxidation processes in WAT and thermogenic adipocytes (brown and beige), secreted cytokines, and other substances (FGF21 and adiponectin) are fundamental in the regulation of systemic metabolic homeostasis.

3. ADIPOSE TISSUE DYSFUNCTION AND METABOLIC AGING

AT function undergoes significant changes in metabolic aging, as evidenced by including the deficiency in browning (especially the activity of UCP1), dysregulation in lipid metabolism (such as a slowing of muscle protein and fibre synthesis and an accumulation of hepatic cholesterol production) [44], impairment of organic cation transporter 3-mediated catecholamine-based insulin sensitivity [45], declined responsiveness to leptin and leptin cognate receptors and the leptin-to-adiponectin ratio [46, 47], and expansion of the aging-dependent regulatory cell (ARC) population in SAT [48].

Most BAT loses metabolic ability of energy dissipation in humans at 60 years of age, which puts AT thermogenesis in a precarious situation due to the potential inactivation of UCP1 [49]. UCP-1-dependent AT energy expenditure depends on β -AR signaling, whereas the aging process promotes diminished β -AR activity, resulting in browning defects due to impaired lipolytic profiles and reduced AT thermogenesis (Figure 1) [50]. Notably, β 3-AR activation is crucial for plasma FFA uptake and utilization, SAT ability, and laying the foundation for poor glucose handling [51, 52]. Improved lipid metabolism, which is characterized by an increased circulating adiponectin level, altered fat depots, and decreased fat mass, was reported in aged mice after a direct sustained stimulation on β 3-AR through lipid turnover and *de novo* lipogenesis [53]. However, β 3-AR silencing compromises mitochondrial mass Foxhead P1 (Foxp-1), a transcriptional factor consistently overexpressed in adipocytes, resulting in adipocyte differentiation, adaptive thermogenesis impairment, and diet-induced metabolic syndrome [54]. Moreover, β 3-AR-mediated histone modification substantially influences H3K18cr levels and targets on the enhancer and promoter sites of PGC-1 α /UCP1, resulting in varied beige adipocyte energy expenditure in the context of obesity-associated complications [55]. In addition to facilitating fatty acid oxidative metabolism in the obesity-related aging process, PGC-1 α promotes UCP1-dependent browning [56].

However, adipocyte-specific PGC-1 α deficiency in BAT blunts the beneficial metabolic effects and aggravates age-associated adiposity [57, 58].

Cold exposure might not be inductive to the changed transcriptome profiles of thermogenic genes in aged BAT [59]. Moreover, SNS activity in response to cold environment decreases with advancing age, ultimately driving delayed responsiveness of β -ARs (Figure 1) [60]. Current studies have identified direct effectors linking SNS-triggered catecholamine signaling to increased UCP1 in response to acute cold exposure [61]. This action is potentially due to activation of protein kinase A [PKA] (Figure 1). Specifically, cold-induced AIDA (a direct substrate of PKA)-dependent thermogenesis potentially establishes a direct mechanistic link between sympathetic input and UCP1-mediated adaptive thermogenesis via regulation of lipolysis and oxidative stress production [62]. Moreover, the effect of cold-induced SNS activation on UCP1 is gender- and location-based [63]. Thus, it is essential to more thoroughly investigate how aging interacts with SNS-dependent UCP1 in AT using the above different models.

Impaired browning may significantly contribute to sarcopenic obesity and can be stimulated by FGF21 expression, a peptide hormone [64]. FGF21, which is primarily synthesized and released by the liver, is also expressed in BAT and subcutaneous white adipose tissue (sWAT) following specific stimuli, such as cold exposure or adrenergic activation. In murine models, FGF21 triggers a PGC-1 α -mediated signaling cascade that upregulates UCP1 expression and activates thermogenic programs, with sWAT showing greater responsiveness (Figure 1). During age-related metabolic decline, an elevation of FGF21 was shown to be accompanied by accelerated browning of sWAT by dietary change and a promise to extend life span [65]. It has also been shown that leptin has a significant role in counteracting starvation-induced increases in circulating FGF21 levels, although endogenous FGF21 expression and browning markers in eWAT are markedly reduced. Mechanistically, the PPAR- β/δ pathway is involved in the upregulation of FGF21 expression induced by leptin, leading to an alteration in visceral fat mass and browning capacity [66]. However, a biased understanding of FGF21 was proposed by a biomarker study involving healthy centenarians; specifically, 'the lower the expression of FGF21, the healthier the aging process' [67]. The increased level of Parkin is correlated with insufficient energy expenditure in the course of aging. Parkin inactivation downregulates the FGF21 concentration and restores the age-dependent decline in WAT browning and leptin excess. Hence, a so-called "FGF21 resistance" situation in aging emerges, which remains understudied.

When longer able to sustain its function as an energy "sink" through continued growth, increased fat accumulates and is stored in the central region of the body by deteriorating the utilization of FAs, lipid, and metabolic elasticity in AT [68-70]. Lipids accumulate in AT with

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increased lipolysis (hydrolysis of TGs) and decreased FA β -oxidation, which mainly takes place in BAT to produce heat and leads to uncontrolled circulating FFA levels by regulation of PPAR-associated signaling pathways [71, 72]. Adipokines supplementation ameliorates age-dependent muscle sarcopenia, as evidenced by fat mass re-distribution [73]. Integrative studies indicate that fatty acid metabolism is mediated by but not limited to β -AR and adipokine (especially leptin) signaling and is also involved in indirect communication between SNS and BAT thermogenic programs during aging [74]. For example, Janus kinase (JAK) is essential for maintaining leptin functionality. One JAK2 binding protein (Sh2b1) could recover obese-aged-associated SNS degeneration in AT [75].

Additionally, age-related adiposity with a marked increase in AT, liver, and skeletal muscle fat causes shrinkage of the pancreatic β -cells mass. Pancreatic β -cells increase insulin production as a compensatory mechanism, ultimately leading to insulin resistance [76]. Mechanistically, this fat re-distribution encourages ARCs to inhibit the adipogenic potential and proliferation of adipose progenitor cells by expanding AT size to store excess nutrients and lipids, as well as Glut4 translocation, resulting in insulin resistance in aging [77-81]. In addition, there are two major models indicating the causal link between energy expenditure, fat storage in AT, and insulin levels; one model is the conventional model and the other model is the “carbohydrate-insulin model” in disease models. The recognized “carbohydrate-insulin model” suggests that increased adiposity induces dysregulated glucose metabolism and further intervenes with energy balance in AT [82].

The initiation of β -AR signaling is also essential because β -ARs couple to Gs subunits of heterotrimeric G proteins and activate adenylylcyclase to generate cAMPs, which significantly decreases fat mass, mediates catecholamine-induced energy expenditure, and improves insulin sensitivity [83]. Furthermore, activation of the G protein-coupled receptor, GPR40, is responsible for an increase in cytosolic Ca^{2+} levels, ultimately resulting in the stimulation of insulin exocytosis induced by non-esterified fatty acids (NEFAs) [84]. GPR40 is predominantly associated with $\text{G}\alpha_q/\text{G}\alpha_{11}$, which then triggers activation of phospholipase C (PLC). Consequently, this cascade results in the production of inositol 1,4,5-trisphosphate (InsP_3) and the subsequent release of calcium from the endoplasmic reticulum (ER), where ATGL was originally located (Figure 2) [85-88]. This finding highlights the protective role of targeting GPR40 in conditions of metabolic stress, such as conditions induced by elevated NEFA/FFAs in aging and obesity [89]. So, how does the role of GPR40 in insulin secretion change with aging and what impact does this have on age-related metabolic disorders?

Moreover, sarcopenic obesity-induced insulin resistance has a high likelihood to result from several transcriptional or post-transcriptional factors, such as the

aryl hydrocarbon receptor, and acetylation of key molecules in AT, such as fatty acid-binding protein 4 (FABP4) [90, 91]. Multiple facts have demonstrated that host metabolic rhythms are largely regulated by PPAR- γ acetylation. However, aging interferes with PPAR- γ dynamics and the downstream target (adipsin) to influence insulin sensitivity and stabilize a core pro-adipogenic factor (BMAL1) in AT [92]. The increased level of Kindlin-2 in aged adipocytes promotes FABP4, one PPAR- γ downstream target via FAS signaling, thereby resulting in decreased β -cell activity and skeletal muscle mass [93]. PPAR- γ is also associated with disturbances in miRNAs functionality of pre-adipocyte differentiation and insulin signaling [94]. Several miRNA biogenesis and editing alterations (especially miR-29a-3p and miR-30a-3p) in aged WAT have been implicated in the inactivation of AKT in insulin signaling affected by Dicer1, one key enzyme to promote the maturation of miRNAs [95]. A small number of studies concluded that with respect to the role of miRNAs in aged BAT insulin sensitivity is also correlated with Dicer1 expression [96]. Yet Dicer deficiency in adipocytes may potentially exacerbate insulin resistance accompanied by the aging process resulting from mTORC1 agitation [97]. Exosomal miR-29b-3p derived from adipocytes regulates sirtuin (Sirt1) action to promote β -cell degeneration with aging [98]. Additionally, activation of the JNK/MAPK pathway is regulated through miR-503-3p in the progression of the age-induced glucose metabolism decline in AT and liver [99].

In contrast, AT dysfunction is a significant contributor to aging, primarily because AT dysfunction fails to balance FFA metabolism (also known as NEFA) as a substitute fuel source for the liver and skeletal muscle, which results in lipodystrophy. Recent studies have focused on utilizing obesity-associated genetic modifications of adipocytes to elucidate aging development. Inositol hexakisphosphate kinase 1 (IP6K1) enhances fatty acid biosynthesis by stimulating AMPK phosphorylation in AT, whereas ablation of IP6K1 hinders age-induced weight gain and metabolic dysfunction [100]. SWELL1 is able to handle excessive lipolysis and accumulated lipotoxicity in the liver. However, adipocyte-specific SWELL1 knock-down may heighten the risk of developing age-related metabolic diseases [101]. Nonetheless, which AT dysfunction factors influence metabolic aging remains to be further established.

Therefore, a direct inhibition of those age-related factors and stimulation on β -ARs in AT can serve as a promising strategy to improve healthspan against metabolism aging.

4. AT-ASSOCIATED IMMUNE RESPONSES IN AGING

Low-grade AT inflammation is usually accompanied by an increase in VAT activity and a decrease in BAT activity, which is directly causal to various metabolic consequences, such as insulin resistance in individuals

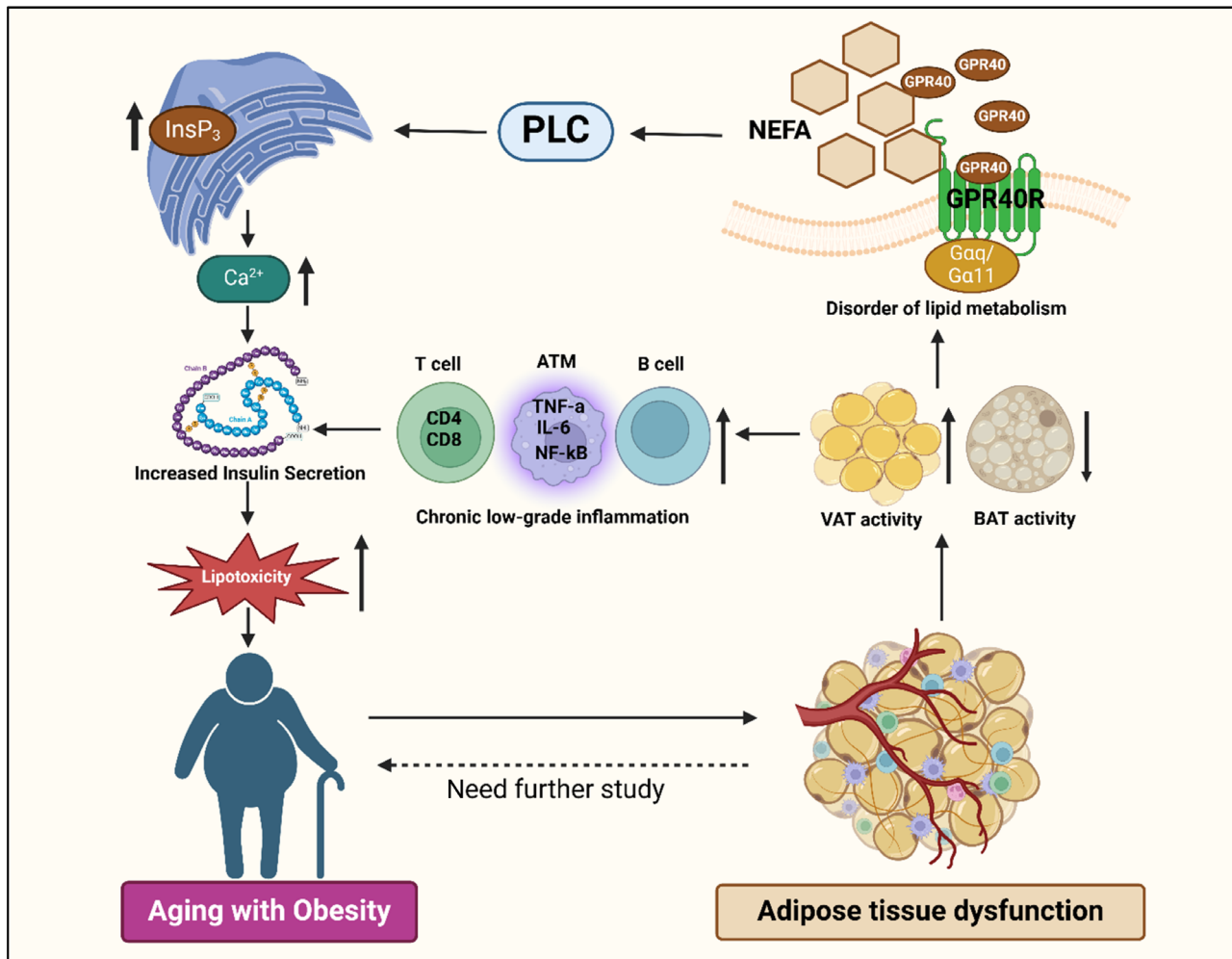


Figure 2 | The relationship between adipose tissue dysfunction and aging.

Adipose tissue dysfunction releases NEFA and GPR40. These factors activate Gq/Ga11 and subsequently the PLC pathway is activated by increasing InsP_3 in the ER and accelerating release of Ca^{2+} . Increased Ca^{2+} levels promote insulin secretion, resulting in lipotoxicity in the aging obese population. In addition, this dysfunctional tissue induces chronic low-grade inflammation by activation of ATMs, T cells, and B cells, which may also lead to insulin resistance. As a result, an imbalance in the adipose tissue metabolism has a critical role in accelerating the pathophysiologic process of aging in obese individuals. Created in BioRender. Hdinhg, D. (2025). <https://BioRender.com/gwcqwcvi>.

with sarcopenic obesity through regulation of Akt/PI3K signaling according to the scientific world's consensus (Figure 2) [102-105]. In contrast, aging-induced susceptibility to insulin results in heightened FFA levels and altered adipokine release, which contributes to an expansion in the immune cell population [106, 107]. Those immune cells, including ATMs, T cells, and B cells, are potent contributors to the secretion of pro-inflammatory cytokines and chemokines, including interleukin 1beta (IL-1 β), IL-6, TNF- α , monocyte chemotactic protein-1 (MCP-1), and C-X-C motif chemokine ligand 14 (CXCL14) in adipocytes, especially WAT, as evidenced by prior *in vivo* and *in vitro* studies, which further exacerbates systemic low-grade inflammation in aging [108-113]. A change in the macrophage profile (increased

M1 macrophage markers [CD11c/ CD68] and decreased M2 macrophage markers [CD206]), as well as AT expansion occurs in aging AT [114]. There is a reduction in the frequency of F4/80⁺CD11b⁺ ATMs and regular polarization in aged mice, while CD11c⁺CD206⁺ ATMs accumulate in young mice [115]. Notably, some advanced studies revealed that the eosinophil-to-macrophage ratio declines with age and transplanted eosinophils from young and lean subjects into the WAT of sarcopenic obese animals successfully increased the number of M2 macrophages, indicating a high therapeutic potential of conferring immune cells in the treatment [116].

Moreover, many factors are considered promoters of ATM-associated inflammation in aging, such as SUMO-specific protease 3 (SEN3), interferon regulatory factor

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3 (IRF3), and leukotriene B4 receptor 1 (BLT1). SENP3 stimulates inflammatory ATM infiltration by generating posttranslational modification of Yes-associated protein 1 induced by IL-1 β after exposed to the aging stimulus [117]. IRF3 is one modulator of PPAR- γ -mediated adipogenesis. However, IRF3 function is impaired in sarcopenia obese individuals due to the loss of IFN- β and F4/80+ CD11c+ macrophages are increasingly infiltrated into WAT to elicit inflammation [118]. The age-associated decline in WAT function is accompanied by a growing signature of mast cells and M1-type ATMs that is likely mediated by CXCL14. However, an upregulated CXCL14 level often occurs in overweight elderly individuals, the role of which in lean elderly individuals remains to be studied [119]. Nuclear factor-kappaB (NF- κ B) is persistently activated in aging AT, which leads to upregulation of proinflammatory cytokines, such as TNF- α and IL-6 and exacerbates metabolic decline (Figure 2) [120]. The cross-talk between BLT1 and the BLT1 ligand (LTB4) facilitates NF- κ B phosphorylation, the increased frequency of M1 macrophages, and the production of IL-6 in aged VAT. Previous studies revealed that the cytokine production of BLT1 is induced by ERK1/2, JNK1/2, and AKT. However, the putative mechanism underlying BLT1 in inflammaging needs further elucidation [121]. AMPK has been shown to increase cAMP expression and repress the NF- κ B inflammatory cascade during life span regulation by connecting with the Sirt family. *Sirt6* is a proven longevity and anti-inflammatory gene that deacetylates H3K9 chromatin to inactivate NF- κ B ability. This crosstalk between AMPK and NF- κ B is supported by a study with suppression of phosphodiesterase 4, which upregulates circulating cAMP [122]. NLRP3 inflammasome activation is dependent on NF- κ B but the full extent of the interactions between NF- κ B influencers directly or indirectly and inflammasome signaling in aged ATMs is unknown.

In addition to innate immunity, adaptive immunity immunosenescence (T and B cells) are affected with aging. The increased presence of ATMs and the associated NLRP3 inflammasomes may collaborate with activated T and B cells to promote inflammation in aged AT (Figure 2) [123, 124]. T cells downregulate CD28 expression and subsets of CD4⁺CD28⁻ and CD8⁺CD28⁻ T cells emerge with age. In addition, decreased regulatory T cell (Treg) activity recruited by ATMs are identified in epididymal white adipose tissue (eWAT) and liver in aged mice, thereby affecting glucose metabolism and insulin sensitivity and exacerbating local and systemic inflammation [125, 126]. In addition, during disease progression, some identified signatures of Tregs in eWAT are altered, including *Il1r1*⁺ or *Tbx21*⁺ enrichment and loss of *Ppar γ* ⁺ [127]. Senescent CD4⁺ and CD8⁺ T cells secrete high levels of S100A8, which inhibits adipose RNA-binding motif protein 3 expression via CXCL1-CXCR2 axis, inducing age-like BAT dysfunction [128]. In addition, senescent T cells are polarized to produce large amounts of IL-6 and IFN- γ . T cell-specific deficiency of IL-6 receptor- α (IL-6R α T-KO)

in mice exacerbate inflammation in eWAT tissue after 16 weeks [129]. T cell-derived IFN- γ suppresses brown adipocyte differentiation with advancing age, provoking the inflammatory process [130]. Group VII A platelet activating factor acetylhydrolase (PLA2G7) is secreted by macrophages to regulate NLRP3 inflammasome activation. Deletion of PLA2G7 improves AT metabolism in aged mice by lowering inflammation, reducing B cell, T cell, and CD11c+ macrophage signature profiles, and enlarging the pool of CD206+ macrophages [131]. Dysregulated B cells accumulate in visceral WAT during sarcopenic obesity. Camell et al. discovered a growing subset of resident non-senescent aged adipose B cells which depend on the NLRP3 inflammasome if depletion inhibits IL-1 signaling and increases lipolysis during aging [132]. However, Camell et al. pointed out that the NLRP3 inflammasome does not affect age-related CD4⁺ and CD8⁺ T cell expansion in VAT. This finding deserves more in-depth studies to elucidate the precise differences in T and B cells in different types of AT in sarcopenic obese individuals.

Recent research has highlighted the importance of the extracellular matrix (ECM) in regulating adipocyte function with aging-associated ECM remodeling leading to fibrosis, reduced adipogenesis, and altered adipocyte metabolism [133]. M2 macrophage-derived TGF- β induces DNA damage and mitochondrial ROS, further leading to cellular senescence in adipose progenitor senescent cells (APSCs). Therefore, it has been suggested that M2 macrophages are the donors for TGF- β and senescent APSCs are the recipients that suppress adipogenic potential and induce fibrotic genes [134]. The TGF- β superfamily determines the phosphorylation of SMAD2/3 to direct ATM activity in aging individuals. A marked increase in CD11c+ macrophages in aged adipocytes are mediated by growth differentiation factor 3 (GDF3), a member of TGF- β superfamily, which acts on SMAD2/3 and NLRP3 inflammasomes [115, 135]. In addition, the concentration of immunoglobulin G (IgG) tends to increase, especially in WAT of aging individuals. This finding may lead to macrophage infiltration by activation of Ras/MEK/ERK signaling and subsequent AT fibrogenesis through regulation of the TGF- β /Smad cascade. However, the ablation of B cells prevents the development of fibrosis, emphasizing the connection between IgG, B cells, and macrophages in the context of aging-associated inflammatory responses [136, 137].

5. CELLULAR SENESCENCE IN AGING-ASSOCIATED ADIPOSE TISSUE DYSFUNCTION

Cellular senescence is a process characterized by a limited ability for proliferative growth and life in culture with apoptosis resistance partially triggered by telomere shortening. Senescent cells (SCs) exhibit a multi-fold increase in individuals > 65 years of age compared to youngsters and mainly influence immune cells and fibroblasts. Physiologically, SCs can be eliminated by

the immune system. However, when the burden caused by SCs exceeds immune system capacity, the progression of aging-related diseases may accelerate. Thus, cellular senescence is inducible to inflammaging. In addition, the accumulation of SCs is often tissue-specific, especially at age-affected pathologic sites, like the AT [138]. These cells can be found in various components of the AT, including adipocytes (fat cells), pre-adipocytes (adipocyte precursors), and stromal vascular cells (e.g., immune cells and fibroblasts).

SCs exhibit a range of morphologic and molecular changes that differ from proliferating cells. SCs are often larger and flatter in size, become multinucleated, have more cytoplasmic granules, and display an accumulation of vacuoles in culture compared to SC counterparts. This finding indicates a failure in cell division or cell fusion events, along with waste products or degraded cellular component build-up. DNA damage, especially double-strand breaks, often occurs in SCs. This damage is marked by phosphorylation of the histone variant, H2AX, forming γ H2AX foci in nuclei and serving as a biomarker of the DNA damage response (DDR). Although SCs have permanent cell cycle arrest, SCs are metabolically active. Senescence-associated proteins are

increasingly and uniquely expressed, including senescence-associated β -galactosidase (SA- β -gal), p16^{INK4a}, p21^{CIP1}, and senescent-associated secretory phenotype (SASP) in aging AT [139, 140].

SCs are more susceptible to metabolic stresses, such as mitochondrial ROS, mitochondrial unfolded protein response (mtUPR), and telomere erosion, leading to DDR. Although still lacking evidence of the relationship between ADSCs and mtUPR, the expression of cellular senescence-related proteins (p53 and p21) in AT are enhanced by mitochondrial ROS [141]. This finding is due to high O₂ levels inducing telomere shortening, ultimately leading the cells to senescence [142]. Furthermore, telomere erosion also manipulates DDR under stressed conditions. DDR, with respect to transient mitochondrial DNA double-strand breaks, is activated by increasing levels of ROS to accelerate AT aging, which can be induced by DNA protein kinase (DNA-PK) and eotaxin-1/CCL11 independent of the p53/p21 pathway (Figure 3) [143-145]. This very redox state subsequently triggers the release of pro-inflammatory cytokines, such as TNF- α , IL-8, and IL-6 [144, 146]. IL-6, upon binding to the IL-6 receptor, forms a complex with two GP130 molecules, resulting in activation of

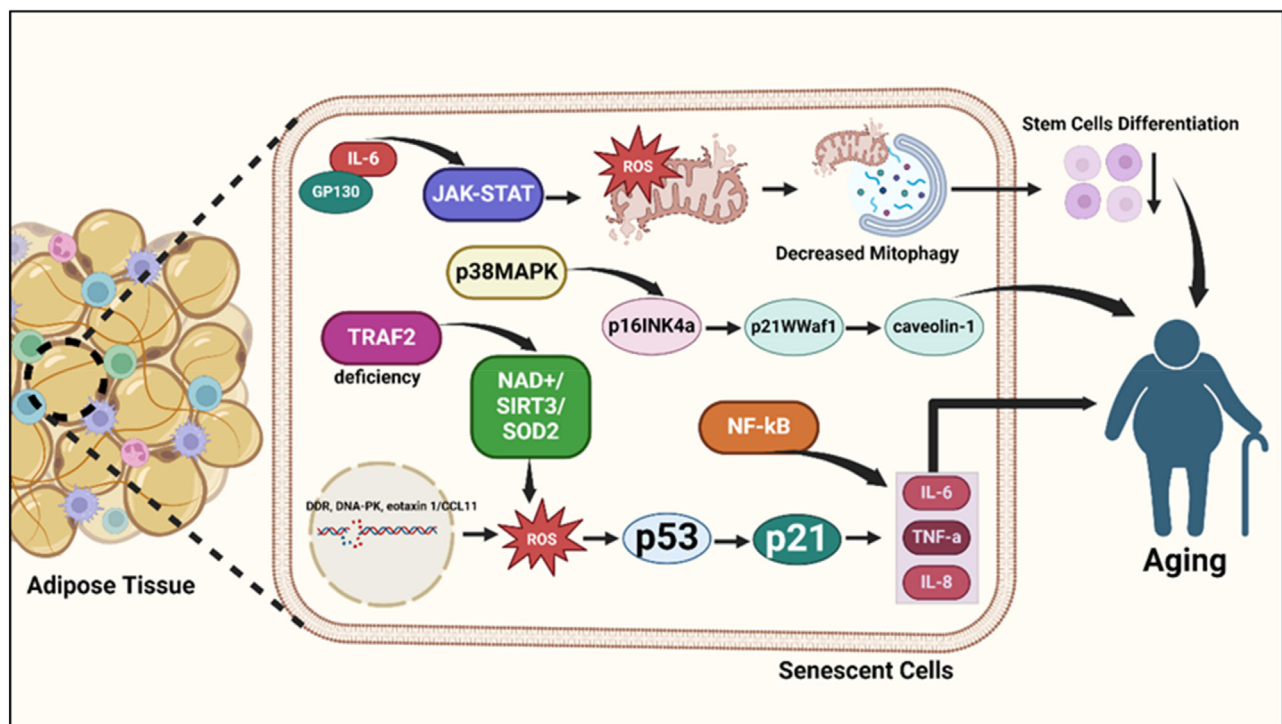


Figure 3 | Cellular senescence in white adipose tissue in aging obese individuals.

Cellular senescence has a crucial role in triggering WAT in aging obese individuals. Elevated levels of DNA damage response (DDR) induces ROS, which increase p53, p21, and NF- κ B, which in turn induces IL-6, TNF- α , and IL-8. In addition, IL-6 and the GP130 complex activates the JAK-STAT pathway, which promotes ROS and results in decreased mitophagy and stem cell differentiation. p38MAPK induces p16INK4a, p21, WAF1, Caveolin1, and p16INK4a, which triggers NF- κ B. As a result, these pathways are responsible for cellular senescence in white adipose tissue and exacerbates obesity and aging. Created in BioRender. Hdingh, D. (2025). <https://BioRender.com/gwcqwc1>.

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the JAK-STAT signaling cascade, which ultimately hinders mitochondrial function (Figure 3) [147]. The decline in nicotinamide adenine dinucleotide (NAD) levels is observed in age-related diseases by regulating cellular senescence. NAD is a key determinant of cellular senescence that usually works together with Sirt1. Yu et al. confirmed that depletion of Sirt1 significantly upregulated p16 levels and SA- β -gal activity, and compromised subcutaneous fat with small adipocytes only during adipogenic differentiation due to impaired oxidative stress responses [148]. However, because NAD metabolism affects all Sirt activity [149], other family members are needed to exhibit roles in SCs. In addition, NAD is an essential cofactor for ADP-ribose polymerases (PARPs). Sterol regulatory element-binding protein 1c (SREBP1c) has been shown to mediate metabolic stress responsiveness and lipid metabolism in AT. SREBP1c directly binds to the interacting protein, PARP1, at the DNA binding domain to improve genome stability and senescent adipocytes with SASP against DNA damage, resulting in alleviated WAT inflammation in sarcopenic obesity. This finding was evidenced by a decline in γ H2AX and the SA- β -gal signal [150]. It has also been shown that SCs with SASP trigger macrophages to express high levels of CD38 through ecto-enzymatic activity to reduce NAD levels in AT, which displays a causal link between cellular senescence and inflammaging [151, 152].

ADSCs are a type of cell with SASP that may have autocrine, paracrine, or endocrine function in AT. ADSCs have been implicated to secrete numerous inflammation-associated factors and increase immune cell infiltration to drive age-related tissue dysfunction and local and systemic inflammation [153]. p38 MAPK/ NF- κ B signaling is a crucial regulator of the p53/p21 axis and SASP generation. Specifically, ADSC function is intimately associated with over-activation of the p38 MAPK signaling pathway under exposure to an obesogenic environment, which in turn promotes senescent outcome. This finding is evidenced by upregulation of cellular senescence indicators, such as p16^{INK4a}, p21^{Waf1}, and caveolin-1, when ADSCs progressively lose replication potential (Figure 3) [154, 155]. The NF- κ B system is also involved in progression, which largely contributes to abnormal immune responses in ADSC-derived small extracellular vesicles (EVs) and exosomes (Figure 3) [156]. p38 MAPK/ NF- κ B signaling-mediated cellular senescence has been reported to be controlled by mTOR [157]. Transforming growth factor-activated kinase 1 (TAK1) is known as a key mediator of inflammation, which is stimulated by TNF- α via cytoplasmic adaptor molecule TNF receptor-associated factor 6 (TRAF6). TAK1 has been confirmed to be the upstream effector of p38 MAPK/ NF- κ B signaling and influence cell cycling [158, 159]. Protein tyrosine phosphatase non-receptor type 2 (PTPN2) has a direct effect on TAK1 inactivation to repress p38 MAPK/ NF- κ B signaling-driven adipocyte senescence [160].

Moreover, SCs in AT with SASP facilitate senescence in neighboring cells, which accelerates cellular senescence.

SCs act through autocrine factors by re-enforcing cellular senescence, especially the secretion of SASP-related IL-6 [161] and paracrine factors by inducing cellular senescence in neighboring non-senescent cells, such as TGF- β family ligands [162], which further contributes to age-related disorders. Taken together, due to secreted SASP factors, targeting SCs can be a means to manage the low-grade chronic inflammation that occurs in dysfunctional AT.

Elimination of SCs has been introduced to promote healthspan in the clinical setting. Senotherapies, especially senolytics and senomorphics, are utilized to target aged AT dysfunction via cellular senescence. Senolytics directly reduce SC burden through apoptosis. The first senolytic to be discovered was the combination of quercetin and dasatinib, which suppress age-related increase in senescence-associated β -galactosidase and the level of inflammation in AT [163]. Additional agents, consisting of natural compounds, such as fisetin (flavonoid) and Bcl family inhibitors (A1331852), were subsequently shown to be beneficial to cellular senescence [164]. Senomorphics act as SASP inhibitors without cell killing. However, the long-term administration of senomorphics might cause some adverse effects on host immune system homeostasis. These senomorphics include JAK inhibitors (ruxolitinib), mTOR inhibitors (rapamycin), and NF- κ B inhibitors (metformin) [165-167]. Because this therapeutic strategy has been promising to date, future research should focus on developing senolytics and senomorphics to selectively eliminate SCs and modulate SASP factors with an emphasis on improving mitochondrial function and reducing oxidative stress, as well as elucidating specificity and cautions for broader applications [168]. Additionally, investigating the role of p38 MAPK and PPAR γ pathways in AT and other metabolic organs could uncover new therapeutic targets. Clinical translation will require identifying reliable biomarkers of senescence and conducting trials to evaluate the efficacy of these interventions in treating obesity and age-related metabolic disorders.

6. MITOCHONDRIAL IMPAIRMENT OF AGING-ASSOCIATED ADIPOSE TISSUE DYSFUNCTION

Mitochondria are one of the most affected organs by cellular senescence. During the process, minority mitochondrial outer membrane permeabilization could translocate the mitochondrial DNA into the cytosol with the help of BAX/BAK macropores and drive SASP by regulation of the cGAS/STING pathway [169]. Thereafter, dysfunctional AT witnessed mitochondrial architecture and dynamic alterations, excessive mitochondrial ROS production, and SASP creation, ultimately leading to metabolic decline. This process worsens with age [170, 171].

The mitochondrial respiration rate is markedly decreased and mitochondrial ROS is exceedingly accumulated in aged AT by the Sirt and thyroid hormone

pathway and may further lead to a decline in PPAR γ -associated adipogenesis [172, 173]. Nuclear factor erythroid 2-related factor 2 (Nrf2) shows promise as a master regulator of antioxidant responses by reducing the expression of critical antioxidant enzymes, like superoxide dismutase (SOD) and catalase, thereby enhancing the ability of aged AT to counteract oxidative stress. Specifically, Nrf2 activates Sirt3 to delay the aging of adipocytes by eliminating oxidative species and reducing inflammation [174]. In contrast, mitochondria provide vast ATP for adipocyte differentiation. However, a mild intervention on the mitochondrial ATP synthesis may block adipocyte differentiation and reduce inflammation (TNF- α , IL-6, C-reactive protein [CRP], and leptin) in AT to extend the healthspan [175].

UCP1 loss is detrimental to mitochondria function in AT and potentially results from aging [176]. In addition, USP1 is a well-known co-factor with β 3-AR that increased factors confirmed to influence the UCP1 level in BAT aging. Syntaxin 4 is positively correlated with longevity and restoration of syntaxin 4 could prevent a decrease in UCP1 expression and BAT involution, an age-dependent degenerative process, of aged mice by restraining pyroptosis [177]. Follistatin-like protein 1 (FSTL1) may work with UCP1 to prevent BAT involution via Wnt signaling [178]. Moreover, normal UCP1 function is believed to largely depend on post-translational modifications. For example, after Sirt5 modification, UCP1 function is enhanced to further result in better mitochondrial flexibility, adaptation to cold and mitophagy (mitochondrial autophagy) [179]. Autophagic and lysosomal machinery responsible for mitochondrial degradation is altered in transcription factor EB (TFEB)-deficient BAT and primary adipocytes. This deficiency suggests that TFEB is crucial for BAT-associated mitochondrial breakdown [180]. Blocking cyclin-dependent kinase 6 (CDK6) and mammalian target of rapamycin (mTOR) activity enhances TFEB transport into the cell nucleus, while increased CDK6 levels partially counteract UCP1 promotion [181]. Intriguingly, UCP1 may even facilitate inguinal AT and skeletal muscle functionality to compensate for BAT involution [182].

Mitophagy is critical for maintenance of mitochondrial quality because mitophagy can eliminate redox species. However, in the context of aging, the changed plasticity of BAT, WAT, and beige fat is particularly concerned with reduced mitophagy. Recent studies have reported that Parkin-mediated mitophagy, which is crucial for removal of damaged mitochondria, has been shown to decline with age. This decline results in the accumulation of dysfunctional mitochondria and impaired thermogenic plasticity, which exacerbates metabolic dysfunction within BAT and WAT [183]. However, mitophagy, which is critical for maintenance of mitochondrial quality, is now understood to have a dual role in the plasticity of beige fat. Recent findings suggest that while mitophagy is necessary for browning of white adipocytes (conversion to beige fat), excessive

mitophagic degradation of mitochondria in aged tissues may actually contribute to the loss of beige fat characteristics, which promotes a return to white fat. This insight emphasizes the need for balanced mitophagic activity to maintain the beneficial properties of beige fat during aging [183, 184].

Furthermore, adipose Schwann cells have been shown to regulate synaptic nerve plasticity and influence energy homeostasis, as well as serve as a bridge between neurons and AT through the release of EVs during aging. These EVs in aged conditions carry bioactive molecules that influence the mitochondrial function of adipocytes, potentially exacerbating mitochondrial dysfunction [185, 186]. Emerging research shows that ADSCs can actively transfer mitochondria to damaged or SC within AT. This mitochondrial transfer can rejuvenate cellular function and has been shown to improve the metabolic profile of aging adipocytes. These findings suggest that enhancing the activity or number of ADSCs could be a promising strategy to counteract age-related mitochondrial dysfunction and improve overall AT plasticity [184].

Future research should focus on enhancing mitochondrial quality control in aging BAT, potentially through targeted modulation of Parkin-mediated mitophagy and TFEB activity. Mitochondrial transplantation to restore mitochondrial function in whitening BAT represents a promising therapeutic avenue. Therefore, studies should focus on refining transplantation techniques and evaluating the long-term efficacy and safety in larger animal models and clinical trials. This approach could open new doors for treating age-related metabolic disorders by directly addressing mitochondrial dysfunction in AT.

7. A NOVEL THERAPEUTIC APPROACHES OF MITOCHONDRIAL TRANSPLANTATION

Given that mitochondrial function is crucial for controlling AT dysfunction in aging, lines of evidence suggest that exogenous supplementation with mitochondria isolated from proper healthy donor cells or tissues transferred to recipient cells could be a promising therapeutic strategy for mitochondrial-related diseases by enhancing mitochondrial bioenergetics and generating mitochondria-associated pathways. The MT approach holds great promise in age-related performance, such as congenital skeletal muscle dysfunction [187], cognitive decline [188], degenerative joint diseases [189], and sarcopenia [190]. Because aging results from mtDNA mutations or changes in mtDNA copy counts, the introduction of new mitochondria partially alleviated mitochondrial dysfunction caused by chronic stress in elderly rats [191]. Thus, MT is believed to restore functional tissues of recipients, such as AT, especially in aging [192]. We speculated that transplantation of mitochondria from AT and/or bone marrow can protect the host from aging and metabolic disorders by inducing

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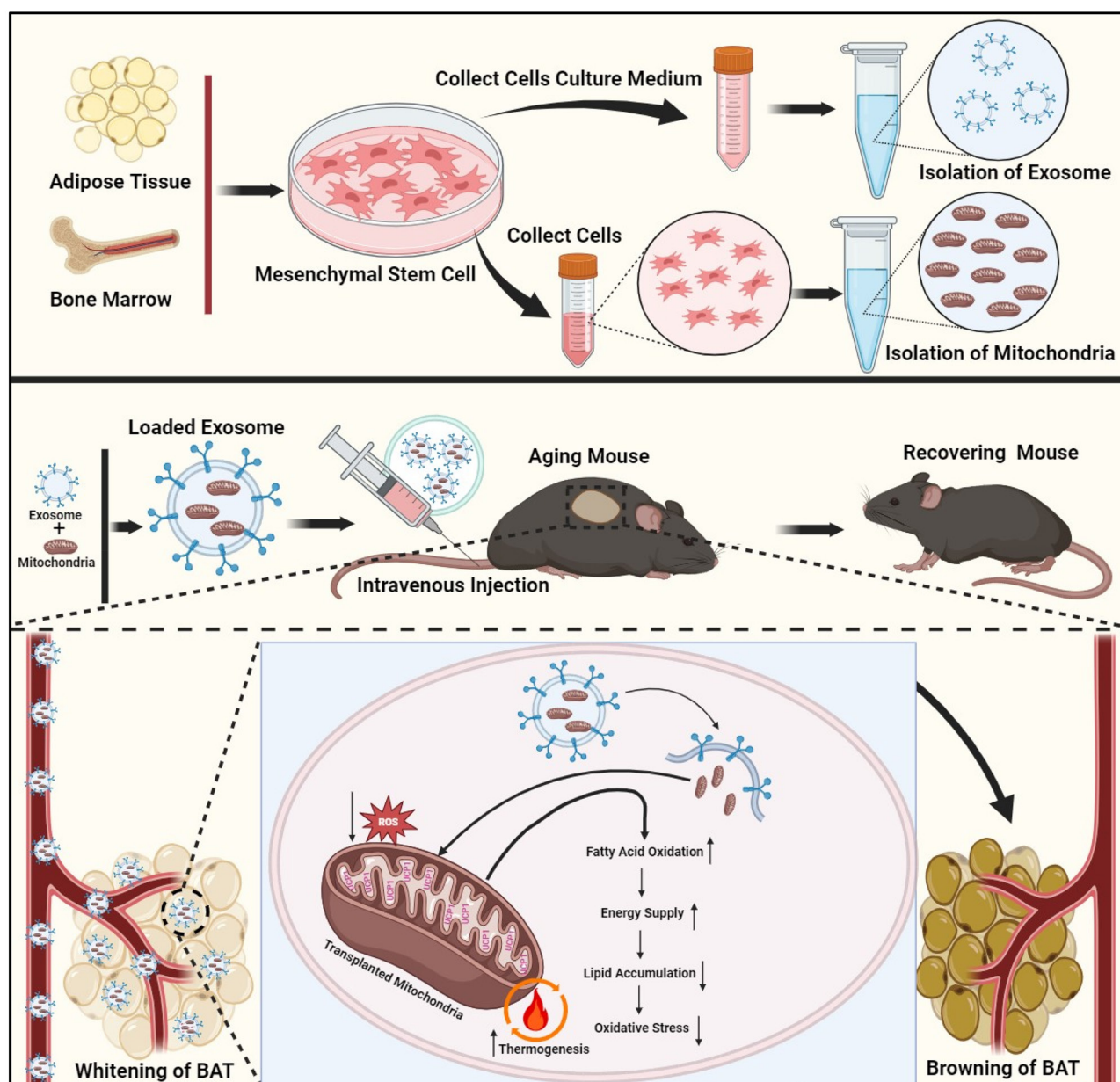


Figure 4 | A novel approach of mitochondria transplantation.

This schematic presentation demonstrates mitochondria and exosomes as cargo isolated from adipose tissue and bone marrow. Therefore, exosomes were loaded with mitochondria for intravenous tail vein injection into aging mice. This administration into the BAT through the systemic circulation and exerts reduced ROS levels, reduced oxidative stress, and increased thermogenesis. As a result, increased browning of BAT in aging for better metabolic health with longevity of life. Created in BioRender. Hdingh, D. (2025). <https://BioRender.com/gwcqwcvi>.

thermogenesis, increasing fatty acid oxidation and the energy supply, and reducing lipid accumulation and oxidative stress (Figure 4).

Successful transplantation of isolated mitochondria from external sources into various recipient cells has been demonstrated in several controlled laboratory and live animal settings [193]. The success of this experiment relies on the quality of donor mitochondria

so that basic mitochondrial function and integrity measurements are required, including membrane integrity analysis, intracellular ATP content, and mitochondrial complex analysis. After a quality check, donor mitochondria could be integrated by direct injection, co-incubation, centrifugation, cell-penetrating peptide, biocompatible polymers, photothermal nano-blades, and EVs [194]. EVs are among the most important

routes for the intercellular transport of mitochondria. EVs transfer whole mitochondrial particles and mtDNA between cells to restore cellular function. Exosomes are a kind of EVs from intraluminal vesicles of the endosomal system < 150nm in diameter, which have recently been the focus of research as potential drug carriers exhibiting lower toxicity than synthetic nanoparticles, such as liposomes [195, 196]. Exosomes can be enclosed by a lipid membrane that contain cargo (mitochondria). These cargos can be subsequently delivered to target cells precisely by membrane fusion, cargo internalization, and interactions with ligands and/or receptors [197-199]. Recent investigations involving the characteristics of exosomes interpreted that tetraspanins (CD63, CD9, and CD81) are activated during mitochondria-related diseases, thus exosomes are essential in conducting precise drug discovery [200]. During the past few years, there has been an expansion of research on utilizing EVs and exosome-loaded MT in the treatment of age-related functional impairments resulting in improvements in cell metabolism, mitochondrial bioenergetics, and the immune system, despite the difficulty in scalable manufacturing, high-tech equipment, and quality monitoring [201].

Based on the source of mitochondria, MT can be classified as autologous MT (donor and recipient of mitochondria are the same) and allogeneic MT (recipient receives the mitochondria from another donor). Stem cell-derived MT is gaining interest in recent years because stem cells enjoy a high capacity for differentiation and self-renewal, and can transfer mitochondria to adjacent cells to improve whole-body immunity [202]. In addition, ongoing clinical trials have confirmed that allogeneic ADSCs could effectively alleviate aging-related symptoms by increasing mitophagy [203, 204]. Several studies have shown that autologous ADSC and adipose tissue-derived mesenchymal stem cell (AdMSC) mitochondria could increase the quality of oocytes related to advanced maternal age [205, 206]. Autologous MT has a safer applied process compared to allogeneic MT because there will be no immune rejection. However, the greatest difficulty is the sole origin of mitochondria. Specifically, AdMSCs have multiple advantages, including abundant source, low immunogenicity, and renewal properties [207]. However, to date only a few clinical trials with AdMSCs have been approved because there still exists some unresolved issues about doses, purity, and safety. When combined with the advantages from exosomes and AdMSCs, exosomes from AdMSCs have recently emerged as a new cell-free alternative for treating diseases, including AT dysfunction and aging. Recipient cells can internalize exosomes through processes, such as phagocytosis, micropinocytosis, and endocytosis, to recover the disease [208]. Notwithstanding obstacles, numerous benefits render exosome treatment appealing and a potential transporter for pharmaceuticals.

8. CONCLUSION AND FUTURE PERSPECTIVES

Aging is intricately linked with significant alterations in AT function, leading to metabolic disorders, such as insulin resistance and obesity. Thus, this review underscores the importance of understanding the molecular mechanisms underlying the decline in AT activity with age, as well as potential ways to mitigate disease progression. Alterations in energy metabolism, FFA metabolism, and insulin sensitivity are observed in aged AT driven by inflammatory responses, cellular senescence, and mitochondrial metabolism impairment. Recent studies have focused on addressing abnormal immune reactions and enhancing mitochondrial quality control to develop effective therapies aimed at improving metabolic health and extending longevity, especially through approaches, such as the administration of senolytics and senomorphics and the promising field of MT. The potential of introducing MT as new avenues for clinical interventions with modulation of key pathways, such as p38 MAPK and PPAR γ , and mitophagy to improve the healthspan of aging populations has been the focus of this review. Further studies are warranted to understand MT for specific mitochondrial molecular mechanisms in dysfunctional AT. Finally, our deepened understanding of these complex interactions between AT and sarcopenic obesity and targeted therapies, particularly MT, may offer new hope in mitigating the burdens of aging and metabolic disease.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

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