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Aging and adipose tissue: potential interventions for diabetes and regenerative medicine

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ABSTRACT

Adipose tissue dysfunction occurs with aging and has systemic effects, including peripheral insulin resistance, ectopic lipid deposition, and inflammation. Fundamental aging mechanisms, including cellular senescence and progenitor cell dysfunction, occur in adipose tissue with aging and may serve as potential therapeutic targets in age-related disease. In this review, we examine the role of adipose tissue in healthy individuals and explore how aging leads to adipose tissue dysfunction, redistribution, and changes in gene regulation. Adipose tissue plays a central role in longevity, and interventions restricted to adipose tissue may impact lifespan. Conversely, obesity may represent a state of accelerated aging. We discuss the potential therapeutic potential of targeting basic aging mechanisms, including cellular senescence, in adipose tissue, using type II diabetes and regenerative medicine as examples. We make the case that aging should not be neglected in the study of adipose-derived stem cells for regenerative medicine strategies, as elderly patients make up a large portion of individuals in need of such therapies.

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1. Adipose tissue: relevance in aging

Adipose tissue is a large and dynamic endocrine, immune, and regenerative organ that can readily adapt to changes such as temperature, nutrient availability, beta-adrenergic tone, and tissue damage in young, healthy individuals. Adipose tissue is responsible for energy storage, nutrient sensing, and temperature regulation and has important functions in immune modulation, wound healing, and tissue regeneration. Aging is associated with a decline in tissue function and an increase in disease burden, and adipose tissue is no exception. With aging, adipose tissue undergoes significant changes in abundance, distribution, cellular composition, and endocrine signaling, and plays a central role in the development of insulin resistance, metabolic dysfunction, inflammation, and impaired regenerative capacity with age (Fig. 1) (Tchkonia et al., 2010). Several fundamental age-related changes occur at the cellular level in adipose tissue that may contribute to age-related adipose dysfunction. Adipose tissue is often the largest organ, making up over 40% of total body mass for example in women with BMI >35 (Bonora et al., 1992; Romero-Corral et al., 2008). However even in lean individuals, adipose tissue has systemic influence on inflammatory signaling and insulin sensitivity through secretion of adipokines and adipose-derived hormones (Tilg and Moschen, 2006). It can affect the function of other organs including muscle, bone, liver, and the brain. Adipose tissue is also being turned to as a key source of mesenchymal stem cells, which are being increasingly explored as therapeutics for multiple degenerative diseases (Zuk et al., 2002). Many interventions that extend lifespan in lower organisms and mammals have significant effects in adipose tissue, often through the modulation of nutrient availability (Huffman and Barzilai, 2010; Picard and Guarente, 2005; Tchkonia et al., 2010). Furthermore, when single-gene mutations found to extend lifespan in lower animals are restricted to adipose tissue, similar lifespan extension can be seen (Bluher et al., 2003; Giannakou et al., 2004). Dysfunction of adipose tissue, such as that in obesity, is associated with a shortened lifespan and increase in age-related disease prevalence, including cancer and dementia (Gilbert and Slingerland, 2013; Kivipelto et al., 2005). The abundance of adipose tissue, along with its varied functions, importance to whole-body physiology, and constellation of aging changes, makes it a highly relevant organ for the study of aging. Further understanding of aging adipose tissue could be valuable for the discovery and testing of therapeutic strategies to target fundamental aging processes and age-related disease.

2. Age-related changes in adipose tissue composition and function

2.1. Fat redistribution with aging

Through middle- or early old age (*e.g.*, 40–65 years of age), body mass and body fat percentage increase in both men and women (Guo

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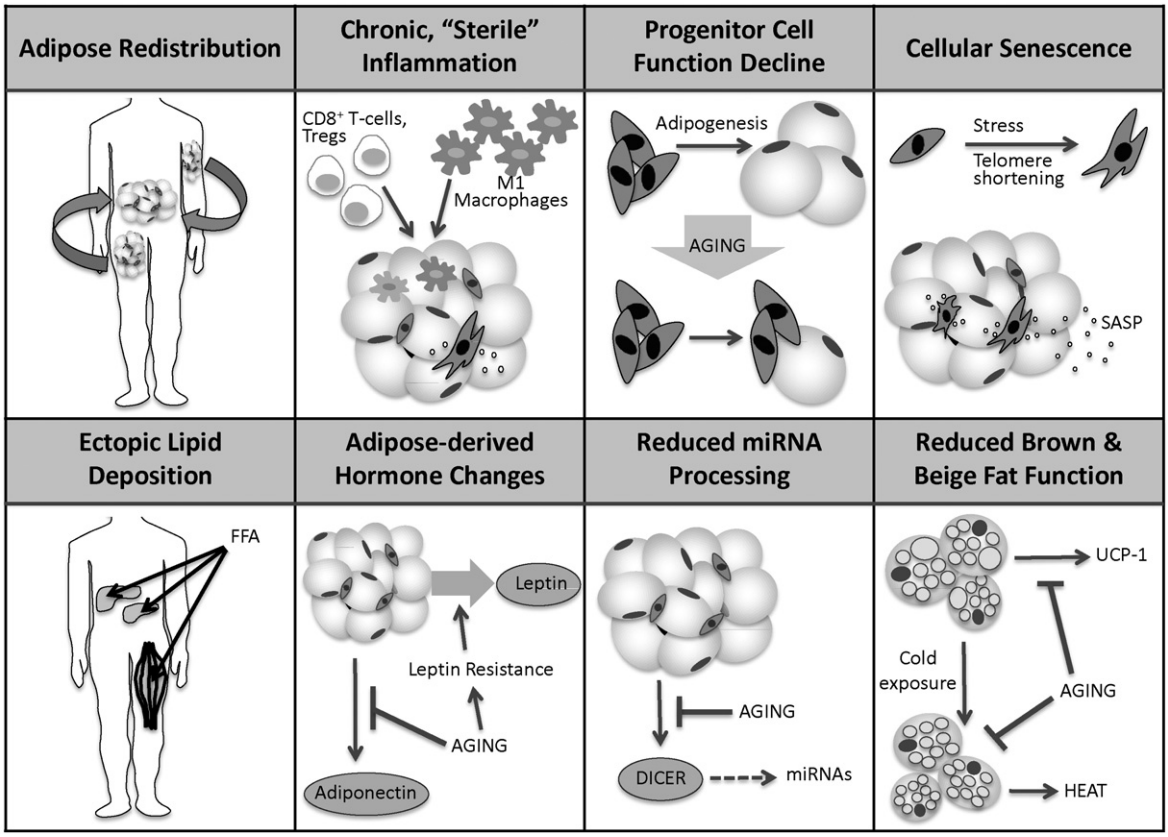

Fig. 1. Adipose tissue changes with aging. With aging, adipose tissue undergoes numerous changes, affecting distribution, inflammatory status, progenitor function, senescent cell burden, deposition of lipid in ectopic sites, adipose-derived hormone production and action, miRNA processing, and brown and beige adipose function.

et al., 1999). This age-related increase in adiposity has been suggested to underlie reduced insulin sensitivity with age (Karakelides et al., 2010). From middle age, the distribution of adipose tissue shifts from primarily subcutaneous depots to visceral depots, which are more closely associated with development of metabolic syndrome and insulin resistance (Fox et al., 2007; Preis et al., 2010). In addition to metabolic effects, redistribution of adipose tissue is also partially responsible for esthetic changes with aging that are related to subcutaneous fat loss, such as sunken cheeks, thinning of the skin over the hands and legs, and increased prominence of wrinkles (Coleman and Grover, 2006; Donofrio, 2000).

The location and function of adipose tissue have been suggested to be more important than the absolute amount of adipose tissue in terms of its effect on insulin sensitivity (Jensen, 2008). It is also important to note that insulin resistance occurs even in individuals with normal BMI, not only in obese individuals (McLaughlin et al., 2004). Gluteofemoral adipose tissue is associated with increased insulin sensitivity and lower diabetes and cardiovascular disease risk, while increased waist circumference, which reflects visceral adipose mass, is associated with insulin resistance and metabolic syndrome (Manolopoulos et al., 2010; Snijder et al., 2003). In fact, waist to hip ratio may be a better predictor of 5-year mortality than BMI alone (Folsom et al., 1993). In the elderly, the ratio of limb fat to trunk fat was found to correlate positively to insulin sensitivity, while no differences in percent body fat or absolute amount of trunk fat were found in the same groups (Gavi et al., 2007). Increased limb:trunk fat ratio, but not limb fat or trunk fat independently, was also correlated with higher levels of adiponectin, an adipose-derived hormone associated with improved insulin sensitivity (Gavi et al., 2007). This indicates that the distribution of adipose tissue may be more important than the amount of adipose tissue in the regulation of adiponectin levels.

Subcutaneous and visceral adipose depots are very different in terms of their effects on metabolism (Atzmon et al., 2002; Jensen, 2008; Tchkonia et al., 2013a). In mice, transplantation of subcutaneous fat into the visceral depot of recipient mice caused improvements in glucose homeostasis as well as decreased body weight and fat mass, whereas the opposite experiment, visceral adipose tissue transplanted to the subcutaneous depot of recipient mice, had little effect (Tran et al., 2008). Adipose tissue dysfunction is likely to originate in subcutaneous fat, which is a larger depot than visceral fat in young individuals. With age, macrophages accumulate in subcutaneous fat, but no significant change is seen in visceral depots, which suggests that the sentinel site of inflammation with aging is likely the subcutaneous fat (Jerschow et al., 2007; Lakowa et al., 2015). Telomere length is also shorter in subcutaneous *versus* visceral adipose tissue, independently of BMI or diabetic status, and this difference is localized to the stromovascular fraction, not adipocytes (Lakowa et al., 2015; Tchkonia et al., 2006b). Accordingly, subcutaneous but not visceral adipose telomere length shortens with aging, and also correlates with obesity and diabetes (Lakowa et al., 2015). This shorter basal length and age-related shortening of telomeres in subcutaneous depots may make subcutaneous adipose tissue a key contributor to increasing senescent cell burden with aging. Because of the impact that subcutaneous fat has on systemic metabolism, sentinel changes in subcutaneous fat with aging could be the harbinger for metabolic dysfunction, and represent an opportunity for intervention that could have significant impact on age-related disease.

Identification of the amount and distribution of adipose tissue that is healthy in elderly individuals has been difficult. Loss of subcutaneous fat is a common feature with advancing age (Sepe et al., 2011). Although visceral fat is associated with worse metabolic phenotypes in younger individuals, the maintenance of adipose tissue seems to be beneficial in old age, sometimes independently of its location. For example, one

study found that elderly individuals classified as "robust" according to their functional status had increased visceral and pericardial adipose tissue, normally considered to be sites of ectopic lipid deposition, compared to their "frail" counterparts (Idoate et al., 2015). However, increased waist diameter was associated with the highest frailty within each BMI category in another study, indicating that adipose distribution favoring visceral adipose is still harmful when normalized for total adipose tissue (Hubbard et al., 2010). The relationship between frailty and BMI is U-shaped, with extremely low and extremely high BMI predicting frailty and mortality (Allison et al., 1997; Blaum et al., 2005; Hubbard et al., 2010). Interestingly, certain interventions that improve frailty in mice also maintain adipose tissue mass (Xu et al., 2015a, 2015b).

2.2. Chronic, sterile inflammation

Sterile inflammation, or the presence of inflammation in the absence of known, identifiable infection, is a common feature of aging and is certainly increased in aging adipose tissue. Adipose tissue is thought to be a major contributor to the chronic, low-grade inflammation seen in aging (Tchkonia et al., 2010; Wu et al., 2007). A variety of endogenous substances or stimuli, for example hypoxia, excess nutritional elements such as fatty acids, or products of cell death, which is persistent at a low level in obesity, may trigger sterile inflammation in adipose tissue (Chen and Nunez, 2010; Itoh et al., 2011). Adipose-derived cytokines and chemokines, termed adipokines, play a key role in immune cell recruitment to adipose tissue. Adipose tissue macrophages (ATMs) represent a significant source of pro-inflammatory substances such as IL-6 with aging (Tilg and Moschen, 2006; Wu et al., 2007). Numbers of ATMs increase in human subcutaneous fat until 30–35 years of age and then slightly decline in lean individuals (Ortega Martinez de Victoria et al., 2009). ATMs in visceral adipose tissue do not change substantially in number during aging, but the ratio of pro-inflammatory M1 macrophages to anti-inflammatory M2 macrophages appears to increase with aging (Garg et al., 2014; Lumeng et al., 2011). Adipose tissue T cell populations also change with aging. Specifically, $CD4^+$ T-lymphocytes, particularly regulatory T cells (Tregs), increase in visceral adipose tissue in aging mice, along with an increase in $CD8^+$ T-cells (Lumeng et al., 2011). Senescent cells also accumulate significantly with age in adipose tissue. Through their senescence-associated secretory phenotype (SASP), senescent cells are themselves the source of many pro-inflammatory cytokines and chemokines (Lumeng et al., 2011; Xu et al., 2015a, 2015b).

In addition to the chronic changes in adipose inflammatory signaling and macrophage populations with aging, adipose tissue immune system components can also undergo acute changes in response to nutrient status, stress, or other short-term changes. For example, M2/M1 macrophage ratios have been shown to increase in response to a 24-h fast in mice (Asterholm et al., 2012). Interestingly, these acute changes are dampened in mice on a high fat diet, suggesting an impairment of adipose tissue to respond to acute changes when under metabolic stress (Asterholm et al., 2012).

2.3. Progenitor cell function decline

Adipose tissue is composed of many different cell types, generally divided into two fractions: the adipocyte fraction (AF), which contains primarily mature adipocytes, and the stromovascular fraction (SVF), which comprises progenitor cells, lymphocytes, endothelial cells, pericytes, and fibroblasts. Adipose progenitor cells isolated from old individuals have reduced function and adipogenic potential compared to progenitors isolated from their young counterparts (Caso et al., 2013; Karagiannides et al., 2001; Tchkonia et al., 2010). This is also seen in progenitors isolated from obese subjects when compared to lean age-matched controls (Tchkonia et al., 2010).

Preadipocytes acquire insulin sensitivity during differentiation to adipocytes through increased expression of the critical transcription factors peroxisome proliferator-activated receptor gamma (PPARγ) and CCAAT/enhancer binding protein alpha (C/EBPα) (Hamm et al., 1999). Preadipocytes that are less able to differentiate appear with aging and may contribute to the limited ability of adipose tissue to be insulin responsive. This may be a significant contributor to the insulin resistance of old age, in addition to contributions from other organs (*e.g.* pancreas, skeletal muscle, and liver) (Tchkonia et al., 2010).

Additionally, the replication and differentiation of preadipocytes is crucial for hyperplasia and hypertrophy, the two ways that adipose tissue responds to an increased demand for energy storage. Decline in adipogenic potential has been postulated to drive insulin resistance by limiting the ability of adipose tissue to expand in the face of excess nutrients (Danforth, 2000). In addition, inability to recruit progenitor cells to the adipogenic lineage to execute hyperplasia can lead instead to hypertrophy of existing adipocytes. The resulting increase in adipocyte size has been associated with insulin resistance, especially in obesity (Gustafson et al., 2015). Limited plasticity of adipose tissue with aging, leading to adipocyte hypertrophy in the face of nutrient excess, may be one mechanism by which older individuals are predisposed to insulin resistance (Kim et al., 2014).

Targeting age-related changes in adipose tissue, such as cellular senescence, has some promise in improving adipose progenitor function (Xu et al., 2015a) and can prevent or reverse age-related fat loss in mice (Xu et al., 2015a). Individuals with Hutchinson–Gilford progeria syndrome suffer from lipodystrophy, which may be explained in part by progenitor exhaustion in the adipose tissue (Mansilla et al., 2011; Mazereeuw-Hautier et al., 2007). Similarly, mice with progeria have dysfunctional progenitor cells and lipodystrophic features, which may be attributable to progenitor dysfunction, cellular senescence, or immune clearance of cells with persistent DNA damage (Baker et al., 2008; Karakasilioti et al., 2013).

In addition to having implications for regenerative medicine, as will be discussed, adipose progenitor cell function plays a crucial role in lipid handling, adipose tissue expansion, and insulin sensitivity. Further study is needed to understand the role that age-related adipose tissue progenitor cell decline plays in age-related metabolic disease. Progenitor cell function decline with age in other organs, such as skeletal muscle, may also have contributory or independent roles in age-related insulin resistance. The respective contributions of reduced adipogenesis, *versus* dysregulation of lipid metabolism and/or glucose metabolism, to the development of age-related insulin resistance are unknown. In addition, it is not known what percentage of progenitor cells become dysfunctional with age, what threshold of progenitor dysfunction is necessary to cause physiologic changes such as lipodystrophy or insulin resistance, or whether progenitor dysfunction alone is sufficient to cause such changes (Kirkland and Dobson, 1997; Kirkland et al., 2002).

2.4. Cellular senescence

Adipose tissue is a site of considerable senescent cell accumulation, in the settings of both obesity and aging (Tchkonia et al., 2010). Cellular senescence is an essentially irreversible cell fate, in which cells stop dividing in response to an insult such as telomere shortening, oncogene activation, or metabolic stress (Tchkonia et al., 2013b). Senescent cells adopt an enlarged phenotype, exhibit positivity for senescence-associated beta galactosidase, and can secrete a multitude of chemokines, cytokines, growth factors, and matrix metalloproteinases, comprising the SASP (Coppe et al., 2008). SASP factors are expressed *in vivo*, as demonstrated in experiments where PAI-1 and IL-6 expression were increased in p16-positive cells isolated from mouse inguinal fat (Baker et al., 2011). In addition, the SASP has been identified *in vivo* in mouse models of wound healing, liver fibrosis, and embryonic development (Demaria et al., 2014; Krizhanovsky et al., 2008; Storer et al., 2013). The composition of the SASP may vary based on the

senescent cell type, tissue, or senescence inducer, an area that merits further research.

In co-culture experiments, senescent cells have been shown to affect the function of adipose-derived progenitors as well as impair insulin sensitivity of adipose tissue (Xu et al., 2015a, 2015b). Therapeutic targeting of the SASP may be beneficial in alleviating age-related insulin resistance (Xu et al., 2015a, 2015b). We recently reported that removing senescent cells from older mice allows for improved adipogenesis (Xu et al., 2015a). Removing senescent cells might therefore facilitate adipose tissue expansion in the face of nutrient excess, concurrent with improved insulin sensitivity, promoting a "metabolically healthy obesity" phenotype. Indeed, adipose tissue expansion occurs in humans after treatment with thiazolidinediones, which activate PPARγ, or JAK1/2 inhibitors, which we recently reported to be SASP inhibitors (Xu et al., 2015b), both of which improve insulin sensitivity (Fonseca, 2003; Verstovsek et al., 2010), On the other hand, senescent cell removal may allow for proper nutrient handling, mitochondrial function, and lipolysis that would limit expansion. However, the effects of senescent cell removal on adipose tissue dynamics have yet to be tested.

Strategies for selective elimination of senescent cells are beginning to emerge (Roos et al., 2016; Zhu et al., 2015a, 2015b). These advances follow the discovery that genetic clearance of senescent cells in mice is effective in preventing or reversing age-related dysfunction including loss of subcutaneous adipose tissue (Baker et al., 2011; Xu et al., 2015a). Because strategies to eliminate senescent cells generally only remove a portion of senescent cells, the effects of removing all senescent cells from a tissue is unknown. However, reduction of 30–70% of senescent cells does not appear to have detrimental effects on health of experimental animals (Baker et al., 2011; Demaria et al., 2014). In addition, several beneficial roles of senescent cells have been identified, for example in wound healing, which may have implications for adipose tissue remodeling (Demaria et al., 2014). If they exist, detrimental effects of senescent cell clearance could be avoided through the use of strategic, intermittent treatment, which is possible with senolytic therapies (Roos et al., 2016). This is in contrast to SASP inhibitors such as JAK1/2 inhibitors, which would need to be continually administered to exert their effects. The high burden of senescent cells found in adipose tissue, and its role at the nexus of aging, obesity, and insulin resistance, makes adipose tissue senescence a promising target for alleviating age-related metabolic dysfunction (Palmer et al., 2015; Tchkonia et al., 2013b).

2.5. Ectopic lipid deposition

Aged preadipocytes are less able to differentiate and properly store lipid, leading to a spillover of toxic free fatty acids that can cause ectopic lipid deposition in sites such as the liver, muscle, and pancreas (Cartwright et al., 2007; Guo et al., 2007; Marcus et al., 2010; Tchkonia et al., 2006a). This infiltration of lipid into non-adipose tissues can cause lipotoxicity and accelerate age-related disease. For example, ectopic lipid deposition may contribute to the increased prevalence of non-alcoholic fatty liver disease with aging, in addition to other risk factors such as increased fasting glucose and serum triglycerides (Koehler et al., 2012). In the pancreas, lipotoxicity can cause apoptosis of beta cells, having a significant impact on an individual's ability to produce insulin (Unger and Zhou, 2001). Intermuscular adipose tissue, which increases with aging, can contribute to declining muscle quality, a feature of sarcopenia and frailty (Delmonico et al., 2009). Some have proposed that the increase in visceral adipose tissue with aging is also a type of 'ectopic' lipid deposition, resulting from overflow of toxic free fatty acids due to the inability of subcutaneous depots to properly store lipid due to age-related dysfunction (Jensen, 2008). Another site of fat infiltration with age is the bone marrow, where adipocytes are thought to have a negative impact on hematopoiesis, which could have implications for bone marrow transplantation in patients of advanced age (Naveiras et al., 2009).

2.6. Adipose-derived hormone secretion and sensitivity change with age

Prevalence of insulin resistance and type II diabetes risk increases with age, mainly due to decreased peripheral insulin sensitivity and age-related pancreatic beta cell dysfunction (Chen et al., 1985; Defronzo, 1979). In addition to insulin resistance, aging predisposes to resistance to other metabolic hormones, such as leptin. Leptin levels increase with aging in rodents and humans, suggesting that leptin sensitivity declines with age (Gabriely et al., 2002). Old rats given recombinant leptin do not have a decrease in visceral fat, as occurred in young rats, and do not suppress leptin gene expression in adipose tissue as well as young rats (Ma et al., 2002). In contrast to other adipose-derived hormones, adiponectin, which is produced by mature adipocytes, is positively correlated with metabolic health. Adiponectin improves preadipocyte differentiation and enhances insulin sensitivity (Fu et al., 2005). Adiponectin levels decline with aging, but are positively correlated with longevity. For example, one study found that centenarians had higher levels of circulating adiponectin than BMI-matched young controls (Atzmon et al., 2008). Adiponectin signaling has therefore been explored as a therapeutic target in obesity and diabetes (Yamauchi and Kadowaki, 2013). More research is needed to determine whether modulation of adipose-derived hormones could have an impact on age-related metabolic dysfunction or other age-related diseases.

2.7. Adipose tissue miRNA processing declines with age

Increased stochasticity in gene expression with aging occurs in several tissues and may contribute to the loss of resilience, or ability to properly respond to external stressors, with age (Raj and van Oudenaarden, 2008). Differential expression of one particular class of gene regulatory elements, microRNAs (miRNAs), is a generalized phenomenon in aging and has been identified in multiple tissues including adipose, brain, liver, and skeletal muscle (Pincus et al., 2011). Expression of Dicer, which processes miRNAs, declines with aging in the adipose tissue of mice, the intestine (primary fat storage organ) of *C. elegans*, and human preadipocytes (Mori et al., 2012). In mice, an adipose-specific knockout of dicer, with reductions of dicer expression in subcutaneous, perigonadal, and brown adipose tissues, caused lipodystrophy. These mice exhibited decreased white adipose tissue mass and "whitening" of the brown adipose tissue, as well as inflammation and insulin resistance (Mori et al., 2014). Remarkably, dicer was also found to be downregulated in patients with HIV, who exhibit a similar partial lipodystrophy syndrome. Caloric restriction, which extends lifespan, prevented age-related downregulation of dicer, and knockdown of dicer led to premature senescence in murine preadipocytes (Mori et al., 2012). Downregulation of miRNAs may impair the ability of adipose tissue to respond to metabolic stress or fluctuation and may play a role in age-related metabolic dysfunction. Therefore adipose miRNA processing may represent a useful target for drugs that modulate fundamental aging processes and age-related metabolic disease (Mori et al., 2012).

2.8. Brown and beige adipose changes with age

Although activation of brown adipose tissue is known to occur most significantly in response to cold exposure, it may also offer a defense against age-related weight gain by increasing energy expenditure. A significant amount of functional brown fat is present in adult humans in the interscapular fat depot (Cypess et al., 2009; van Marken Lichtenbelt et al., 2009; Virtanen et al., 2009), which shares characteristics of beige fat, rather than classical brown fat (Wu et al., 2012). UCP1 expression declines with aging in rodents in subcutaneous white fat, suggesting that brown-like adipose tissue function ("beige" or "brite" adipocytes) is reduced with aging (Rogers et al., 2012; Tan et al., 2015). Additionally, brown fat itself may become dysfunctional with age (Saito et al., 2009; Yamashita et al., 1999; Yoneshiro et al., 2011).

The absolute amount of brown adipose tissue is decreased in elderly humans, and its activation as measured by FDG-PET during cold exposure is dampened in old *versus* young individuals (Saito et al., 2009). Whether loss of brown-like features of adipose tissue might predict the development of insulin resistance with aging is not clear. In mice, age-related decline in BAT function is prevented by dietary restriction, which is known to delay age-related dysfunction in other tissues (Valle et al., 2008). Brown fat may play a role in preventing age-related dysfunction and disease, but this remains to be established (Mattson, 2010).

3. Adipose plays an integral role in longevity

3.1. Interventions that improve longevity impact adipose tissue

The majority of interventions that are known to affect lifespan, including single gene mutations (*e.g.*, in the GH/IGF-1 axis) and dietary or pharmacologic interventions (*e.g.*, caloric restriction, metformin, rapamycin, 17α-estradiol, acarbose) affect fat tissue directly or indirectly, often through pathways related to nutrient signaling or processing. For example, growth-hormone-deficient and -resistant mice, which exhibit lifespan extension, have less ectopic lipid deposition, reduced cellular senescence in adipose tissue, and improved adipose progenitor function (Stout et al., 2014). Caloric restriction, which extends lifespan in species ranging from flies to primates, acts partially through a decrease in total adipose tissue mass, in addition to intracellular mechanisms within adipose tissue such as decreasing inflammation, increasing autophagy and DNA repair mechanisms, reducing cellular senescence, and preventing age-related changes in gene expression (Fontana and Klein, 2007; Linford et al., 2007). 17α-estradiol, which has lifespan extension effects in male mice, reduces inflammation in visceral adipose and decreases visceral adiposity (Stout et al., 2016). Metformin, which causes modest yet significant lifespan extension in rodents and may have lifespan-extending effects in humans, reduces body mass in humans mainly through a decrease in adipose tissue (Martin-Montalvo et al., 2013; Stumvoll et al., 1995). The effects of metformin on lifespan in humans have recently been demonstrated by a surprising increase in survival of diabetic patients treated with metformin beyond that of age-matched, non-diabetic controls (Bannister et al., 2014). However, these data should be interpreted in light of a 4–9% rate of undiagnosed type II diabetes in the general population over 65, the onset of which can occur years before symptoms emerge or a diagnosis is made (Harris et al., 1992; Menke et al., 2015). In sum, these examples indicate that adipose tissue is a useful target for the development of therapies to extend healthspan and alleviate or delay age-related disease.

3.2. Adipose-specific interventions affect longevity

In lower animals, lifespan-extending mutations that are restricted to adipose tissue can confer the same lifespan extension as whole-organism mutations (Katic et al., 2007). Other than the brain, adipose tissue is arguably the only tissue in which organ-specific interventions extend lifespan. For example, reduction of insulin/insulin-like growth factor signaling specifically in the fat body of female Drosophila extends lifespan (Giannakou et al., 2004). Fat-specific insulin receptor knockout (FIRKO) mice are leaner and exhibit a significant lifespan extension, as also occurs in whole-body insulin receptor knockout animals (GIRKO). Because FIRKO mice have similar food intake to WT mice, this suggests that adiposity itself has some effect on longevity (Bluher et al., 2003). Bariatric surgery, which causes caloric restriction and reduction in adipose tissue mass, reduces mortality in severely obese individuals (Sjostrom et al., 2007). Interestingly, it does not seem that surgical removal of adipose tissue in humans has the same benefits for metabolism as reduction of adipose tissue by other methods such as caloric restriction or exercise (Klein et al., 2004). However, these experiments have been focused on removal of subcutaneous fat by liposuction. The effects of removing adipose from different depots, such as visceral adipose tissue, may have different effects. For example in rats, selective surgical removal of visceral adipose tissue increased median and maximum lifespan (Muzumdar et al., 2008). Removal of omental adipose also showed beneficial effects on insulin sensitivity in healthy dogs (Lottati et al., 2009). Experiments to remove omental adipose tissue in humans were conducted in obese, diabetic individuals undergoing gastric bypass surgery and did not find additional beneficial effect on metabolic health (Fabbrini et al., 2010; Herrera et al., 2010). However, it may be possible that removal of visceral adipose tissue would be beneficial in different contexts, for example in aging or before the development of diabetes (Tchkonia et al., 2013a). Therefore more research is needed to determine whether visceral adipose tissue is a useful target for interventions to alleviate age-related metabolic diseases in humans (Huffman and Barzilai, 2009). Similarly, little is known about the effects that interventions to reduce adipose tissue mass or create negative energy balance, such as exercise, bariatric surgery, or calorie restriction, may have on markers of aging, for example cellular senescence. Research is underway to address these questions.

4. Obesity: accelerated aging?

4.1. Markers of aging increase in obesity

Several changes seen in aging adipose tissue also occur in the setting of obesity. For example, plasma and adipose tissue from obese mice exhibit increased oxidative stress compared to lean mice, and systemic markers of oxidative stress are elevated in obese humans (Furukawa et al., 2004). Adipose tissue from obese individuals also contains an increased burden of senescent cells compared to lean age-matched controls (Minamino et al., 2009; Tchkonia et al., 2010). In addition, telomere shortening is found in white blood cells and in subcutaneous adipose tissue from obese patients (Valdes et al., 2005). As in aging, chronic, low-grade sterile inflammation of adipose tissue develops in obesity, with elevated production of adipokines and decreased adiponectin levels (Fernandez-Real et al., 2003). Brown adipose UCP1 expression also decreases in obesity and is lower in obese humans with diabetes than obese humans without diabetes (Timmons and Pedersen, 2009). More research is needed to determine the relationship of these markers of aging to the development of obesity, namely to understand whether they have a pathogenic role in obesity, or whether they are markers of established disease. Another interesting question is whether or not markers of aging, for example senescent cell numbers, are lower in individuals with "healthy" obesity *versus* obese individuals with metabolic syndrome. Efforts to understand aging mechanisms in adipose tissue may inform strategies to improve outcomes in obesity, and *vice versa*.

4.2. Obesity predisposes to age-related diseases including cancer

Age is the leading risk factor for most chronic diseases, including dementia, cardiovascular disease, type II diabetes, and cancer, even in lean individuals. Age-related diseases are more prevalent in obese individuals at younger ages than lean individuals, suggesting that obesity predisposes to age-related disease and is in some ways a state of premature aging. Might adipose tissue dysfunction, seen in both aging and obesity, be the common denominator? An increased understanding of adipose tissue dysfunction with aging could help in understanding the predisposition to age-related diseases in obesity, and in identifying strategies to prevent these comorbidities.

As in aging, there is a significantly increased risk of cancer deaths in obesity, and this is not due to an increase in hormonally regulated cancers alone (De Pergola and Silvestris, 2013; Samanic et al., 2004; Wolk et al., 2001). Rather, it is due to a general increase in age-related cancers. Individuals with a BMI over 40 have over 50% higher cancer death rates

than their lean counterparts, and 14–20% of cancer deaths in individuals over 50 years old are estimated to be due to obesity (Calle et al., 2003). Obesity-induced inflammation in adipose tissue may be one driver of cancer risk, with certain adipokines (*e.g.*, CCL2, VEGF, IL-6, and IL-8) serving as chemoattractants that enhance migration of tumor cells and support metastasis (Gilbert and Slingerland, 2013). In addition, senescent cells, which increase in aging and obesity, are known to potentiate tumorigenesis of epithelial cells, likely mediated by SASP components (Laberge et al., 2015; Parrinello et al., 2005; Tchkonia et al., 2010). These examples highlight how fundamental aging mechanisms that occur with greater frequency in obesity could help to drive tumorigenesis.

Interestingly, calorie restriction, which is known to decrease tumor incidence in experimental animals, was unable to affect tumor incidence when hunger signals were dampened by blocking neuroendocrine pathways (Minor et al., 2011). This hints that the relationship of nutrient intake and cancer incidence is complicated and may be affected more by the post-absorptive state than has been previously appreciated. Accelerated aging in obesity may not be solely due to the effects of nutrient excess and body composition, but may also be affected by mechanisms in place during the post-absorptive state.

5. Treating age-related adipose tissue dysfunction

5.1. Targeting age-related adipose tissue dysfunction in type II diabetes

Experimental strategies to target adipose tissue-specific mechanisms such as macrophage infiltration and adipokine secretion have shown some efficacy in improving metabolic function in mouse models of diabetes (Kanda et al., 2006; Lumeng et al., 2007; Okada-Iwabu et al., 2013). Senescent cell burden is increased in the adipose tissue of diabetic patients, and senescent cells have been identified as a potentially useful therapeutic target in type II diabetes, especially in the setting of novel senolytic agents (Palmer et al., 2015; Tchkonia et al., 2013b; Xu et al., 2015a; Zhu et al., 2015a, 2015b). On the other hand, some of the most effective therapeutics for diabetes, especially metformin, have significant effects on fundamental aging mechanisms, and show lifespan-extending effects in rodents (Martin-Montalvo et al., 2013). This impact on longevity may also be present in humans as discussed previously (Bannister et al., 2014). Treatment of age-related adipose tissue dysfunction may impact diabetes in several ways, for example prevention of lipotoxicity by improving adipogenic capacity and lipid storage, or improvement of peripheral insulin sensitivity by reducing pro-inflammatory adipokine release.

5.2. Impact of aging on adipose-based regenerative strategies

Adipose-derived progenitors have been increasingly utilized in regenerative medicine strategies, and could overtake bone marrow-derived stem cells (BMSCs) as an abundant source of progenitor cells (Strioga et al., 2012; Zuk et al., 2002). Adipose-derived mesenchymal stem cells (ADSCs) have been suggested to be superior to BMSCs in some orthopedic applications (Wyles et al., 2015). However, most studies of this type have been conducted in subjects less than 60 years of age. It is possible that effects of aging may complicate this picture, and that strategies to mitigate effects of aging on these cells will need to be employed to optimize their use in older individuals. Progenitors isolated from different adipose depots within the same individual have different properties, and these properties can be affected by aging (Schipper et al., 2008; Tchkonia et al., 2013b). Aging is a significant hurdle for the advancement of regenerative medicine strategies, because many patients needing this type of intervention will be members of the growing elderly population. It is possible that age-modifying treatments will need to be given to patients before isolating progenitor cells, or to cells *in vitro* before being returned to the patient (Fig. 2). In the context of allogeneic applications, transplantation of young or revitalized progenitor cells into old recipients may also have limited efficacy due to the effects of an aging microenvironment (Conboy et al., 2005).

For example, TGFβ family members interfere with stem cell function and have been implicated in age-related progenitor dysfunction (Carlson et al., 2009; Conboy et al., 2015). A member of the TGFβ superfamily, activin A, increases in plasma with aging, and is secreted by senescent adipose progenitor cells. Blocking activin A *in vitro* using neutralizing antibodies or receptor blockers improves adipogenic potential of adipose-derived progenitor cells (Xu et al., 2015a). JAK 1/2 inhibitors prevent activin A secretion by senescent cells, and reduce circulating activin A *in vivo*, as does senescent cell elimination in old INK-ATTAC mice (Xu et al., 2015a). JAK 1/2 inhibitors restored fat mass and insulin sensitivity in old mice, and also restored adipogenic capacity of adipose-derived progenitors to express transcription factors necessary for differentiation (Xu et al., 2015a). Thus, TGFβ family members secreted by senescent cells contribute to adipose-derived progenitor dysfunction, and this is amenable to pharmacologic intervention. Administration of therapies that target age-related dysfunction, for example senolytics, to patients receiving transplanted cells may mitigate host effects that could dampen the regenerative potential of transplanted cells (Fig. 2) (Kirkland and Tchkonia, 2015; Zhu et al., 2015a, 2015b).

Cell-free regenerative strategies represent a unique opportunity to circumvent these aging "seed *vs.* soil" barriers by distilling the therapeutic potential of progenitor cells into deliverables not containing cells. For example, secretome components or exosomes could be administered, avoiding the use of cells isolated from aging patients (Katsuda et al., 2013; Ranganath et al., 2012). More investigation of these regenerative strategies is necessary to determine their efficacy in age-related disease.

Significant work is needed in preclinical and human studies to characterize ADSCs isolated from aged and obese individuals. Aging effects on progenitor quality require more study, and potential therapeutics to mitigate these effects to enhance regenerative potential should be carefully tested in preclinical models. Understanding the effects that aging has on regenerative capacity of progenitor cells as well as the potential of a recipient to garner benefit from these therapies will be essential for application of regenerative medicine approaches to the elderly population.

6. Looking forward: adipose tissue as a therapeutic target in aging

Many classical aging mechanisms, for example cellular senescence, chronic inflammation, and mitochondrial dysfunction, occur in adipose tissue. Therefore, emerging interventions that target fundamental aging mechanisms should have an effect on adipose tissue. This opens the possibility of using adipose tissue as an indicator of the efficacy of such therapies. In addition, adipose tissue itself may prove to be a worthwhile target for novel technologies that target fundamental aging mechanisms. Therapies that extend lifespan and target fundamental aging mechanisms tend to have major effects on adipose tissue. Conversely, it may be possible to use our knowledge of adipose tissue aging in order to design therapies that specifically target aging mechanisms that operate in fat. Because adipose tissue function is so intricately linked to insulin sensitivity and inflammation, targeting adipose tissue aging could be a new frontier for therapies to combat age-related type II diabetes, metabolic syndrome, and their complications. Frailty and age-related fat loss could be other applications of therapies that specifically target fundamental aging processes in adipose tissue. Better understanding of adipose tissue aging and its effects on progenitor cell function could also have broad implications for regenerative medicine. Thus, adipose tissue aging is valuable for the study of basic aging mechanisms, and is a potent therapeutic target for the development of new therapies to combat effects of aging and age-related disease.

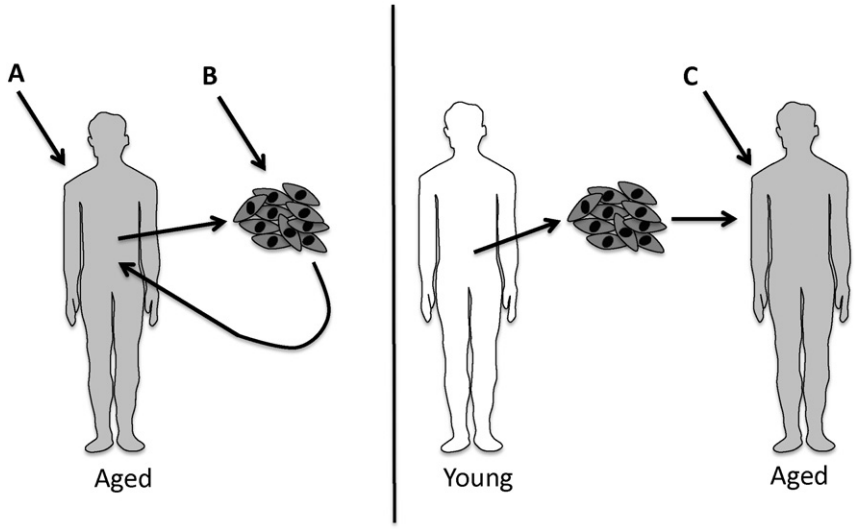

Fig. 2. Possible points of intervention for adipose-derived stem cell therapies in aged individuals. Adipose-derived stem cells are becoming increasingly utilized in regenerative medicine. Many patients who would benefit from such therapies are elderly, and the effects of aging on adipose tissue and progenitor function may reduce efficacy of these therapies. This may be due to both inherent dysfunction of isolated progenitor cells and the aged microenvironment of the recipient. Strategies to mitigate effects of aging on these cells may need to be used to optimize their use in older individuals. Points at which such strategies could be employed include (A) before isolating progenitor cells, (B) *in vitro* before returning cells to the patient, and (C) in allogeneic applications, administration of age-modifying therapy to the recipient before transplantation of young or revitalized progenitor cells.

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