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Age-Induced Changes in White, Brite, and Brown Adipose Depots: A Mini-Review

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Abstract
Aging is a time-related process of functional decline at organelle, cellular, tissue, and organismal level that ultimately limits life. Cellular senescence is a state of permanent growth arrest in response to stress and one of the major drivers of aging and age-related disorders. Senescent cells accumulate with age, and removal of these cells delays age-related disorders in different tissues and prolongs healthy lifespan. One of the most studied aging mechanisms is the accumulation of reactive oxygen species damage in cells, organs, and organisms over time. Elevated oxidative stress is also found in metabolic diseases such as obesity, metabolic syndrome and associated disorders. Moreover, dysregulation of the energy homeostasis is also associated with aging, and many age-related genes also control energy metabolism, with the adipose organ, comprising white, brite, and brown adipocytes, as an important metabolic player in the regulation of whole-body energy homeostasis. This review summarizes transformations in the adipose organ upon aging and cellular senescence and sheds light on the reallocation of fat mass between adipose depots, on the metabolism of white and brown adipose tissue, on the regenerative potential and adipogenic differentiation capacity of preadipocytes, and on alterations in mitochondria and bioenergetics. In conclusion, the aging process is a lifelong, creeping process with gradual decline in (pre-)adipocyte function over time. Thus, slowing down the accumulation of (pre-)adipocyte damage and dysfunction, removal of senescent preadipocytes as well as blocking deleterious compounds of the senescent secretome are protective measures to maintain a lasting state of health at old age.

Introduction

The increased life expectancy and the expansion of the elderly population are promoting research into aging, as aging is the single largest risk factor for a plethora of chronic

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diseases. Aging is a time-related process of functional decline at organelle, cellular, tissue, and organismal level that ultimately limits life. Several major contributors to biological aging are known, among them cellular senescence, oxidative stress, and dysregulation of the energy homeostasis.

Cellular senescence is one of the major drivers of the aging process and of age-related disorders. It is a state of permanent growth arrest in response to stress, telomere shortening or oncogenic signaling, characterized by morphological alterations, concomitant-persistent DNA damage response, expression of senescence-associated β-galactosidase (SA-β-gal), accumulation of the cyclin-dependent kinase inhibitor $p16^{INK4a}$, senescence-associated secretory phenotype (SASP), and senescence-associated heterochromatin foci [1]. Senescent cells accumulate with age, and removal of these cells delays tumorigenesis and age-related disorders in different tissues and prolongs healthy lifespan, in vivo [2].

The free radical theory of aging, also referred to as oxidative stress theory, is one of the most studied aging-promoting mechanisms which proposes that cells, organs, and organisms age because they accumulate reactive oxygen species (ROS) damage over time. There has been significant progress in our understanding of mechanisms that regulate aging, and it has been shown that changes in single genes can dramatically extend lifespan and increase resistance to many diseases. For example, mice with a mitochondrial-targeted overexpression of catalase, a common enzyme that decomposes hydrogen peroxide to water and oxygen thus protecting the cell from ROS-mediated oxidative damage, demonstrate an extension of lifespan compared to wild-type mice [3].

Elevated oxidative stress is a defect also found in obesity, metabolic syndrome and associated metabolic diseases for which the prevalence is dramatically high and continues to rise consistently in Western and developing countries [4, 5]. Upon obesity, features of premature accumulation of senescent cells, such as a higher expression of SA-β-gal, p53, and cyclin-dependent kinase inhibitors, have been found in the adipose tissue. Consequently, maintenance of a lean phenotype characterized by lower proportion of body fat content by either genetic modulation, visceral fat removal or caloric restriction extends lifespan [6–8].

A fundamental process associated with aging is dysregulation of the energy homeostasis, and many age-related genes belong to evolutionarily conserved pathways that also control energy metabolism, with the adipose organ as an important metabolic player in the regulation of whole-body energy homeostasis [9]. The main parenchymal cells of the adipose organ are adipocytes, and so far two cell types of opposing functions have been reported: adipocytes in the white adipose tissue (WAT) usually store energy surplus in the form of lipids in two compartments, the subcutaneous (sWAT) and the visceral (vWAT) white adipose depot, and are characterized by a large unilocular lipid droplet and a low density of mitochondria, whereas adipocytes in the brown adipose tissue (BAT) can massively dissipate energy via nonshivering thermogenesis and are characterized by multilocular small lipid droplets and a high abundance of mitochondria. Moreover, BAT possesses a dense sympathetic innervation and vascularization compared to WAT [10]. Interestingly, brown-like adipocytes also appear in WAT upon cold exposure or adrenergic stimuli sustaining energy dissipation via thermogenesis.

In this review, we summarize changes that occur in the adipose organ upon increasing age, with particular emphasis on age- and cellular senescence-induced transformations in adipose depots, in metabolism of WAT and BAT, in (pre-)adipocyte regenerative potential and adipogenic differentiation capacity, as well as on age-induced alterations in mitochondria and bioenergetics.

Adipose Tissue Redistribution with Aging

Functional adipose tissue controls energy balance with favorable effects on metabolic health and longevity. It has been known for a long time that aging is associated with a redistribution of body adipose tissue, with a relative loss of sWAT particularly from the limbs and an accumulation of adipose tissue in trunk and visceral areas (Fig. 1) [11, 12]. While sWAT is associated with improvement or maintenance of insulin sensitivity and reduced risk of developing metabolic disorders, visceral adiposity leads to chronic inflammation and lipotoxicity and is often associated with a number of comorbidities such as hyperinsulinemia, hypertension, insulin resistance and glucose tolerance, leading to reduced life expectancy. Indeed, loss of peripheral sWAT and increased abundance of vWAT are associated with metabolic abnormalities, particularly insulin resistance [13, 14], with increased risk of diabetes [15] and cardiovascular disease [16].

Adipose Metabolism and Lifespan

Moreover, adipose tissue-specific dysfunctions with impact on the development of metabolic syndrome and deleterious effects on whole-body energy homeostasis are

also related to aging [17]. Of importance, key processes of adipose tissue physiology affect molecular pathways that regulate lifespan [18]. For example, SIRT1 levels decline with age in several tissues, including adipose tissue, and this reduction is acerbated in a mouse model of accelerated aging contributing to aging-induced obesity, impaired browning, and the development of metabolic syndrome [19]. Another key regulator in aging is signalling of the serine/threonine protein kinase mTOR. Rapamycin, an inhibitor of the mTOR pathway, is able to extend lifespan in genetically heterogeneous mice, even when administered late in life [20]. Another way of inhibiting mTOR signaling and to counter aging is caloric restriction [21]. The bone morphogenetic protein (BMP) receptor 1A has an important role in the formation of brown adipocytes, and the deletion of BMPR1a in premature and mature adipocytes attenuates age-related onset of systemic insulin resistance [22].

The enhancement of brown and brite adipocyte activity increases energy expenditure and is thought to counteract adipose tissue dysfunction and the development of obesity [23–25]. However, the amount of detectable BAT declines with increasing age [26], just like the adrenergic agonist-dependent inductive ability of brite adipocytes in WAT [27]. Of interest, recent studies have shown that there is a cross talk of molecular pathways in different adipose depots. For example, the winged helix factor forkhead box protein A3 (FOXA3), a transcription factor that regulates the expansion of mouse vWAT, is increased in the adipose tissue during aging, which leads to a reduction in BAT and reduced browning in aged mice. Accordingly, FOXA3 KO mice show increased BAT and enhanced browning upon aging, accompanied by increased longevity and protection against obesity and insulin resistance [28]. These data suggest that improved browning may lead to an increased health span.

Another piece of evidence for the interrelationship of adipose metabolism with aging is that metformin, a drug approved to treat diabetes, appears to target a number of pro-aging activities, as it suppresses adipocyte proinflammatory responses, decreases ROS levels as well as adipose DNA damage and improves the balance of brown/white adipose upon obesity [29–31]. At organismal level, retrospective observational studies associate metformin with increased human lifespan, fewer age-related diseases, improved cognitive function and decreased cancer incidence, which cannot be explained by lowering blood glucose levels alone [32]. Furthermore, metformin reduced all-cause mortality of overweight diabetes patients enrolled in the UK Prospective Diabetes Study (UKPDS) [33]. However, only clinical prospective studies with metformin in healthy individuals, such as TAME [32], will be able to establish a clear association between metformin and healthy lifespan and will likely contribute to a better understanding of the impact of adipose metabolism on human aging.

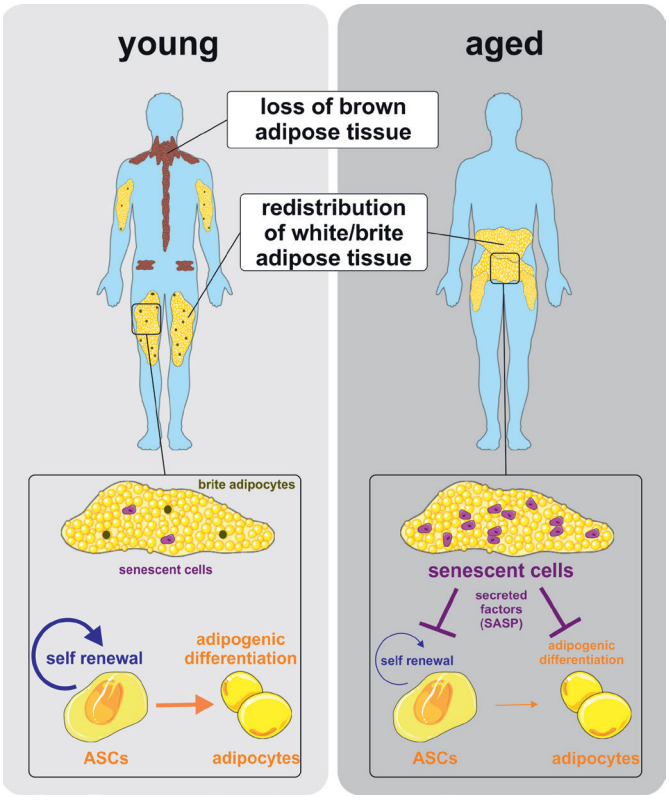

Fig. 1. Overview of anatomical changes in the white, brite, and brown adipose tissue during aging. Accumulating senescent cells in the adipose depots that change functionality of the adipose organ with age.

Impact of Age on the Function of Adipocyte Precursors

Adipose tissue is primarily composed of mature adipocytes, which are derived from adipose stromal cells (ASCs) and store energy as fat. In contrast to mature adipocytes, ASCs still proliferate and have the potential to differentiate into adipocytes, chondrocytes, osteoblasts and myocytes, thus rendering these cells as promising tools in regenerative medicine. In this context, several groups studied the relationship between donor age, proliferative capacity, and differentiation potential of ASCs.

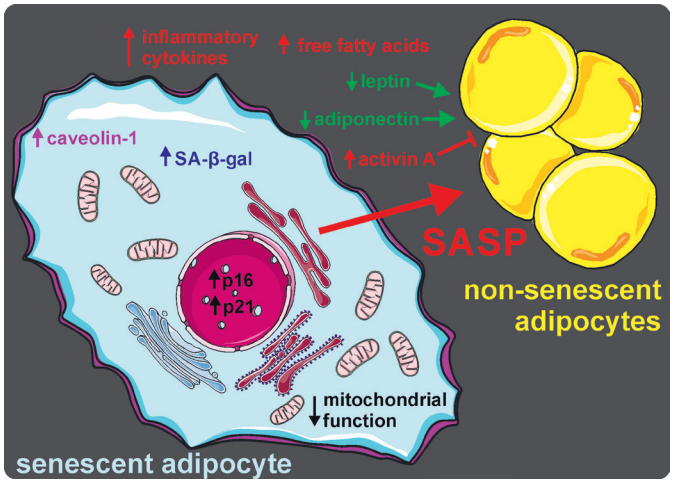

Fig. 2. Pathways modulated in senescent adipocytes. Senescent adipocytes are characterized by increased intracellular expression of p16, p21, caveolin-1, and senescence-associated β-galactosidase (SA-β-gal). The senescence-associated secretory phenotype (SASP) comprises decreased levels of the pro-adipogenic adipokines leptin and adiponectin, as well as increased levels of inflammatory cytokines, free fatty acids, and anti-adipogenic activin A.

Schipper et al. [34] isolated human ASCs (hASCs) from different subcutaneous fat depots of 12 female donors and observed a decrease in both the replicative potential, and the differentiation capacity towards the adipogenic lineage with increasing age of the donor. The decrease in hASC replication with increasing donor age was also described in another study, but in this case, adipogenic differentiation was not significantly correlated with donor age. However, the authors observed that osteogenic differentiation of hASCs was diminished with increasing age, indicating that the loss of differentiation potential is not specific to a single mesenchymal lineage [35]. As hASC donor age was also inversely correlated with angiogenic differentiation potential in a matrigel assay [36], hASCs from old donors might only have a limited suitability for use in regenerative medicine.

Impact of Age on Adipocyte Function

With age, white fat depots decline and dysfunctional adipocyte-like cells appear in WAT that are smaller and less insulin responsive than fully differentiated adipocytes [37]. Increasing age of brite adipocytes progressively leads to a white adipocyte phenotype, which prevents browning of adipocytes in older mice and humans (Fig. 1). This age-related phenotype can be rescued by adipocyte-specific induction of lysine-specific demethylase (Lsd1), an epigenetic eraser enzyme positively regulating differentiation and function of adipocytes, and by targeting the p38/Ink4a-Arf pathway [38, 39]. A very similar phenotype has also been observed in BAT: the proliferative capacity and UCP1 expression in response to cold stimulus seems to be abolished in aged brown adipocytes [40]. However, despite the fact that recruitment and activation of brown adipocytes represents a promising pharmacological target to ameliorate metabolic diseases, mechanisms of age-induced changes in the replicative potential and the differentiation capacity of brown adipocyte precursors with impact on whole-body energy homeostasis remain to be elucidated.

Impact of Cellular Senescence on (Pre-)Adipocyte Function

During normal aging of the adipose organ, ASCs exhaust their capacity to replicate and enter cellular senescence, characterized by upregulation of senescence markers and caveolin-1. Similar to the chronological age of the donor, also serial passaging of hASCs in vitro diminishes their ability to differentiate into mature adipocytes. Moreover, hASCs display increased expression of SA-β-gal, caveolin-1, as well as of the senescence markers $p16^{INK4a}$ and $p21^{Waf1}$ towards the end of their replicative lifespan (Fig. 2). Interestingly, overexpression of caveolin-1 in hASCs of early passage number decreases adipogenic differentiation, indicating that upregulation of caveolin-1 during replicative aging of hASCs is responsible for their reduced adipogenic differentiation potential [41].

Recent evidence suggests that senescent adipocyte precursors indeed progressively accumulate in inguinal and epididymal WAT in 3-, 12-, and 18-month-old mice. Consistent with that, adipocyte size decreases and fat loss occurs between 12 and 18 months of age. However, selective killing of senescent cells counteracts accumulation of senescent cells, fat loss and decreased adipocyte size in aged animals, and extends their lifespan [2]. Taken together, these findings indicate that cellular senescence of ASCs is one of the major drivers of the functional decline of the adipose organ with age, which ultimately affects fitness and lifespan at organismal level (Fig. 1).

Cellular senescence is often accompanied by a complex SASP that induces generalized low-grade inflammation and thereby promotes aging phenotypes and pathologies [42]. Consequently, also the secretome of senescent

subcutaneous hASCs is remodeled towards increased secretion of free fatty acids and reduced expression of the two adipokines leptin and adiponectin, which are both important for the stimulation of insulin sensitivity and fatty acid oxidation [43]. Another deleterious component of the senescent secretome is activin A, which directly inhibits adipogenesis of nonsenescent hASCs. Activin A levels increase in fat tissue of mice during normal aging, whereas clearing of senescent cells from 18-month-old mice reduces circulating activin A, blunts fat loss, and enhances adipogenic transcription factor expression within 3 weeks [44]. Thus, the secretome of the adipose organ is remodeled with increasing age, further diminishing the functionality of surrounding (pre-)adipocytes (Fig. 2) and ultimately compromising health and promoting aging at the organismal level. Clearance of senescent ASCs by senolytic drugs [45] or specific blocking of deleterious SASP components might represent promising strategies to counteract this process.

Impact of Age-Induced Macromolecular Damage on (Pre-)Adipocyte Function

Shortening of telomeres due to cellular proliferation is, however, not the only factor that induces cellular senescence of ASCs and functional decline of the adipose organ with age. Damaged macromolecules, such as DNA and proteins, progressively accumulate, and pathways counteracting extrinsic or intrinsic stressors, as well as degradation and repair pathways, become less effective.

In various segmental progeroid syndromes, such as Werner syndrome [46], Cockayne syndrome or trichothiodystrophy, both aging and adipose tissue redistribution occur at an accelerated pace due to mutations in different components of DNA repair pathways [47]. Another DNA repair factor implicated in aging and adipogenesis is $SNEV^{hPRP19/hPso4}$. Overexpression of this gene extends replicative lifespan of endothelial cells, organismal lifespan of fruit flies and improves stress resistance at both cellular and organismal level [48, 49]. Knockdown of $SNEV^{hPRP19/hPso4}$ impairs adipogenesis of hASCs, as well as in *Caenorhabditis elegans* [50]. However, not only diminished repair capacity of cells but also extrinsic factors induce elevated levels of DNA damage and thereby promote dysfunction of ASCs. Ultraviolet A (UVA) light, for instance, affects the adipogenic differentiation potential of hASCs even at very low doses. This loss of function is accompanied by a decrease of PPARγ expression and a reduced accumulation of triglycerides in mature adipocytes [51]. Furthermore, UVA irradiation causes loss of proliferative potential and stemness of hASCs [52].

UVA irradiation induces DNA damage that profoundly affects skin health and beauty, which are probably the most obvious age-associated alterations in humans. Interestingly, recent evidence suggests that also dermal white adipose tissue (dWAT) plays a pivotal role in this process. In human skin, dWAT appears as cone-shaped depots surrounding pilosebaceous units in close proximity to the epidermis and protruding into the sWAT. Thus, dWAT cones are suggested to transmit UVA-induced damage signals from the surface to the sWAT. In addition, soluble cytokines are produced in the upper epidermis upon UV exposure and diffuse into the sWAT, causing loss of PPARγ expression, as well as reduced free fatty acid and triglyceride content. In mice, chronic exposure to UVA causes transition of dermal adipocytes to myofibroblasts, leading to replacement of dWAT with fibrotic tissue and thereby promoting morphological and functional alterations in the skin [53]. Taken together, these processes induce loss of sWAT and concurrent accumulation of vWAT in the skin with age, promoting the typical appearance of aged skin. Current methods to restore the youthful appearance of facial skin include invasive procedures such as fat grafting. Thus, novel strategies to block macromolecular damage of ASCs or to restore the activity of repair enzymes might not only improve organismal health, but also ameliorate visible signs of skin aging.

Impact of Age on Mitochondria: Biogenesis, Function, Bioenergetics

Mitochondria are the core functional unit in metabolic control in numerous cells, including BAT and WAT. They are both origin and target of various extracellular and intracellular signals, which are required for various physiological responses to maintain cellular functionality such as glucose and lipid homeostasis [54]. In addition, mitochondria have been suggested as key components in the process of white adipocyte formation through ROS signaling [55]. Furthermore, mitochondrial function has been linked to the white adipocyte endocrine functionality as it was shown that secretion of adipokines such as adiponectin are dependent on mitochondria [56]. Similar to white adipocytes, it is well established that brown adipocytes rely on mitochondrial function for maintaining intracellular metabolism. In addition, brown adipocyte mitochondria are functionalized by

uncoupling protein-1 (Ucp1) which allows the translocation of protons to dissipate energy in the context of nonshivering thermogenesis.

In the context of aging, it has been reported that mitochondrial enzyme expression is reduced in adipose tissue from old mice, yet little is known regarding mechanisms that could be mediating these changes [57]. Similarly, it is well established that human WAT mitochondrial function measured by oxygen consumption of the tissue is reduced both in obesity as well as during aging [58].

So far, it has remained unclear why aging and obesity influence mitochondrial functionality. One hypothesis for the alteration in mitochondrial function is lipotoxicity, which has mostly been discussed in the context of muscle and liver and which can occur during adipose tissue hypertrophy, usually coupled to adipose tissue insulin resistance, when storage capacity of the adipocyte is exceeded. In this context, it was reported that the mitochondrial phosphoproteome is substantially altered, in response to a lipid overload; however, it remains unclear whether altered mitochondrial function is the driver of lipotoxicity or vice versa [59].

Several interventions have been described, which can reverse the phenotype of reduced mitochondrial function in WAT in obesity, the two most prominent examples being caloric restriction and treatment using PPARγ agonists [60]. Interestingly, this can be related to BAT as well, since PPARγ is considered one of the main regulators of BAT function as well as formation and since it was recently shown that caloric restriction induces BAT mass and functionality [61]. Taken together, it is tempting to speculate that the induction of a brown fat phenotype by the abovementioned interventions, which would result in an increased mitochondrial functionality, could be the reason for the observed beneficial effects on aging and metabolism. In general, every intervention in cellular bioenergetics needs to face safety considerations; thus, we need to generate more knowledge on putative side effects of pharmacologically increased BAT mass and functionality [62, 63]. Nevertheless, inducing BAT activity in general might serve as an efficient strategy to increase energy consumption also in humans, making BAT a good candidate organ to treat obesity and possibly also to slow the aging process.

Conclusion

In this review, we focused on alterations in the adipose organ, which are manifested by aging and cellular senescence. On the one hand, aging induces on the organismal level a reallocation of fat mass from subcutaneous towards visceral adipose depots, while senescence on the cellular level impairs regenerative potential and differentiation capacity of adipocyte precursors which finally leads to a loss of function in the adipose organ. Energy-sensing as well as DNA repair pathways in adipose tissue are affected by aging and are able to regulate lifespan. Similarly is the induction of mitochondrial function beneficial for the extension of lifespan as well as for the amelioration of metabolic diseases. Moreover, senescent cells exhibit a remodeled secretome, also called SASP, which diminishes the functionality of surrounding (pre-)adipocytes, thus ultimately compromising health and promoting aging at organismal level.

In conclusion, slowing down the accumulation of (pre-)adipocyte damage and dysfunction, removal of senescent preadipocytes, blocking deleterious compounds of the senescent secretome, as well as inducing BAT activity are protective measures to maintain a lasting state of health at old age.

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Disclosure Statement

J.G. is co-founder of Evercyte GmbH and TAmiRNA GmbH. All other authors declare no conflicts of interest.

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