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Review

Obesity and aging: Molecular mechanisms and therapeutic approaches

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ABSTRACT

The epidemic of obesity is a major challenge for health policymakers due to its far-reaching effects on population health and potentially overwhelming financial burden on healthcare systems. Obesity is associated with an increased risk of developing acute and chronic diseases, including hypertension, stroke, myocardial infarction, cardiovascular disease, diabetes, and cancer. Interestingly, the metabolic dysregulation associated with obesity is similar to that observed in normal aging, and substantial evidence suggests the potential of obesity to accelerate aging. Therefore, understanding the mechanism of fat tissue dysfunction in obesity could provide insights into the processes that contribute to the metabolic dysfunction associated with the aging process.

Here, we review the molecular and cellular mechanisms underlying both obesity and aging, and how obesity and aging can predispose individuals to chronic health complications. The potential of lifestyle and pharmacological interventions to counter obesity and obesity-related pathologies, as well as aging, is also addressed.

1. Introduction

Obesity is characterized by the excessive accumulation of adipose tissue in the body. Fundamentally, it is a condition of energy imbalance caused by an excessive calory intake over its expenditure. According to the World Health Organization, in 2016, more than 650 million adults (individuals over 18 years old) were obese, and in 2015, 36.5% of the adult population of the United States alone were estimated to be obese (Greenberg and Obin, 2006). The Centers for Disease Control and Prevention (CDC) indicates that in 2017–2018 the prevalence of obesity among young adults (age range: 20–39 years), middle-aged adults (age range: 40–59 years), and elderly individuals (age range: 60 years and above) was 40.0%, 44.8%, and 42.8%, respectively (CDC, 2020). Obesity is a major public health concern and a predictor of poor clinical outcome (Marseglia et al., 2014). It is estimated that at least 2.8 million people die every year from obesity-associated complications (Fontaine et al., 2003). Obesity is also associated with decreased life expectancy due to the dramatically increased risk of comorbidities (Tchkonia et al., 2010; Tzanetakou et al., 2012; Yazdi et al., 2015).

The metabolic risk related to obesity is, at least in part, associated with common diabetes and cardiovascular disease (CVD) risk factors, including hyperglycemia, hypertension, and dyslipidemia. This cluster of metabolic risk factors is called “metabolic syndrome” (Rochlani et al., 2017). Obesity is also strongly associated with insulin resistance (Ferrannini et al., 1997), which is a key risk factor for the development of diabetes and may also be an independent risk factor for CVD (Reaven, 1988; Rutter et al., 2005; Despres et al., 1996; Bonora et al., 1997).

Obesity-related diseases appear to be associated with the acceleration of cellular processes observed during normal aging (Ahima, 2009). Inflammation and oxidative stress seem to be important mediators of this association. For instance, one of the major hallmarks of aging is increased levels of pro-inflammatory molecules, which in turn is an important cause of the adipose tissue enlargement that accompanies obesity. The chronic inflammatory cellular environment that is associated with the obese adipose tissue can, in turn, lead to increased production of reactive oxygen species (ROS) which can overwhelm oxidative stress defenses, resulting in oxidative stress and mitochondrial dysfunction, which results in further ROS formation and exacerbation of

Abbreviations: CVD, cardiovascular disease; IL, interleukins; FFA, free fatty acids; ROS, reactive oxygen species; RNS, reactive nitrogen species; TG, triglycerides; mtDNA, mitochondrial DNA; CRP, C-reactive protein; SASP, senescence-associated secretory phenotype; IGF, Insulin-like growth factor; GH, growth hormone; AD, Alzheimer’s Disease; PD, Parkinson’s Disease; Aβ, amyloid β; BMI, body mass index; CR, caloric restriction; IF, intermittent fasting; ADF, alternate day fasting; PS, phytosterols and phytostanol; TZDst, hiazolidinediones; HFD, high-fat diet; NAFLD, nonalcoholic fatty liver disease.

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inflammatory processes (de Mello et al., 2018).

The striking similarities between chronic obesity-related and normal aging-related pathologies and organ deterioration suggest that obesity accelerates the onset of age-associated diseases, such as diabetes, CVD, cancer, and neurodegenerative diseases (Tchkonia et al., 2010; Zhang et al., 2015; Salmon, 2016).

This review aims at critically discussing the biochemical, molecular, and cellular similarities between events that accompany both obesity-induced and aging-associated tissue dysfunction and how such understanding can help repurposing therapeutics designed for one process to tackle the other. An in-depth evaluation of the intricate connections between obesity and aging can help to better understand the aging process and pave a new path toward developing novel therapeutic strategies to treat obesity-associated comorbidities, including obesity-related cancers.

2. Adipose tissue

Over the past decades, our understanding of the physiological role of the adipose tissue has been greatly redefined and expanded. It is now widely recognized that the adipose tissue is a complex and highly active metabolic and endocrine organ, that plays a key role in regulating energy homeostasis (Marseglia et al., 2014; Ahima and Flier, 2000; Fruhbeck et al., 2001).

Adipocytes, the major cell types in the adipose tissue, are responsible for the synthesis of fatty acids (lipogenesis) and their storage in the form of triglycerides during periods of abundant energy supply. In mammals, the adipose tissue is primarily found under the skin and around the visceral organs; it has two distinct forms: brown adipose tissue and white adipose tissue (Cinti et al., 2005). In humans, brown adipose tissue is generally found only in infants and is specialized in heat production through non-shivering thermogenesis (Cannon and Nedergaard, 2004). In contrast, lipids stored in white adipocytes serve as a long-term energy reserve that can be mobilized to meet general energy requirements under calory deficiency (Giordano et al., 2014). White adipose tissue can further be divided into subcutaneous and visceral adipose tissue. Subcutaneous adipose tissue is located under the skin, particularly in the abdominal and gluteal-femoral area, and is responsible for storing about 80% of total body fat. Visceral adipose tissue is located around the internal organs, particularly in the space contained between the two layers of visceral peritoneum near the digestive organs, representing about 20% of total body fat (Tsiloulis and Watt, 2015). Besides anatomic location, subcutaneous and visceral adipose tissue differ substantially in terms of cell composition and function, particularly adipocyte type, lipolytic activity, vascularity, and innervation, as well as their responsiveness to insulin and other hormones (Wajchenberg, 2000).

Besides adipocytes, the adipose tissue contains a matrix of connective tissue, nerve tissue, stromovascular cells, and immune cells (Frayn et al., 2003). It has been estimated that 20–30% of genes expressed in the white adipose tissue encode secreted proteins (Maeda et al., 1997, 2002). The array of proteins and other molecules secreted by adipocytes are collectively termed “adipokines” or “adipocytokines”. Adipokines include pro-inflammatory cytokines and cytokine-related proteins, complement and complement-related proteins, fibrinolytic proteins, renin-angiotensin system proteins, and a variety of other biologically active proteins that exert hormone-like actions (Falcao-Pires et al., 2012). Some adipokines, such as leptin, are synthesized and secreted almost exclusively by adipocytes; others, such as adiponectin, are produced and secreted by both adipocytes and non-adipocyte cells (Fain et al., 2004, 2008); others still, such as tumor necrosis factor-alpha (TNF-α) and interleukins- 6 and -8 (IL-6, IL-8), originate largely from non-adipocyte cells (Fain et al., 2004). Many adipokines perform local autocrine or paracrine actions that affect adiposity, adipocyte metabolism, and inflammatory responses in the white adipose tissue. Adipokines also play important roles in the regulation of systemic energy metabolism through endocrine and systemic actions in the brain, liver, and muscle (Trayhurn and Wood, 2004; Lafontan and Viguerie, 2006).

Our understanding of the importance of adipocytes in maintaining normal metabolism has tremendously benefited from the use of genetically engineered mice lacking adipocytes. These fatless, or lipoatrophic, mice display elevated levels of fatty acids, hyperglycemia, and hypertriglyceridemia, as well as insulin resistance. Transplantation of adipocytes into lipoatrophic mice causes normalization of many of these metabolic parameters (Gavrilova et al., 2000).

In summary, the adipose tissue acts as an endocrine organ that plays an active role in modulating normal health and maintaining whole-body energy homeostasis and immune functions.

3. Role of inflammation and oxidative stress in the development of obesity

The development of obesity involves a coordinated increase in fat cell size (adipocyte hypertrophy) and number (adipocyte hyperplasia) (DeClercq et al., 2008; Avram et al., 2007). Adipocyte enlargement is the main cause of metabolic dysfunction associated with obesity and related comorbidities (Fuster et al., 2016). The expansion of white adipose tissue along with the ensuing local hypoxia promotes the secretion of several inflammation-related adipokines and activates the recruitment of immune cells, particularly monocytes and lymphocytes, through yet not completely understood mechanisms (Harford et al., 2011). In particular, a role for tissue-resident macrophages in obesity-induced low-grade chronic inflammation has been proposed (Wang et al., 2020a; Davies et al., 2013). Immune cell-mediated release of pro-inflammatory cytokines interferes with the insulin signaling pathway, leading to the altered insulin sensitivity and dysregulated glucose and fatty acid metabolism that accompanies obesity (Tanti et al., 2013). Cytokines and adipokines secreted by macrophages and adipocytes mediate the interaction between these two cell types. Adipokines stimulate the production of pro-inflammatory cytokines, such as TNF-α and IL-6, from macrophages. Consequently, increased endothelial vascular permeability results in enhanced leukocyte recruitment and adhesion (Manna and Jain, 2015). Besides, TNF-α acts on adipocytes by inhibiting the secretion of adiponectin, which plays a significant role in regulating whole-body insulin sensitivity, anti-inflammatory responses, and cardiac health (Vachharajani and Granger, 2009). Collectively, these events are responsible for the chronic low-grade inflammation associated with obesity (Fuster et al., 2016).

On the other hand, enlarged obese adipocytes express fewer insulin receptors and become less susceptible to the anti-lipolytic effect of insulin. This increases lipolysis and stimulates the release of free fatty acids (FFA) into circulation. High FFA levels result in insulin resistance in peripheral tissues, oxidative stress, and tissue injury (Fernández-Sánchez et al., 2011). Lipolysis and FFA release are also stimulated by pro-inflammatory cytokines expressed in the adipose tissue. The increased level of circulating FFA and their accumulation in non-adipose tissues, including cardiac and vascular tissues, leads to lipotoxicity. Obesity-related cardiac lipotoxicity and associated cardiac dysfunction are responsible for 11% and 14% of heart failure cases in men and women, respectively (Ebong et al., 2014).

With the expansion of visceral fat, the generation of reactive oxygen species (ROS) increases in adipocytes, which in turn enhances the expression and secretion of inflammatory adipokines (Otani, 2011; DeMarco et al., 2010). The ensuing oxidative stress causes insulin resistance in the adipose and peripheral tissues.

From a cellular and molecular standpoint, several phenomena account for enhanced oxidative stress in obesity. For instance, the increased mechanical load and muscle activity of obese individuals is associated with higher oxygen consumption and increased mitochondrial respiration, resulting in electron leakage from the mitochondrial electron transport chain (ETC), increased ROS production, and oxidative stress (Manna and Jain, 2015). Moreover, increased triglyceride levels (TG) can affect the normal functioning of the ETC, leading to inhibition

of adenine nucleotide translocation and increased production of the superoxide radical (Monteiro and Azevedo, 2010). Similarly, enhanced FFA levels can contribute to mitochondrial dysfunction, resulting in enhanced ROS production in obesity (Martinez, 2006).

Oxidative stress has been proposed as a major causative factor for obesity-associated comorbidities. For instance, by inducing a pro-inflammatory environment or directly acting on insulin receptors to cause peripheral insulin resistance, oxidative stress promotes the development and progression of metabolic dysfunction (Salmon, 2016; Park et al., 2009; Hurrle and Hsu, 2017). Moreover, chronic oxidative stress can disrupt the blood-brain barrier, ultimately causing brain damage and accelerating the onset of neurodegenerative disorders (Roh et al., 2017). The state of chronic inflammation observed in obesity may also be responsible for the increased incidence of certain types of cancer in obese individuals (Marseglia et al., 2014; Incio et al., 2016; Kolb et al., 2019; Arendt et al., 2013; Kolb et al., 2016; Park et al., 2010).

4. The obesity-aging connection

Altered metabolic regulation, insulin resistance, inflammation, and impaired immune function are not only the hallmarks of obesity but also of aging. Interestingly, obese and elderly individuals exhibit strikingly similar immunological profiles in adipose tissues, suggesting a significant overlap between the mechanisms that drive both processes (reviewed in (Trim et al., 2018)).

Aging is characterized by a stochastic accumulation of molecular damage and progressive failure of maintenance and repair mechanisms, resulting in increased frailty and ultimately death. The progressive and irreversible accumulation of ROS-induced oxidative damage plays an important role in the age-related impairment of physiological functions and loss of cellular homeostasis that leads to disease development and ultimately death (Harman, 1972). Being the main intracellular source and target of ROS, mitochondria are closely associated with the aging process. ROS can damage multiple mitochondrial constituents, including mitochondrial DNA (mtDNA) (Harman, 1972; Miquel et al., 1980; Pak et al., 2003). The progressive accumulation of ROS-induced mutations in mtDNA throughout the lifetime of an individual can, in turn, contribute to the disruption of proper ETC functioning and further production of ROS, resulting in the inability to maintain a sufficient supply of energy to the cells that leads to their progressive functional decline and death (Jang et al., 2018).

Aging is also accompanied by a chronic, low-grade systemic and sterile (in the absence of overt infection) inflammation, a condition termed “inflammaging” (De la Fuente et al., 2005; De la Fuente, 2008; Franceschi et al., 2000a; Franceschi and Campisi, 2014). Like oxidative stress, inflammation also accelerates the onset of aging and age-related diseases (Herbert et al., 2008). Inflammaging is characterized by a general increase in the production of pro-inflammatory cytokines such as IL-6, IL-1, and TNF-α, followed by increased plasma levels of key inflammatory markers, such as C-reactive protein (CRP) and serum amyloid A (SAA) (Franceschi et al., 2000b; Franceschi, 2007). This generalized pro-inflammatory status can contribute to the onset of the most important age-related diseases, such as CVD, atherosclerosis, type 2 diabetes, neurodegeneration, arthrosis and arthritis, osteoporosis, and osteoarthritis, sarcopenia, frailty, and cancer (Franceschi et al., 2007; Cevenini et al., 2013). Interestingly, centenarians whose lifespan is expected to be close to the maximum human lifespan maintain a delicate balance between pro-inflammatory and anti-inflammatory markers, which possibly explains the delayed disease onset in these individuals (Gerli et al., 2000). The involvement of inflammation in aging is also supported by the observation that the immune cells of long-lived species maintain better function and redox state than those of short-lived ones (De la Fuente et al., 2004; Vina et al., 2006). Likewise, subjects displaying enhanced oxidative and inflammatory stress markers tend to have a lower lifespan compared to their counterparts of the same chronological age (Guayerbas et al., 2002a, b; Guayerbas and De La Fuente, 2003).

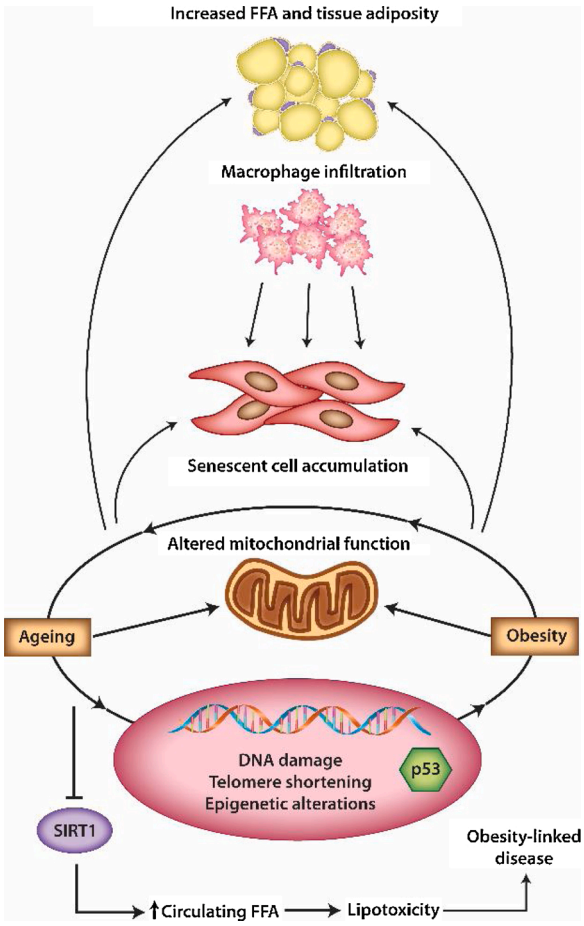

Fig. 1. Mechanistic similarities between obesity and aging. Both aging and obesity are characterized by oxidative stress and low-grade inflammation caused by dysregulation of mitochondrial function, senescence, DNA damage and telomere shortening. FFA – free fatty acids. Reproduced with permission from Perez et al. (2016).

Besides age, increased levels of pro-inflammatory factors, ROS, and senescent cells, as well as viral or bacterial infections, are among the main underlying causes of inflammaging. Moreover, inflammaging can be influenced by many non-immunological factors that are not directly related to inflammation, such as microRNAs, circulating mtDNA, glycans, and metabolites produced by the intestinal microbiota. These factors trigger various signaling pathways, ultimately leading to nuclear translocation of the transcription factor NF-κB. Cytoplasmic sequestration of NF-κB via interaction with IκB inhibitor proteins results in attenuated DNA-binding and transcriptional activation. Phosphorylation of IκB proteins results in their degradation, allowing translocation of NF-κB into the nucleus where it transcriptionally activates multiple genes that encode pro-inflammatory mediators such as TNF-α, interleukins, and cytokines (Sarkar and Fisher, 2009).

Importantly, advanced age is typically accompanied by increased fat deposition around the internal organs (visceral adipose tissue), in which adipocyte precursor cells (preadipocytes) tend to lose their specialized characteristics, undergo dedifferentiation, and acquire a senescent-like pro-inflammatory state; this results in increased production of pro-inflammatory cytokines and chemokines and induction of visceral adipose tissue inflammaging (Tchkonia et al., 2010; Conte et al., 2019).

Given the etiological similarities between obesity and aging, it is valid to speculate that obesity might accelerate the rate of aging and the onset of age-related diseases (Salmon, 2016). Accordingly, obese mice have a shorter lifespan and increased levels of oxidative stress markers

compared to their lean counterparts (Zhang et al., 2015; Silberberg and Silberberg, 1954; Harrison et al., 1984; Baur et al., 2006). Likewise, extreme obesity is associated with substantially elevated rates of total mortality, with most of the excess deaths due to diseases typically associated with old age, including heart diseases and cancer (Kitahara et al., 2014). More recently, it has been predicted that obese individuals might lose up to 8 years of life compared to normal-weight individuals (Grover et al., 2015). Remarkably, in rats, maternal obesity was found to accelerate the metabolic aging of the offspring in a sex-dependent manner (Rodriguez-Gonzalez et al., 2019).

4.1. Mechanistic links between obesity and aging highlight pathways to intervention

Over the last decades, the clinical consequences of obesity have become increasingly amenable to therapeutic interventions that target inflammation and fat tissue cellular composition. Given the similarities between obesity and age-related fat tissue dysfunction, i.e. the changes in cellularity, insulin-responsiveness, secretory profiles, and inflammatory state of adipose tissue that are associated with aging (Stout et al., 2017), it is valid to speculate about the existence of similarities in the mechanisms underlying both conditions. Accordingly, analogous interventions might be used to address both obesity-related dysfunctions and age-associated pathologies. The mechanistic similarities between obesity and aging are schematically summarized in Fig. 1.

The association between aging and obesity is evident from the similarity in certain pathophysiological tissue changes, such as those in the liver, that accompany both processes. Non-alcoholic fatty liver disease (NAFLD) is a progressive disease that is characterized by excessive hepatic fat accumulation (liver steatosis) and is associated with oxidative stress, obesity, insulin resistance, and dyslipidemia ((Bril et al., 2016; Sinton et al., 2019; Perla et al., 2017)). NAFLD is found in 30%–40% of the general population and in up to 95% of those with morbid obesity (LaBrecque et al., 2014). NAFLD is also prevalent in the elderly, correlating with increased risk of mortality in those between 60 and 74, but not on subjects older than 75 (Golabi et al., 2019). Oxidative stress and inflammation, processes that accompany both aging and obesity, can contribute to the progression of NAFLD to more serious conditions, such as nonalcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma (HCC). Accordingly, aging has been reported to significantly enhance the progression of NAFLD to NASH and fibrosis, predisposing to increased mortality in elderly subjects with NAFLD (Regev and Schiff, 2001; Frith et al., 2009). Age-associated enhanced fat uptake, increased *de novo* lipogenesis, decreased β-oxidation, and/or decreased synthesis/secretion of very-low-density lipoproteins have been proposed to be involved in the liver steatosis that characterizes NAFLD (Cohen et al., 2011). Importantly, a link between NAFLD and neurodegeneration, characterized by reduced brain volume (Weinstein et al., 2018) and impaired cognitive performance (Seo et al., 2016) has been reported. Further, NAFLD was found to induce and accelerate Alzheimer's disease potentially as a result of chronic inflammation (Kim et al., 2016). Molecules traditionally characterized by age-modulating properties, such as resveratrol, have also been found to ameliorate NAFLD (Bujanda et al., 2008; Shang et al., 2008; Faghihzadeh et al., 2014).

The similarities between obesity and age-related fat tissue dysfunction are also evidenced by the fact that multiple energy metabolism and energy-sensing pathways, as well as regulators of oxidative stress and inflammation, play similar roles in both obesity and aging and their associated pathologies. These pathways represent potential druggable targets for both obesity and aging (further discussed in Section 5).

Insulin/IGF-1 signaling (further examined in Section 3.1.3) plays an important role in regulating lifespan and healthspan (Cheng, 2019). Such a role was originally proposed after the observation of an association between low IGF-1 plasma levels in mice with hypopituitary dwarfism and extended longevity (Cheng, 2019). Further confirmation was later achieved in studies in mice with disrupted or lacking the insulin receptor or with mutated IGF-1 encoding genes (Holzenberger et al., 2003; Blüher et al., 2003). This lifespan extending effect of reduced insulin signaling appears to be mediated by increased expression of pathways involved in DNA damage and surveillance, protein folding, oxidative stress and innate immunity (Murphy et al., 2003). Altered IGF-1/insulin signaling also plays a crucial part in the pathophysiology of obesity (Spielman et al., 2014). Obesity-associated IGF-1 resistance has been hypothesized to contribute to neurodegeneration associated with obesity (Murphy et al., 2003) and to enhanced predisposition to cancer in obese individuals (Renehan et al., 2006).

AMPK (AMP-activated protein kinase) is a metabolic stress-sensing enzyme that monitors the balance between energy supply and energy demand and appropriately modulates metabolic pathways involved in glucose, fatty acid, and protein metabolism to ensure homeostasis. Due to its energy-sensing role, AMPK is an important modulator of the cellular and functional changes that accompany the development of obesity, and AMPK activation is a target for obesity therapeutics (Wu et al., 2018; Bijland et al., 2013). AMPK activity is diminished in the adipose tissue of individuals with obesity and metabolic syndrome (Ruderman et al., 2013), possibly contributing to the enhanced oxidative and inflammatory status of the adipose tissue of individuals with such conditions (Galic et al., 2011; Xu et al., 2012). Enhanced AMPK signaling also has a lifespan extending effect in *C. elegans*, *Drosophila,* and yeast (Harkness et al., 2004; Tschäpe et al., 2002; Apfeld et al., 2004), and AMPK is the target of several lifespan-extending pharmacological and dietary interventions as well (reviewed in Section 5) (Apfeld et al., 2004; Greer et al., 2007). The observation that AMPK loss results in a significant increase in neurodegeneration in flies suggests a neuroprotective role for AMPK (Tschäpe et al., 2002). Importantly, AMPK activation by the phytochemical resveratrol (discussed in Section 5) and subsequent promotion of autophagy has been shown to decrease the levels of the amyloid-β (Aβ) peptide that contributes to the development of Alzheimer's disease (Vingtdeux et al., 2010).

The nuclear hormone receptors designated peroxisome proliferator-activated receptors (PPARs) are important regulators of cellular energy metabolism and oxidative stress that play crucial roles in the normal aging process (Erol, 2007). Accordingly, genome-wide association studies have identified an association between certain PPARγ polymorphisms and increased longevity (Barbieri et al., 2004) and, in some cases, reduced age-related cognitive decline (Yaffe et al., 2008; Johnson et al., 2008). PPARγ expression and activity are reduced during aging in rodents, and this may contribute to age-associated loss of function (Haramizu et al., 2011). Reduced PPARγ signaling (by genetic deletion of various PPARγ isoforms from either the white adipose tissue or the entire body) results in reduced longevity in mice (Argmann et al., 2009). PPARs also play a role in obesity via modulation of glucose metabolism, adipocyte differentiation, lipolysis, and fat storage (Stienstra et al., 2007). Selective ablation of PPARγ in the subcutaneous adipose tissue was associated with increased adipose tissue expansion and insulin resistance (Xu et al., 2018) and PPARα −/− mice were found to gain more adipose mass compared to wild-type animals under the same diet (Costet et al., 1998). Studies using synthetic PPARα agonists further support an anti-obesity role for PPARα (Guerre-Millo et al., 2000; Vásquez et al., 2001; Mancini et al., 2001). PPARs not only affect adiposity in obesity but also obesity-induced inflammation via effects on both adipocytes and adipose tissue-resident macrophages that include direct transcriptional downregulation of pro-inflammatory genes and indirect effects on lipid metabolism (Xu et al., 2003; Tontonoz et al., 1994; Ricote et al., 1998; Okuno et al., 1998). Importantly, agonist (thiazolidinedione)-mediated activation of PPARγ was found to attenuate age-related inflammation and oxidative stress by suppressing NF-κB activity (Sung et al., 2006), with such a protective effect being impaired by age-associated senescence (Briot et al., 2018).

mTOR signaling, modulated by branched-chain amino acids, has been implicated in both aging and age-related dysfunction, as well as the development of obesity. Chronic activation of mTOR in the adipose

tissue of obese individuals seems to be linked to obesity-associated cancers, inflammation, β-cell adaptation preceding type 2 diabetes, NAFLD, and other health complications (Laplante and Sabatini, 2009). Accordingly, abrogation of the mTORC1 complex of the mTOR pathway reduced obesity and improved insulin responsiveness (Um et al., 2004). Modulation of lipid metabolism by mTORC1 appears to be mediated by mTORC1-induction of the expression of the lipogenic transcription factors SREBP1/SREBP2 and their proteolytic cleavage to mediate translocation of the active transcription factors to the nucleus where they promote the expression of genes involved in fatty acid and cholesterol synthesis (Lewis et al., 2011).

mTORC1 inhibition has also been reported to extend lifespan and reduce the incidence of age-related pathologies (Lamming et al., 2012; Kaeberlein et al., 2005; Harrison et al., 2009; Kapahi et al., 2004; Vellai et al., 2003) potentially by modulating mitochondrial gene expression (Bonawitz et al., 2007) and reducing the accumulation of intracellular ROS (Halicka et al., 2012). Deletion of the S6K1 component of the mTOR signaling pathway resulted in increased lifespan and decreased insulin resistance and amelioration of age-related pathologies (Um et al., 2004; Selman et al., 2009; Um et al., 2006; Al-Ali et al., 2017). Interestingly, the gene expression pattern of knockout mice lacking S6K1 were similar to those observed following AMPK activation, as well as with caloric restriction (Selman et al., 2009). Several pharmacological and physiological interventions that target both obesity- and age-related dysfunction exert their action at least partially via modulation of mTOR signaling and are further examined in Section 5.

The Forkhead Box O (FOXO) subfamily of transcription factors (FOXO1, FOXO3a, FOXO4, and FOXO6) regulates the expression of genes involved in DNA damage and repair response, apoptosis, metabolism, cellular proliferation, stress tolerance, and longevity (van der Horst and Burgering, 2007; Calnan and Brunet, 2008). FOXOs also regulate genes responsible for controlling hepatic glucose production, insulin secretion in β-cells and β-cell growth and differentiation, and fat and muscle mass (Xiong et al., 2013) FOXOs have been identified as a potential therapeutic target for metabolic disorders of insulin resistance, including obesity, diabetes, and NAFLD (Cheng, 2019; Ahn et al., 2013; Moll and Schubert, 2012; Dong, 2017).

Sirtuins are a family of NAD-dependent histone deacetylases (HDACs) consisting of seven mammalian proteins, SIRT1−7. They are present in different subcellular compartments where they control the activity of various proteins and genes that regulate cell survival, differentiation, metabolism, DNA repair, inflammation, and longevity (reviewed in (Saunders and Verdin, 2007; Haigis and Guarente, 2006; Longo and Kennedy, 2006)). The importance of sirtuins in lifespan and healthspan regulation is evident from the fact that sirtuin deficiency is associated with shortened lifespan, neurodegeneration, and metabolic diseases, while increasing sirtuin levels genetically or chemically results in extended lifespan and protection against age-related degeneration (Tang et al., 2017; Sundaresan et al., 2012; Mitchell et al., 2014; Tissenbaum and Guarente, 2001; Rogina and Helfand, 2004; Kaeberlein et al., 1999). Sirtuins have also been found to play a role in obesity and obesity-related pathologies via regulatory effects on adipokine expression, insulin secretion, cholesterol and lipid homeostasis, as well as mitochondrial energy efficiency (Liang et al., 2009). SIRT1 in particular was found to stimulate fatty acid oxidation via induction of adiponectin production and by regulating adipogenesis, lipolysis, and fatty acid mobilization (Iwabu et al., 2010; Çakir et al., 2009). Accordingly, SIRT1 deficiency resulted in hyperglycemia, oxidative stress, and insulin resistance, leading to high-fat diet-induced obesity (Purushotham et al., 2012; Wang et al., 2011). Additionally, mice overexpressing SIRT1 mice were found to display a leaner phenotype compared to littermate controls, accompanied by decreased levels of plasma cholesterol, insulin, and fasting glucose, as well as reduced adiposity (Bordone et al., 2007). SIRT1 overexpression in mice fed a high-fat diet was also found to lessen inflammation, improve glucose tolerance, and protect against hepatic steatosis (Pfluger et al., 2008). Sirtuin agonists are, thus, promising druggable targets for both aging and aging-related dysfunction and obesity and are examined in Section 5.

The effects of SIRT1 on metabolism are, at least in part, mediated by its interaction with the transcriptional co-activator PPARγ co-activator 1 alpha (PGC1α), which is able to sense oxidative stress and modulate gene expression accordingly (Kaeberlein et al., 2005; Harrison et al., 2009; Kapahi et al., 2004; Vellai et al., 2003; Bonawitz et al., 2007). PGC1α is involved in mitochondrial biogenesis, thermogenesis, glucose homeostasis, and oxidative stress responses (Harrison et al., 2009; Halicka et al., 2012; Selman et al., 2009; Um et al., 2006; Al-Ali et al., 2017; van der Horst and Burgering, 2007). Protective effects of PGC1α against neurodegeneration is evidenced by the fact that ectopic expression of PGC-1α in neurons decreases ROS levels, and PGC1α transgenic mice display significantly lower age-related accumulation of oxidative damage compared to wild type controls (St-Pierre et al., 2006). By promoting autophagic pathways and preventing oxidative stress, PGC-1α was also found to protect from Huntington's disease proteotoxicity (Tsunemi et al., 2012). PGC1α also plays a role in metabolic dysfunction diseases, as demonstrated by the fact that upregulation of PGC1α in the skeletal muscle of mice protected against obesity and diabetes development (Wenz et al., 2009).

The role of Nrf2 in the coordination of the cell's response to oxidative stress is well established (Hybertson et al., 2011). Reduced Nrf2 activity has been shown to contribute to all major aging phenotypes, including genetic instability, mitochondrial dysfunction, telomere attrition, epigenetic modifications, stem cell exhaustion, impaired protein homeostasis, altered nutrient sensing, and cellular senescence (reviewed by (Schmidlin et al., 2019)). A role for Nrf2 in obesity has also been revealed, as indicated by its involvement in the regulation of pre-adipocyte to adipocyte differentiation (Murakami and Motohashi, 2015) and mitigation of inflammation in obesity (Kang et al., 2019; Kim et al., 2018, 2019a; Luo et al., 2017). Accordingly, Nrf2 expression is increased in individuals with high-fat percentages (Das et al., 2011), and targeted disruption of NRF2 was found to protect against high fat diet-induced obesity in mice (Pi et al., 2010).

Despite the commonalities between obesity- and age-associated dysfunction, the overall mechanisms associated with fat tissue dysfunction in obesity differ from aging in important ways. For instance, obesity is accompanied by increased fat cell size (Fried and Kral, 1987), followed by fat cell death and macrophage infiltration around the dying cells (Cinti et al., 2005) which contributes to tissue inflammation. In contrast, inflammation is a major initiating factor for age-related fat tissue dysfunction (Bertrand et al., 1978, 1980). Moreover, transcriptional changes that occur in the adipose tissue during aging and progression of obesity are distinct because of the basic differences in the composition of the adipose tissue of obese and elder individuals (Xu et al., 2003; Weisberg et al., 2003; Wu et al., 2007).

4.1.1. The telomere connection

Oxidative stress and inflammation might influence the aging process by accelerating the shortening of telomeres (Hwangbo et al., 2004; Aviv et al., 2006). Telomeres act as the cell's "molecular clock" and contribute to the time-dependent loss of the replicative ability of cells (Stewart and Weinberg, 2006). Telomeres shorten during each cell cycle because the DNA polymerase is unable to work on the single-stranded 3′ end (Aviv et al., 2006; Minamino et al., 2009). The progressive shortening of telomeres leads to genomic instability, reduced cellular renewal, and ultimately cellular senescence (Folini et al., 2005). Oxidative stress negatively impacts telomere maintenance because the activity of telomerase is reduced in the presence of ROS (Borras et al., 2004; Kurz et al., 2004; Passos et al., 2007). Furthermore, due to the high content of guanine residues, telomeric DNA sequences are highly susceptible to oxidative stress-induced damage (Rhee et al., 2011). Telomere dysfunction activates p53-mediated DNA damage response which in turn leads to cell senescence (Campisi, 2005).

Abdominal adiposity in humans has been directly correlated with a

decrease in telomere length (Lee et al., 2011; Nordfjall et al., 2008). The telomeres of obese women are shorter than that of their lean counterparts, which is believed to be caused by obesity-associated oxidative stress and inflammation (Njajou et al., 2012). Obesity-associated pro-inflammatory cytokines in particular are believed to be involved in this process (Tzanetakou et al., 2012; Epel, 2009; Gardner et al., 2005). Besides adiposity *per se*, obesity-associated insulin resistance has been proposed to contribute to telomere shortening (Al-Attas et al., 2010), although divergent results have been reported (Verhulst et al., 2016). Remarkably, obese individuals who underwent gastric bypass surgery displayed telomere lengthening 3–5 years after surgery. This change in telomere length was negatively correlated with age and triglyceride levels, while no correlation with surgery-induced weight loss was observed (Dershem et al., 2017).

These findings suggest that obesity can accelerate human aging by increasing the rate of telomere erosion.

4.1.2. The cellular senescence connection

Cellular senescence, *i.e.*, the irreversible growth arrest of cells, represents another important hallmark of aging (López-otín et al., 2013). While senescence plays a key physiological role during normal development and is needed for tissue homeostasis, senescence during aging represents a stress response elicited by age-related insults, such as genomic instability and telomere attrition.

The possible link between aging and senescence was first described by Leonard Hayflick and Paul Moorhead in 1961 after observing that cultured human primary fibroblasts had a limited proliferation capacity (Hayflick and Moorhead, 1961). This is known as the Hayflick limit; it is associated with the inability of telomeres to maintain their lengths during replication at least in part due to the decline in cellular protection systems during aging (Herranz and Gil, 2018). In addition to shortened telomeres, other senescence triggers include altered proteostasis, mitochondrial deterioration, DNA-replication stress, or oncogene activation (Gorgoulis and Halazonetis, 2010; Wiley et al., 2017; Hernandez-Segura et al., 2018; Ishikawa and Ishikawa, 2020). These "stress triggers" stimulate various signaling pathways that ultimately cause cell growth arrest by upregulating the cell cycle inhibitor p53, its downstream target p21, and tumor suppressor protein 16 (Maruyama et al., 2009).

When senescence is established, cells undergo widespread changes and develop specific characteristics, including increased size and protein content, enlarged nuclei, and lysosomes with elevated senescence-associated β-galactosidase activity (Hayflick and Moorhead, 1961; Young et al., 2009; Kurz et al., 2000). Additionally, the main regulators of the senescence program, p53/p21 as well as p16INK4aINK4a proteins, are upregulated (LeBrasseur et al., 2015; Helman et al., 2016; Nielsen et al., 1999; Beausejour et al., 2003). Another important feature of senescent cells is the development of the "senescence-associated secretory phenotype" (SASP), which is characterized by increased expression and secretion of pro-inflammatory cytokines and chemokines (*e.g.* interleukins IL-6, IL-1, and IL-8), growth factors (*e.g.* IGF-binding proteins and their regulators), extracellular matrix components (*e.g.* matrix metalloproteinases and serine proteases), fibronectin, and reactive oxygen/nitrogen species (ROS/RNS). This in turn leads to activation of the immune response to remove senescent cells (Coppe et al., 2010; Garfinkel et al., 1994; Kuilman et al., 2008; Lee et al., 1999).

Induction of cellular senescence and the SASP are believed to drive the degenerative, hyperproliferative, and inflammatory conditions that accompany aging (Tchkonia et al., 2010). Accordingly, targeted deletion of senescent cells expressing p16INK4a delays the onset of several age-related phenotypes, including cataracts, lordokyphosis (*i.e.*, increased curvature of the spine), and diminished exercise capacity in a mouse model of accelerated aging (Baker et al., 2011). Likewise, pharmacological agents with the ability to selectively kill senescent cells or inhibit the SASP, know as senolytics, exert therapeutic benefits on chronologically aged, progeroid, and/or irradiated mice displaying the hallmarks of aging (Zhu et al., 2015; Xu et al., 2015).

Obese individuals typically have significantly more senescent cells than "normal" weight individuals, displaying an excessive accumulation of senescent cells in their adipose tissues (Tchkonia et al., 2010; Minamino et al., 2009; Conley et al., 2020). Obese individuals also contain more senescent endothelial cells and pre-adipocytes than their lean counterparts (Tchkonia et al., 2010; Salpea et al., 2010). Accordingly, senescence-associated β-galactosidase activity is elevated in obese individuals (Tchkonia et al., 2010), compared to their lean counterparts. Likewise, p53 levels are increased in the adipose tissue of obese individuals (Tchkonia et al., 2010; Minamino et al., 2009).

Cellular senescence in the fat tissue of obese individuals stimulates the infiltration of immune cells, resulting in pro-inflammatory effects on pre-adipocytes. Consistent with this, pre-adipocytes co-cultured with macrophages can induce a pro-inflammatory state by increasing the expression of the inflammatory cytokine TNF-α (Tchkonia et al., 2010; Suganami et al., 2005). Several pro-inflammatory adipocytokines and chemokines secreted by senescent cells in obese individuals are thought to be responsible for obesity-associated metabolic dysfunctions, such as diabetes (Tchkonia et al., 2010). Accordingly, in mice, increased expression of p53 in macrophages and fat cells was found to induce senescence and increase inflammatory cytokine production, resulting in insulin resistance (Minamino et al., 2009). In contrast, the expression of a dominant-negative form of p53 protected against high levels of fat tissue-secreted cytokines, macrophage infiltration, and insulin resistance (Minamino et al., 2009).

The accumulation of immune senescent cells seems to be an important event connecting obesity and aging and age-related diseases (Franceschi, 2017). For instance, senescence-associated β-galactosidase activity and p16 reactivity were found to be increased in the fat tissue of mice displaying an accelerated aging phenotype compared to that of control individuals (Minamino et al., 2009; Baker et al., 2006). Importantly, p16Ink4a ablation prevented the accumulation of senescent cells in mice displaying an accelerated aging phenotype, implicating p16Ink4a in establishing the senescent phenotype in this model (Baker et al., 2008). Interestingly, the administration of senolytics improved glucose tolerance, enhanced insulin sensitivity, reduced circulating inflammatory mediators, and promoted adipogenesis in obese mice, resulting in an overall improvement of the metabolic dysfunction associated with obesity (Palmer et al., 2019).

Together, these findings suggest that senescent cells accumulate in the fat tissue with chronological aging and that these cells might contribute to age-related fat tissue inflammation and dysfunction.

4.1.3. The insulin connection

Another mechanism by which obesity might accelerate the aging process of the adipose tissue is by influencing glucose homeostasis, a process in which insulin plays a critical role (Xu et al., 2003; Minamino et al., 2009). Reduced insulin signaling has been found to extend longevity across several model organisms (Kenyon et al., 1993; Clancy et al., 2001; Bluher et al., 2003). This effect has been attributed to the association between reduced IIS signaling and increased expression of surveillance, protection, and repair genes which, altogether, contribute to lifespan extension (Holzenberger et al., 2003).

The role of IIS signaling in human aging is still poorly understood. Severe deficiencies in insulin secretion in type 1 and type 2 diabetes are associated with reduced life expectancy. On the other hand, enhanced insulin sensitivity, modest reductions in insulin levels, and prevention of dietary-induced or aging-associated hyperinsulinemia are important lifestyle interventions that aim at preventing age-associated diseases.

One of the reasons why the role of IIS signaling in human aging has remained elusive is because the effects of IGF-1 on aging are difficult to separate from those of the human growth hormone (GH), which is the key determinant of IGF-1 levels. Reduced IGF-1 levels due to congenital GH deficiency or resistance have been associated with both exacerbation (Besson et al., 2003) and protection (Shevah and Laron, 2007; Shechter et al., 2007; Menezes Oliveira et al., 2006) from age-associated diseases.

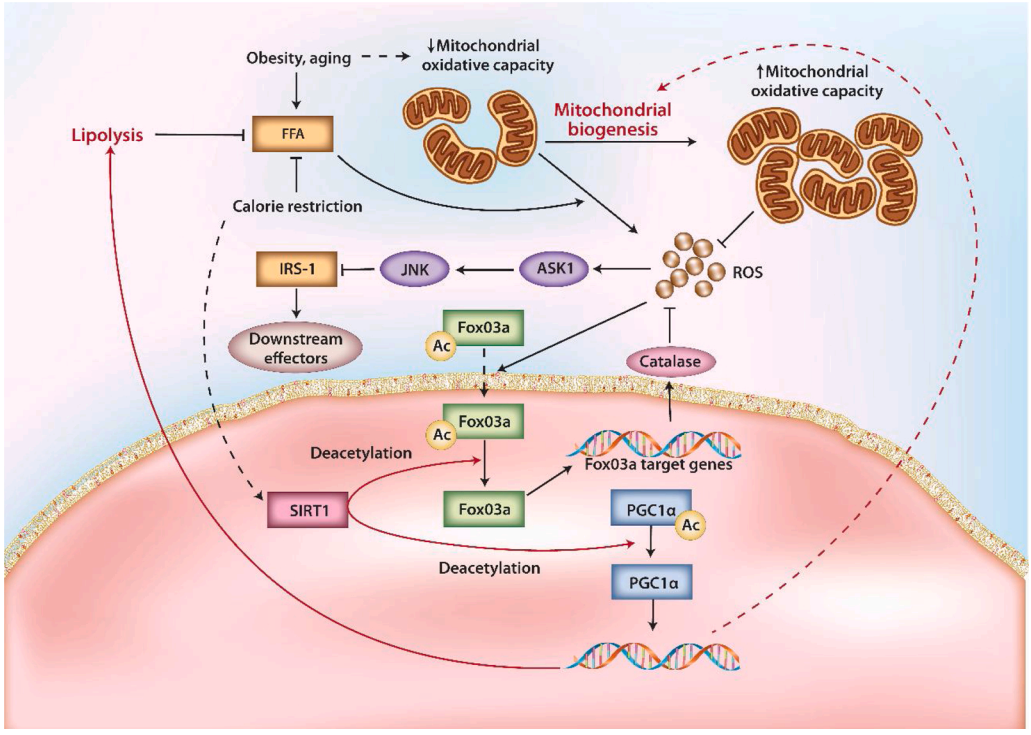

Fig. 2. Role of mitochondria and ROS in obesity and aging. In obese or aging individuals, mitochondrial oxidative capacity is decreased, leading to increased local generation of ROS. SIRT1 activates PGC1α to stimulate mitochondrial biogenesis and lipolysis, resulting in reduced ROS generation. SIRT1 also deacetylates FoxO3a, resulting in the upregulation of the expression of the enzymatic antioxidant catalase, with subsequent reduction of ROS levels. Abbreviations: Ac, acetyl group; FFA, free fatty acids; ROS, reactive oxygen species. Reproduced with permission from Liang et al. (2009).

On the other hand, studies in centenarians suggest that genetic polymorphisms resulting in reduced IIS signaling (Shevah and Laron, 2007; Shechter et al., 2007; Menezes Oliveira et al., 2006), increased adiponectin levels, GH resistance (Ben-Avraham et al., 2017), or IGF-1 resistance (Suh et al., 2008) may play a role in achieving extreme longevity.

Evidence also supports an association between peripheral hyperinsulinemia, insulin resistance, type-2 diabetes and hypertension, and increased risk of neurodegenerative diseases, most notably Alzheimer's disease (AD). Several *in vitro* and *in vivo* studies in mice and humans have shown that insulin and insulin-degrading enzymes regulate amyloid concentrations (Farris et al., 2003; Qiu et al., 1998; Solano et al., 2000). Furthermore, altered insulin resistance may promote AD pathogenesis and other tauopathies, such as Pick's disease, corticobasal degeneration, and progressive supranuclear palsy (Yarchoan et al., 2014), via its effects on the release and clearance of amyloid β (Aβ) (Craft, 2005), which is the main component of amyloid deposits characteristic of AD. Accordingly, inducing insulin resistance by feeding mice a high-fat diet (HFD) was found to increase tau phosphorylation and exacerbate AD, as

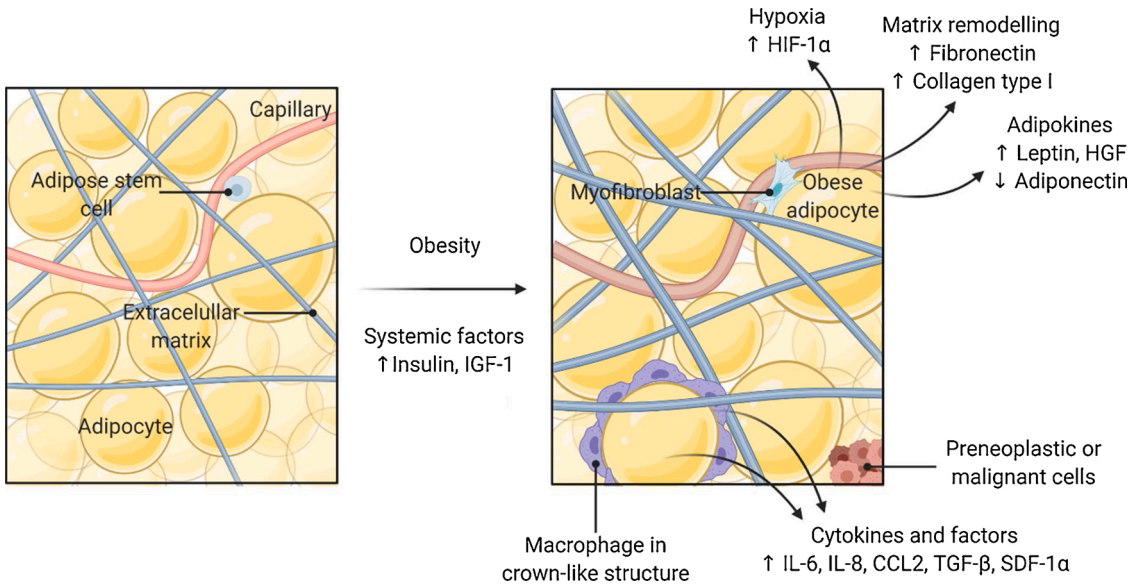

Fig. 3. The obesity microenvironment contributes to cancer progression. Obesity induced systemic changes include increases in circulating insulin and IGF-1. Increased secretion of adipokines such as leptin and diminished secretion of adiponectin contributes to cancer development in the obese adipocyte. Adipocytes and recruited immune cells secrete increased amounts of cytokines and other growth factors. The microenvironment of the obese fat tissue also produces hypoxic conditions which may elevate localized angiogenesis. Increased collagen and fibronectin deposition in the obese tissue contributes to the stiffness of the extracellular matrix which promotes tumor progression. IGF-1 – insulin-like growth factor-1. HIF-1α – Hypoxia-inducible factor-1α. HGF – hepatocyte growth factor. Reproduced with permission from Arendt and Kuperwasser (2015).

reflected by increased levels of Aβ and overall amyloid burden (Calvo-Ochoa et al., 2014; Bhat and Thirumangalakudi, 2013; Arnold et al., 2014; Ramos-Rodriguez et al., 2014). Together, these results suggest that insulin resistance accelerates the onset and progression of AD, especially in cases where there is a predisposition for developing tau pathologies (Craft, 2005).

4.1.4. The mitochondrial connection

Mitochondria play a crucial role in bioenergetic metabolism and ATP production, and maintenance of proper mitochondrial function is essential for general cellular homeostasis.

Due to their central role in multiple cellular functions, most hallmarks of aging including inflammation, cellular senescence, and altered bioenergetics have a significant mitochondrial component [reviewed in (Sun et al., 2016)]. Aging is accompanied by an overall decrease in the efficiency of mitochondrial bioenergetics associated with reduced mitochondrial biogenesis, mtDNA mutations, altered mitochondrial dynamics (imbalance between fission and fusion), or faulty mitophagy (Wang and Klionsky, 2011).

Obesity is also associated with mitochondrial dysfunction. For instance, obese adipocytes display reduced mitochondrial biogenesis and decreased mitochondrial oxidative capacity (de Mello et al., 2018; Rong et al., 2007). In turn, reduced mitochondrial biogenesis contributes to the metabolic alterations, low-grade inflammation, and insulin resistance observed in obese individuals (Heinonen et al., 2015). Additionally, mitochondria of obese individuals show reduced fatty acid oxidation, less-defined internal membranes, and diminished capacity for energy generation (Hernandez-Aguilera et al., 2013). Excessive calorie intake also appears to impair mitochondrial respiratory capacity, which can subsequently sensitize mitochondria to apoptotic stimuli (Hernandez-Aguilera et al., 2013). The role of mitochondria and ROS in obesity and aging is schematically represented in Fig. 2.

5. Obesity, aging, and cancer: common underlying mechanisms

As previously mentioned, obesity represents an overall state of energy imbalance accompanied by systemic effects such as insulin resistance, altered hormone signaling, and high circulating levels of pro-inflammatory mediators. In addition to its systemic effects, obesity is associated with white adipose tissue inflammation. These local and systemic phenomena associated with obesity are likely to contribute to the development and progression of several types of cancer, notably endometrial, colorectal, esophageal, kidney, pancreatic, and post-menopausal breast cancer (Craft, 2005; Iyengar et al., 2015; Calle et al., 2003). A schematic representation of the changes in obese adipocytes that promote cancer development is depicted in Fig. 3.

The variability in the way that obesity affects the incidence, progression, or mortality of various cancers suggests that multiple mechanisms influence the obesity-cancer association. An intricate web of interacting hormones, growth factors, cytokines, oxidative stress, and inflammation mediators seems to promote tumor initiation and growth in obese individuals. Among the key mechanistic molecular factors connecting obesity and cancer are insulin, IGF-1, adipokines, and several inflammation mediators.

Human observational studies have reported an association between increased cancer mortality and obesity and type 2 diabetes, related to hyperinsulinemia, elevated IGF-1, or both. Likewise, increased body mass index (BMI) has been found to closely correlate with increased fasting insulin levels in non-diabetic individuals; enhanced insulin levels, in turn, have been linked to increased risk of distant recurrence and death in breast cancer patients (Gallagher and LeRoith, 2011; Goodwin et al., 2002). Conversely, individuals with low insulin, IGF-1, and IGF-2 levels appear to be relatively protected from cancer (Gallagher and LeRoith, 2011). For instance, type 2 diabetes patients receiving insulin therapy or drugs to stimulate insulin secretion were found to have a significantly higher incidence of cancer than those who received metformin, an antidiabetic drug that works to lower insulin levels (Dowling et al., 2012). Interestingly, metformin has also been found to extend lifespan and healthspan and delay the aging process in several model organisms (Chen et al., 2017; Cabreiro et al., 2013a; Martin-Montalvo et al., 2013). Likewise, caloric restriction (CR), which reduces circulating insulin and IGF-1 levels, seems to be a potent suppressor of the carcinogenic process (Hursting et al., 2010) and confer protection against aging (Weiss and Fontana, 2011).

The role of insulin and IGF as cancer accelerants seems to be mediated by the AKT/PI3K cascade that promotes cell growth and proliferation and inhibits cell survival (Weiss and Fontana, 2011). The Akt/PI3K/mTOR is the most frequently mutated pathway in human cancers (Liu et al., 2009; Kalaany and Sabatini, 2009); it also plays an important role in obesity (Chen, 2011). This pathway is activated by both insulin and IGF-1, which are frequently present at high levels in the serum of overweight and obese individuals (Dann et al., 2007; Moore et al., 2008a; Woods et al., 1998). Conversely, CR, which is frequently associated with decreased cancer incidence, reduces Akt/PI3K/mTOR pathway activation (Moore et al., 2008a; Jiang et al., 2008a). Tumors with PI3K activation are resistant to the anti-cancer action of CR (Kalaany and Sabatini, 2009). Likewise, disruption of the Akt/-PI3K/mTOR cascade resulted in decreased tumor incidence in both humans and animals (Olivo-Marston et al., 2009; Moore et al., 2008b; Novosyadlyy et al., 2010; Fierz et al., 2010). The PI3K/Akt/mTOR pathway has also been found to regulate the replicative senescence of human vascular smooth muscle cells, and contribute to aging and age-related cardiovascular diseases (Tan et al., 2016) and has also been proposed as a therapeutic target for brain aging and neurodegeneration (Heras-Sandoval et al., 2011).

The role of insulin in driving cancer growth has been elucidated using genetically engineered mice with severe muscle, liver, and fat cell insulin resistance and thus elevated insulin levels, and an inability to properly metabolize their diet, phenomena which are similar to what occurs in type 2 diabetes (LeRoith, 2010). However, since these mice are not obese, they allow researchers to dissect the role of high insulin levels in the absence of concurrent obesity on cancer development and progression. These mice were found to be highly susceptible to developing breast cancer. Furthermore, the tumors that developed in mice with elevated insulin levels were bigger and much more aggressive than those that developed in mice with normal insulin levels. Blocking of an insulin receptor or lowering the circulating insulin level abrogated this effect (LeRoith, 2010).

In addition to insulin and IGF, several other hormones, enzymes, and growth factors that govern cellular energy balance and growth, such as AMPK, leptin, and adiponectin, are thought to play vital roles in increasing cancer risk in obese individuals.

6. Therapeutic strategies targeting oxidative stress and inflammation in obesity and aging

Besides surgery, therapeutic interventions to manage obesity and associated comorbidities include dietary interventions, physical activity, and antioxidant and/or anti-inflammatory supplementation. These interventions can also have an “anti-aging” effect, and in some cases, an “anti-cancer” effect, further supporting the mechanistic similarities between these two processes.

6.1. Dietary interventions

6.1.1. Caloric restriction

Caloric restriction (CR) is characterized by a reduction in calorie intake without causing malnutrition. This intervention has been found to improve many parameters associated with inflammation and oxidative stress (Nikolich-Zugich and Messaoudi, 2005). For instance, CR-mediated weight loss improved insulin sensitivity, reduced circulating inflammation-related compounds, and increased the production

of anti-inflammatory factors by adipocytes (Ziccardi et al., 2002; Laimer et al., 2002; Xydakis et al., 2004; Fontana, 2009). Moreover, CR has been found to reduce the serum concentrations of IL-6 and CRP in obese individuals by suppressing the upregulation of NF-κB, cyclooxygenase (COX)-2, inducible nitric oxide synthase (iNOS), and inflammatory cytokines (Heilbronn and Clifton, 2002; Kim et al., 2006; Jung et al., 2009). Maintaining alternate day calorie restriction diet plan for 8 weeks also resulted in a significant reduction in oxidative stress and inflammatory markers and improvement in asthma-related symptoms in asthmatic obese individuals (Johnson et al., 2007). Obese individuals subjected to a low-calorie diet displayed moderate weight loss, accompanied by improved antioxidant status, reduced systemic inflammation, and increased insulin sensitivity (López-Domènech et al., 2019).

Interestingly, CR is the only non-pharmaceutical and non-genetic strategy that can delay the onset of age-related pathologies and extend lifespan in a range of model organisms (Fontana et al., 2010). The beneficial effects of CR on aging and age-related diseases have been attributed to the CR-mediated modulation of mitochondrial activity and decreased oxidative damage. In turn, the effects of CR on mitochondrial activity seem to be regulated by the inhibition of IGF-1 and mTOR-dependent activities, as well as by the activation of AMP-dependent kinase (AMPK) and the sirtuin family of proteins, including SIRT1 (Salminen and Kaarniranta, 2012; Zoncu et al., 2011; Boily et al., 2008; Civitarese et al., 2007; Someya et al., 2010).

The link between CR and mitochondrial biogenesis may also play a role in increasing cellular resistance to inflammation. For instance, an aging-related decrease in peroxisome proliferator-activated receptor gamma coactivator (PGC)-1α, a key regulator of mitochondrial function, is associated with enhanced levels of inflammatory markers in white adipose and liver tissues (Sczelecki et al., 2014). CR has also been found to decrease inflammation and insulin resistance in an age-associated inflammation rat model (Horrillo et al., 2011). This anti-inflammatory activity of CR was hypothesized to be exerted via NF-κB, SIRT1, PPARs, and FoxOs, as well as by modulation of the redox status of glutathione (Chung et al., 2011).

Reduced intake of some specific dietary components has also been found to reduce oxidative stress and promote longevity. For instance, compliance with a low protein/high carbohydrate diet was found to beneficially impact aging and longevity (Bruce et al., 2013). Restricted intake of branched-chain amino acids, particularly methionine, was also found to slow aging processes and extend lifespan (Malloy et al., 2006; Sun et al., 2009; Miller et al., 2005). Interestingly, reduced methionine intake has been reported to delay the onset of NAFLD, the hepatic manifestation of obesity (Malloy et al., 2013), and alleviate high-fat diet-induced obesity (Wang et al., 2020b).

6.1.2. *Intermittent fasting*

Intermittent fasting (IF) is a dietary intervention characterized by a periodic pattern of fasting and eating (Aly, 2014). Periodic fasting has been found to have beneficial effects on weight loss, prevention of chronic diseases, and life expectancy (Mattson et al., 2017). Studies in animal models presenting brain injury (Yu and Mattson, 1999), Parkinson's disease (Yu and Mattson, 1999), and Alzheimer's disease (Halagappa et al., 2007) have also demonstrated the effectiveness of alternate day fasting (ADF), a modality of IF, on improving behavioral symptoms, motor functions, and memory deficits, respectively. Compliance with an ADF diet for 6 months was found to reduce BMI, body weight, body fat mass, and total cholesterol level in overweight adults and reduce the waist circumference in obese adults (40 years of age or older) (Park et al., 2020). In a study comparing the health benefits of 8 weeks of ADF versus CR in obese individuals, the benefits produced by both interventions were found to be similar in terms of the resulting changes in body weight and composition as well as insulin sensitivity (Catenacci et al., 2016).

IF has also been reported to prevent the progression of age-related chronic diseases, such as cardiovascular disease, diabetes, and cancer, thus contributing to increase healthspan. This positive effect has been observed in both normal and obese individuals (Mattson et al., 2017). Accordingly, a recent randomized controlled trial study reported that 4 weeks of strict ADF improved the markers of general health in healthy, middle-aged humans (Stekovic et al., 2019). ADF has also been found to improve cardiovascular markers and fat-to-lean ratio and reduce fat mass. A reduction in sICAM-1 (an age-associated inflammatory marker) and LDL levels after long-term ADF was also reported (Stekovic et al., 2019).

Although not completely clear, the mechanisms underlying the action of IF seem to involve the activation of some of the same signaling pathways that are involved in CR; these ultimately stimulate mitochondrial function, DNA repair, and stem cell regeneration (Mattson et al., 2017). Further research is necessary to characterize the mechanisms and thoroughly understand the effects of IF.

6.1.3. *Dietary supplements*

Antioxidants are molecules capable of neutralizing free radicals by donating an electron. They are involved in suppressing the oxidation of cellular substrates, thus preventing free radical-induced damage to lipids, proteins, and DNA. Therefore, antioxidants play a major role in preventing diseases with an oxidative stress component, including neurodegenerative diseases, obesity, diabetes, CVD, and cancer (Lobo et al., 2010).

A recent meta-analysis aiming at understanding the association between obesity and antioxidant micronutrients revealed generalized lower concentrations of antioxidants in obese individuals worldwide. The same study reported that the levels of carotenoids, vitamins E, and C, as well as zinc, magnesium, and selenium, were inversely correlated with obesity and body fat mass (Tan et al., 2016). The concentration of micronutrients such as vitamin B12 (Baik and Russell, 1999), folic acid (Clarke et al., 2003), niacin, and trace elements (Blumberg, 1997) also seems to decrease with aging, potentially contributing to age-related neurodegeneration and cancer.

Therefore, nutritional intervention strategies aiming at the maintenance of the antioxidant capacity and overall efficiency of cellular functions might be relevant in both obese and elderly individuals. Supplemental nutrient administration and the addition of selective nutrients to food (food fortification) might also be beneficial in mitigating the risk of developing age-associated diseases in healthy young individuals.

6.1.3.1. *Phytochemicals.*

The diet is the most important source of antioxidants for the body. Fruits and vegetables are a rich source of phytochemicals, *i.e.*, plant compounds with health-promoting properties, including antioxidant and anti-inflammatory effects (Pandey and Rizvi, 2009; Arulselvan et al., 2016).

Dietary polyphenols present in plants have been found to reduce adipocyte viability and preadipocyte proliferation, suppress adipocyte differentiation and triglyceride accumulation, stimulate lipolysis and fatty acid β-oxidation, and reduce inflammation (Anderson and Polansky, 2002; Notarnicola et al., 2011; Hwang et al., 2005; Hung et al., 2005; Furuyashiki et al., 2004; Chan et al., 2011; Moon et al., 2007; Liu et al., 2006; Lee and Kim, 2009; Lin et al., 2005; Lee et al., 2009a; Ku et al., 2012, 2009; Kim et al., 2010). The anti-obesity effect of dietary polyphenols is possibly mediated by (1) lowered food intake; (2) decreased lipogenesis; (3) increased lipolysis; (4) stimulation of fatty acid β-oxidation; (5) inhibition of adipocyte differentiation and growth, and (6) attenuation of inflammatory responses and suppression of oxidative stress (Hwang et al., 2005; Moon et al., 2007; Wang et al., 2006a, b; Rayalam et al., 2008; Zhang et al., 2012).

Animal studies have shown significant effects of polyphenols on obesity, including a reduction in body weight, fat mass, and triglycerides levels, associated with polyphenol-mediated enhanced energy expenditure and fat utilization as well as modulation of glucose homeostasis

(Tian et al., 2013; Shimotoyodome et al., 2005; Lu et al., 2012; Klaus et al., 2005; Kim et al., 2009; Friedrich et al., 2012; Cunha et al., 2013; Chung et al., 2012; Chen et al., 2011, 2009; Bruno et al., 2008; Bose et al., 2008; Shen et al., 2012; Axling et al., 2012; Ashida et al., 2004; Sayama et al., 2000; Sae-tan et al., 2011; Richard et al., 2009; Ramadan et al., 2009; Park et al., 2012, 2011; Monteiro et al., 2008). Clinical trials have also revealed an ameliorating effect of polyphenols on inflammatory biomarkers and cardiovascular parameters (Medina-Remon et al., 2017), as well as an association between polyphenol intake and reduced body weight (Guo et al., 2017).

Protective effects of polyphenols on age-related cognitive decline and dysfunction have also been reported in animal models (e.g. (Carey et al., 2017; Bensalem et al., 2018; Tian et al., 2011; Papandreou et al., 2009)). However, results from clinical trials in human subjects are inconsistent, with polyphenols exerting either a non-significant (Bell et al., 2020) or significant protective effect on cognitive function (Lefevre-Arbogast et al., 2018).

Resveratrol, a polyphenol naturally present in red wine and other plants, is perhaps the most widely known antioxidant polyphenol. In animal models, resveratrol has been reported to reduce fat accumulation through the inhibition of adipogenesis in white adipose tissues (Fernandez-Quintela et al., 2017). An ameliorating effect of resveratrol on cognitive function in aged mice has also been reported (Liu et al., 2012; Qi et al., 2019; Zhao et al., 2013; Toth et al., 2014; Harada et al., 2011; Oomen et al., 2009). Despite the small number of participants, at least in one human trial in individuals with mild to moderate AD, resveratrol was found to stabilize Aβ40 levels in the plasma and cerebrospinal fluid, whose decline is associated with dementia and brain pseudoatrophy, as well as lower cancer incidence in the treatment group (Sawda et al., 2017).

However, adverse effects related to the consumption of polyphenolic botanical extracts in beverages have been reported, particularly in subjects with degenerative disease, high blood pressure, thyroid disease, epilepsy, or heart disease (Jackson and Paliyath, 2011).

Another group of phytochemicals with potential to confer protection against diseases with an inflammatory component are phytosterols and phytoestrogens. The anti-inflammatory effects of plant sterols/stanols have been demonstrated *in vitro* and in experimental animal models (Rietjens et al., 2017; Aldini et al., 2014; Hu et al., 2017). Plant sterol-enriched diets were found to prevent long-term cognitive deficits in senescent-accelerated mice strain 8 (SAMP8), in addition to reducing abnormally high amyloid peptide levels in the brain and restoring membrane compartmentalization of presenilin 1, a catalytic component of the amyloidogenic γ-secretase (Perez-Canamas et al., 2016). However, clinical trials have not been able to demonstrate a significant beneficial effect of phytosterols on anthropometric indices (Ghaedi et al., 2019).

Several health benefits of phytoestrogens have been identified, including lowered risks of menopausal symptoms (osteoporosis), cardiovascular disease, obesity, metabolic syndrome, type 2 diabetes, brain disorders, and certain cancer types (Patisaul and Jefferson, 2010; Jungbauer and Medjakovic, 2014; Zhao and Mu, 2011; Bhathena and Velasquez, 2002; Cederroth and Nef, 2009; Hughes, 1988; Adlercreutz, 2002; Yildiz, 2005). In particular, dietary soy consumption has been associated with decreased body weight (Bosello et al., 1988), body fat (Kawano-Takahashi et al., 1986; Aoyama et al., 2000; Velasquez and Bhathena, 2007), and plasma glucose (Kawano-Takahashi et al., 1986; Aoyama et al., 2000), cholesterol, and triacylglycerol levels (Bosello et al., 1988). The phytoestrogen prunetin was found to not only affect body composition but also improve fitness and extend lifespan in male *Drosophila melanogaster* (Piegholdt et al., 2016). Such protective effects are believed to be mediated via the effects of phytoestrogens on pancreatic insulin secretion, antioxidant systems, and/or via estrogen receptor-mediated mechanisms. Phytoestrogens might also modulate the secretory profile of adipocytes (Jungbauer and Medjakovic, 2014).

Phytoestrogens can also exert neuroprotective effects by attenuating toxic insults to neurons and microglial inflammatory responses (Chen et al., 2008). For example, *in vitro* studies have shown that the phytoestrogens genistein and daidzein attenuated toxin-induced plasma--membrane damage in neurons (Zhao et al., 2002) and improved cell viability (Pan et al., 2012). The phytoestrogen flavonoids quercetin and kaempferol were also shown to prevent oxidative stress-induced neuronal cell death (Gagne et al., 2003). Besides its direct effects on brain cells, phytoestrogens can alter the resident gut flora populations and, in turn, affect neurobehavioral functions through the microbiome-gut-brain axis (Marshall et al., 2019). *in vivo* studies have also reported neuroprotective effects of dietary phytoestrogens (MacLusky et al., 2017). For instance, rats fed with a diet containing soy-derived phytoestrogens exhibited improved learning and memory compared to rats on a control diet (Lee et al., 2009b). Additionally, pretreatment with phytoestrogens protected mice from neurotoxicity in chemically-induced Parkinson's disease (PD) (Liu et al., 2008). These studies suggest that phytoestrogens might alter the structure and/or function of both healthy and diseased neurons.

It is important to note that phytoestrogens might act as endocrine disruptors (Patisaul, 2017), potentially causing adverse health effects (Messina, 2008; Hilakivi-Clarke et al., 2010). Since current available information is not sufficient to support a thorough quantitative risk-benefit analysis, a definite conclusion on possible beneficial health effects of phytoestrogens cannot be made (Rietjens et al., 2017).

Studies in animal models have also shown that several herbal polysaccharides with antioxidant and anti-inflammatory capacities display beneficial health effects including anti-obesity and anti-diabetic properties (Friedman, 2016; Li et al., 2011), neuroprotective action (Zhang et al., 2011; Xia et al., 2012) and anti-tumor effects (Sreenivasulu et al., 2010). Whether such effects can be translated to humans remains to be addressed.

6.1.3.2. Polyamines. Polyamines play important roles in cell growth, survival, and proliferation. Aging and age-related diseases are accompanied by changes in polyamine levels. Accordingly, polyamine (spermidine or high-polyamine diet) supplementation has been found to increase lifespan in model organisms in an autophagy-dependent manner and protect against age-associated pathologies including CVD, neurodegeneration, and cancer (Minois et al., 2011).

The reported beneficial effects of dietary spermidine supplementation in animal models include improvements in cognitive (Sigrist et al., 2014; Gupta et al., 2013) and cardiovascular function (Kiechl et al., 2018), glucose homeostasis, and insulin sensitivity accompanied by reduced adiposity and hepatic fat accumulation (Sadasivan et al., 2014). Because its biological and biochemical actions seem to be similar to those induced by caloric restriction, spermidine has been classified as a "caloric restriction mimetic" (Madeo et al., 2014). However, clinical trials addressing the potential health benefits of polyamines are lacking. Importantly, possible contraindications of spermidine include renal failure. Future research should aim at developing artificial spermidine analogs with increased potency and improved pharmacokinetic characteristics.

6.1.3.3. Dietary fats. Dietary lipids not only provide energy but also regulate various cellular functions. Dietary fatty acids can be classified as essential (omega-3 and omega-6 families), saturated, monounsaturated, and polyunsaturated fatty acids (PUFA). Intake of long-chain omega-3 PUFA [eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA)] or fish oil seems to exert beneficial anti-inflammatory effects on cardiovascular, degenerative, neurological, inflammatory, and autoimmune diseases, as well as age-related macular degeneration (Ruxton et al., 2007; Simopoulos, 2002; Watanabe and Tatsuno, 2017; Adkins and Kelley, 2010; Mori and Beilin, 2004; Weber and Leaf, 1991; Woods et al., 2000). The anti-inflammatory properties of omega-3 PUFAs have been attributed to their capabilities to compete with

omega-6 PUFAs and displacing arachidonic acid in membrane phospholipids, thus, decreasing the production of pro-inflammatory eicosanoids (Simonetto et al., 2019). Omega-3 fatty acids can also exert health benefits by regulating other biochemical functions, including cell membrane fluidity, intracellular signaling, and gene expression (Avallone et al., 2019). However, results from clinical trials examining the protective or ameliorating effect of PUFA on age-related cognitive dysfunction are inconsistent (Abbott et al., 2003; de Lau et al., 2005; Burckhardt et al., 2016; Gao et al., 2007; da Silva et al., 2008; Taghizadeh et al., 2017; Kalmijn et al., 1997; Morris et al., 2003; Barberger-Gateau et al., 2007; Huang et al., 2005; Schaefer et al., 2006).

6.2. Physical exercise

The therapeutic value of physical exercise and cardiorespiratory fitness for obesity prevention, management, and/or treatment is well recognized (Hong et al., 2014). The protective effect of regular exercise against chronic metabolic and cardiorespiratory diseases is, at least in part, due to its anti-inflammatory effects (Gleeson et al., 2011; Boule et al., 2003; Pedersen and Saltin, 2006; Booth et al., 2012; Hamer, 2006). Two possible mechanisms have been proposed to explain the anti-inflammatory effects of exercise: (1) increased production and release of anti-inflammatory cytokines from contracting skeletal muscle (Mathur and Pedersen, 2008); and (2) reduced expression of Toll-like receptors (TLRs) on monocytes and macrophages (Flynn et al., 2003) with subsequent inhibition of downstream responses, such as pro-inflammatory cytokine production, antigen presentation, and co-stimulatory molecule expression (Gleeson, 2006). Exercise also inhibits monocyte/macrophage infiltration into adipose tissue (Kawanishi et al., 2010), switches the phenotype of adipose macrophages (Kawanishi et al., 2010), reduces the number of circulating pro-inflammatory monocytes (Timmerman et al., 2008), and increases the circulating number of IL-10 secreting regulatory T cells (Yeh et al., 2006; Wang et al., 2012).

Exercise may also slow the aging process. Regular physical activity has been related to significantly longer telomeres (Tucker, 2017). Interestingly, the association between exercise and telomere length seems to be strongest in people aged 45–65 years old, suggesting that middle age may be the key time to begin or maintain an exercise program to preserve telomere length. Most notably, adults with a high level of physical activity were found to have a “biological aging advantage” of nine years compared to sedentary adults (Tucker, 2017). The protective effects of exercise on telomere length can potentially be attributed to the anti-inflammatory effects of exercise previously described (Gleeson et al., 2011). Also, the production of low levels of ROS during a mild physical training program can potentially induce beneficial adaptive responses via mitohormesis (Ji et al., 2010). Physical activity directly reduces inflammation and indirectly affects inflammation by reducing adiposity, which in turn reduces fat mass and fat-derived inflammatory adipokines (Abramson and Vaccarino, 2002; Pischon et al., 2003; Geffken et al., 2001). Exercise interventions, such as resistance training and aerobic exercise, were found to preserve fat-free mass, enhance aerobic capacity, increase fat oxidation, and reduce the tendency toward increased adiposity in obese elderly individuals (Seim and Holtmeier, 1993). Even in the absence of a significant change in body weight, exercise improved insulin sensitivity, and increased glucose utilization (Seim and Holtmeier, 1993).

While there is a consensus that regular short-lasting moderate-intensity exercise is beneficial for host immune defense, the infection burden is reported to be high among high-performance athletes and is the second most common cause of the number of training days lost during preparation for major sporting events (Simpson et al., 2020). Enhanced oxidative stress associated with increased respiration during physical activity (Powers and Jackson, 2008), as well as altered cytokine production (Maziere et al., 2005; Haddad, 2002), have been proposed to account for such an effect.

6.3. Pharmacological interventions

For many years, the scientific community has searched for a pharmacological cure for obesity. Early therapies included the use of thyroid hormone and appetite suppressants, such as phenylpropanolamine and amphetamine, which were associated with adverse side effects far outweighing the expected benefits (Weigle, 2003). More recent pharmacological therapies for obesity have focused on the use of thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor γ (PPAR-γ) agonists. PPAR-γ is a nuclear transcription factor highly expressed in adipose tissue. Its activation has anti-inflammatory benefits, including attenuation of TNF-α and IL-6 expression, and reduction of plasma FFA and glucose levels. TZDs also inhibit the expression of the leptin gene (Kallen and Lazar, 1996) and increase the plasma levels of adiponectin (Yu et al., 2002), improving insulin sensitivity. Adenosine monophosphate-activated kinase (AMPK), a protein with an important role in controlling energy homeostasis (Heidrich et al., 2010), is also activated by TZDs (Martinez de Morentin et al., 2016; LeBrasseur et al., 2006). Interestingly, in animal models of AD, TZDs have been shown to decrease Aβ deposition (Heneka et al., 2005; Jiang et al., 2008b; Pedersen et al., 2006; Lacombe et al., 2004), inflammation (Heneka et al., 2005; Landreth and Heneka, 2001; Feinstein, 2003), and oxidative stress (Nicolakakis et al., 2008). Although effective, TZDs can cause adverse side effects, including increased fluid retention, increased incidence of heart failure, and increased peripheral fractures (Nesto et al., 2003; Kahn et al., 2008; Desouza and Shivaswamy, 2010).

Orlistat is another anti-obesity drug that exerts its actions via inhibition of gastrointestinal lipases and, therefore, reduces the absorption of dietary fat by about one-third (Hauptman, 2000). Remarkably, a potential therapeutic role for orlistat in AD has also been proposed (Du and Wang, 2009). This suggestion is based on the importance of hyperlipidemia in the etiology of AD (Burgess et al., 2006; Kivipelto and Solomon, 2006) and thus the hypothesis that drugs that inhibit lipase activities, thereby reducing dietary fat intake and ameliorating hyperlipidemia, could confer protection against AD (Du and Wang, 2009).

Acarbose is a complex oligosaccharide that exerts hypoglycemic action by inhibiting glucose absorption in the gut, making it a first-line therapy for newly diagnosed patients with type 2 diabetes (Laube, 2002; Chiasson et al., 2002). Chronic acarbose treatment has been found to significantly reduce body weight and body fat, and improve age-associated glucose dysregulation (Yamamoto and Otsuki, 2006). Acarbose was also found to significantly increase healthspan and lifespan in male mice (Harrison et al., 2014, 2019). Enhanced hepatic mTORC2 signaling, increased Akt activity, and phosphorylation of FOXO1a following acarbose treatment have been hypothesized to play a role in the lifespan extending effects of acarbose, at least in males (Garratt et al., 2017). A role of the gut microbiota in the longevity-enhancing properties of acarbose has also been proposed (Smith et al., 2019). Protective effects of acarbose against age-related neurodegeneration have been suggested (Tong et al., 2015; Yan et al., 2015) and reduced risk of dementia associated with acarbose use in type 2 diabetes patients (Tseng, 2020) have been reported as well.

Sodium glucose cotransporter 2 (SGLT2) inhibitors are also antidiabetic drugs with anti-obesity potential. SGLT2 inhibitors reduce hyperglycemia by inhibiting glucose reabsorption in the proximal tubule of the kidney. Besides hypoglycemic effects, SGLT2 inhibitors such as empagliflozin, tofogliflozin and canagliflozin have been found to reduce fat mass and promote weight loss in both diabetic and non-diabetic obese individuals (Wei et al., 2020; Bays et al., 2014; Matsuba et al., 2018; Stenlöf et al., 2013, 2014; Ferrannini et al., 2010). Canagliflozin, in particular, was found to mitigate HFD-mediated increases in body weight, liver weight, and fat weight (Naznin et al., 2017). The anti-obesity effects of SGLT2 seem to be, at least in part, mediated by the attenuation of the levels of pro-inflammatory biomarkers and macrophage accumulation (Naznin et al., 2017; Bonnet and Scheen, 2018;

Wong et al., 2005). These results suggest that SGLT2 inhibition disrupts the vicious cycle of obesity and inflammation, not only by promoting caloric loss, but also by suppressing obesity-related inflammation in both the nervous system and skeletal muscle (Naznin et al., 2017). Interestingly, preliminary results suggest an effect of canagliflozin on the lifespan of male mice, but not female, similarly to acarbose, denoting the preventative potential of interventions that control daily peak glucose levels against late-life neoplastic and degenerative diseases (Miller et al., 2020).

As previously mentioned, CR has great potential against obesity, cancer, and aging. However, due to the difficulty of complying with a low-calorie diet for an extended period, the identification of chemical agents that could reproduce the beneficial effects of CR without drastic changes in diet and lifestyle is an appealing alternative. The search for CR mimetic drugs has taken two main paths: (1) finding drugs that reproduce the general metabolic state of food deprivation associated with CR; and (2) finding agonists/antagonists of specific molecules upstream of the pathways by which CR exerts its beneficial effects.

The first category includes a structural analog of glucose, 2-deoxy-D-glucose (2-DG), that acts as a competitive inhibitor of glycolysis. 2-DG has been shown to replicate key hallmarks of CR such as reduced body temperature (Ingram et al., 2006), increased torpor (Derous et al., 2016), reduced heart rate (Wan et al., 2004), and reduced circulating levels of glucose and insulin (Lane et al., 1998). Administration of 2-DG in rats was found to reduce plasma insulin levels and body weight (Seim and Holtmeier, 1993). Protective effects of 2-DG against cancer (Aft et al., 2002), epilepsy (Stafstrom et al., 2009), and neurodegeneration (Yao et al., 2011) have also been reported. While 2-DG has been shown to work as a CR mimetic at high doses, chronic high doses of 2-DG have also been linked to increased mortality in rats (Minor et al., 2010). Chronic low-dose dietary administration of 2-DG has been proposed as an effective alternative (Saraswat et al., 2019).

Given the involvement of IGF-1, Akt/mTOR, and sirtuins in CR-mediated protective effects, these pathways have emerged as promising upstream targets for new CR mimetics. Small-molecule inhibitors of IGF-1, antisense inhibitor approaches, anti-IGF-1 antibody therapies, and microRNA-based approaches are under development (Sachdev and Yee, 2007; McKinsey et al., 2011). Pharmacological mTOR inhibitors are also lead candidates for CR mimetics. For instance, treatment with the mTOR inhibitor rapamycin was found to extend lifespan and delay cancer in mice (Harrison et al., 2009). Both rapamycin and its analog RAD001 (everolimus) have also been found to offset the obesity-associated increased growth of mammary and pancreatic tumors (Lashinger et al., 2011; De Angel et al., 2013). Metformin, a biguanide commonly used to treat type 2 diabetes, is another promising CR mimetic that inhibits mTOR signaling and circumvents the side effects of hyperglycemia and insulin resistance that occur with rapamycin (Pollak, 2012). Metformin inhibits gluconeogenesis through indirect activation of AMPK in the liver (Pollak, 2012). Administration of metformin has been found to suppress tumor development and/or growth in multiple experimental models, including colon, mammary, and hematopoietic cancer models (Pollak, 2012). Epidemiological studies have suggested that type 2 diabetic patients treated with metformin have a lower cancer risk and mortality compared to diabetic patients receiving sulfonylurea, insulin, or other therapies (Dowling et al., 2012; Decensi et al., 2010; Currie et al., 2009). Metformin has also been found to increase healthy lifespan in several model organisms (Martin-Montalvo et al., 2013; Ma et al., 2007; Anisimov et al., 2010, 2011; Anisimov et al., 2008; Cabreiro et al., 2013b; De Haes et al., 2014). These effects have been attributed to metformin-induced decrease of insulin levels and IGF-1 signaling (Liu et al., 2011), inhibition of mTOR signaling (Rai et al., 2018; Nair et al., 2014; Kickstein et al., 2010), reduction of endogenous ROS production (Zheng et al., 2012; Bridges et al., 2014; Batandier et al., 2006), activation of AMP-activated kinase (AMPK) (Zheng et al., 2012; Foretz et al., 2010; Lien et al., 2014; Lu et al., 2015; Duca et al., 2015; Cho et al., 2015), and reduction in DNA damage (Algire et al., 2012). Other aging and obesity-associated processes against which a protective effect of metformin has been reported include inflammation (Saisho, 2015) and cellular senescence (Jadhav et al., 2013; Moiseeva et al., 2013). A protective role of metformin against cognitive decline has also been revealed from epidemiologic and observational studies (Ng et al., 2014; Cheng et al., 2014).

Phenformin, another biguanide that has been abandoned for diabetes therapy due to its toxicity from lactic acidosis, is a more potent AMPK inhibitor than metformin and may also have some potential as a CR mimetic for cancer prevention at lower, nontoxic doses (Pollak, 2012). Like metformin, phenformin has been found to extend maximum lifespan in *C. elegans* (Curtis et al., 2006) and non-diabetic rodents (Dilman and Anisimov, 1980; Anisimov et al., 2003), an effect potentially mediated by phenformin-induced reduction of oxidative stress levels (Anisimov et al., 2005). Protective effects of phenformin against neuronal death (Lee et al., 2002) and radiation-induced neurodevelopmental toxicity (Gan et al., 2019) have also been reported. Whether such an effect can be extended to aging and obesity-associated neurodegeneration remains to be investigated.

Another compound that has been classified as a CR mimetic is the ketone body beta-hydroxybutyrate (βHB) (Newman and Verdin, 2014). βHB is naturally produced in the mammalian liver, primarily from the catabolic breakdown of fatty acids, and is used as an alternative energy source when blood glucose is low. It is also a specific inhibitor of class I histone deacetylases and administration of exogenous βHB results in increased histone acetylation of genes encoding the oxidative stress resistance factors Foxo3a and Mt2 promoters, accompanied by increased protection against oxidative stress (Shimazu et al., 2013). βHB supplementation was found to extend the mean lifespan of *C. elegans* by approximately 20%, delay Alzheimer's amyloid-beta toxicity and decrease Parkinson's alpha-synuclein aggregation (Edwards et al., 2014). The lifespan- extending effect of βHB is dependent on SIR-2.1 and the AMP kinase subunit AAK-2 and the DAF-16/FOXO and SKN-1/Nrf longevity pathways (Edwards et al., 2014). In mammals, βHB attenuated the SASP phenotype (SASP) and the senescence of vascular cells (Han et al., 2018). An anti-inflammatory action of β-hydroxybutyrate was recently reported in aging kidneys and this effect was attributed to increased interaction between FoxO1 and PGC-1α induced by βHB (Kim et al., 2019b). Neuroprotective actions of βHB have also been reported in models of age-induced neurodegeneration (Tieu et al., 2003; Kashiwaya et al., 2000). Besides exogenous administration, evidence for the beneficial effects of βHB on lifespan have also been revealed through the ketogenic diet. The ketogenic diet is characterized by a very low carbohydrate content (< 20 g per day), high fat (15–30 g per day) consumption, which results in the production of ketones bodies, including βHB. Ketogenic diets have been reported to reduce weight more effectively than pure calorie restriction or a low-fat diet (Brehm et al., 2003; Moreno et al., 2014; Yancy Jr et al., 2004). The ketogenic diet has also been reported to extend lifespan and healthspan in adult and aging mice (Roberts et al., 2017; Newman et al., 2017; Simeone et al., 2016), at least in part by upregulating PPARα target genes (Newman et al., 2017). Besides weight loss, the ketogenic diet was also found to result in a histologic improvement of NAFLD patients (Tendler et al., 2007). While the effectiveness and safety of the ketogenic diet for the treatment of obesity is well documented (e.g. (Yancy Jr et al., 2004; Goday et al., 2016; Bruci et al., 2020; Pilone et al., 2018; Bueno et al., 2013)), there are still reservations regarding their long-term effects (Ludwig, 2020).

Pharmacologic modulators of SIRT1 (Baur and Sinclair, 2006; Aljada et al., 2010) are also promising therapeutic targets. For instance, SRT1720, a synthetic compound that can activate SIRT1 *in vitro*, has been found to extend both the mean and maximum lifespan of adult mice fed a high-fat diet (HFD) (Mitchell et al., 2014). This lifespan extension was accompanied by health benefits including reduced liver steatosis, increased insulin sensitivity, enhanced locomotor activity, and normalization of gene expression profiles and markers of inflammation and apoptosis. The benefits of this molecule were ascribed to its effects

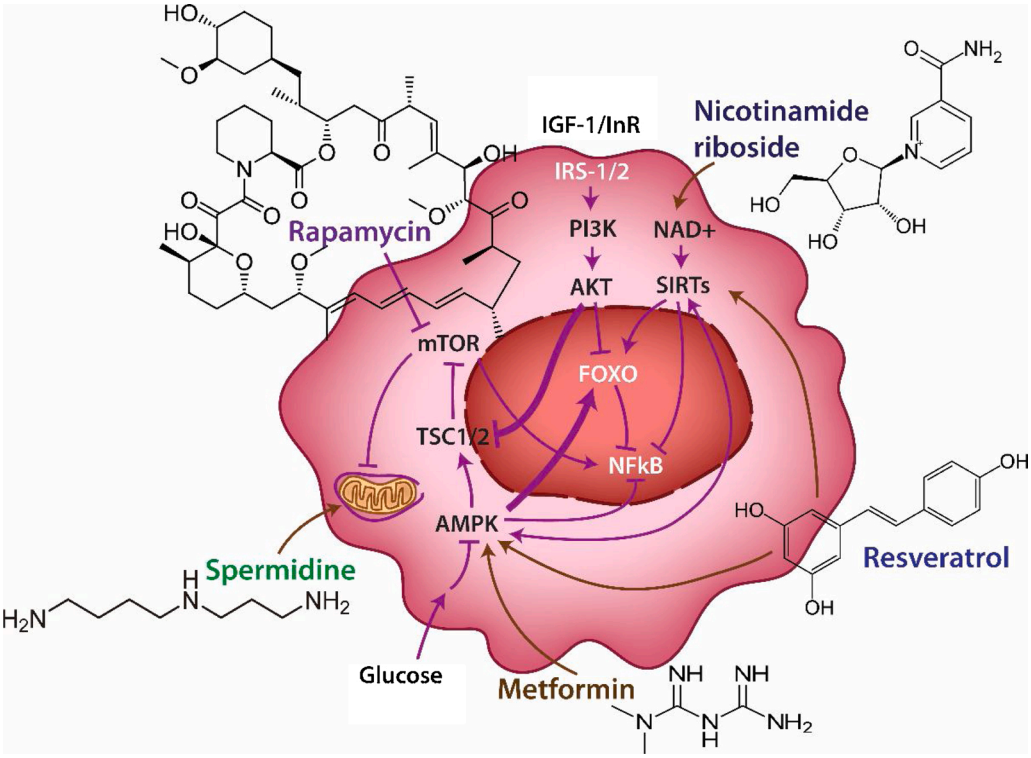

Fig. 4. Pharmacological interventions targeting aging and obesity. The health benefits of rapamycin are exerted via inhibition of mTOR. Metformin activates AMPK to inhibit mTOR and downstream signaling. Spermidine protects and stabilizes mitochondria. AMPK and SIRT1 are involved in resveratrol-mediated protection from metabolic and age-related. The effects of nicotinamide riboside on health and lifespan are mediated via sirtuins. Reproduced with permission from Qian and Liu (2019).

on mitochondrial respiration in a SIRT1- and PGC-1α-dependent manner (Minor et al., 2011). SRT1720 was also found to protect mice against obesity, increase mitochondrial biogenesis, energy metabolism, and glucose tolerance (Feige et al., 2008; Milne et al., 2007), and decrease hepatic lipid accumulation (Walker et al., 2010; Yamazaki et al., 2009). These effects are believed to be mediated by AMPK and SIRT1 activation via interlinked pathways (Park et al., 2017).

Nicotinamide, a precursor of coenzyme NAD^+, is used for NAD^+ synthesis through the salvage pathway (Jackson et al., 1995). Nicotinamide displays a protective effect in a variety of cell types (Sakai et al., 2002; Vaca et al., 2003). For instance, nicotinamide has been found to confer protection against physical and chemical damage in mouse bone marrow cells (Guruprasad et al., 2002), protect brain cells from oxidative damage caused by reperfusion after ischemic infarction (Mokudai et al., 2000; Klaidman et al., 2003), and prevent injury of pancreatic islet cells during free radical exposure (Kallmann et al., 1992). In normal human fibroblasts, nicotinamide has been found to not only attenuate the aging phenotype but also increase the cell's replicative lifespan. This effect was accompanied by reduced levels of ROS and oxidative damage and deceleration of the telomere shortening rate (Kang et al., 2006).

Chronic nicotinamide supplementation in mice on HFD was found to improve glucose homeostasis, accompanied by reduced hepatic steatosis and inflammation, concurrent with increased glycogen deposition and flux through the pentose phosphate and glycolytic pathways. This effect was associated with nicotinamide-enhanced acetylation of some of SIRT1's targets (Mitchell et al., 2018). These results are consistent with previous reports that the NAD^+ precursor nicotinamide ribonucleoside can activate SIRT1 and SIRT3, resulting in enhanced oxidative metabolism and protection against HFD-induced metabolic abnormalities (Canto et al., 2012). Some of the most relevant pharmacological interventions to target aging and obesity are represented in Fig. 4.

7. Conclusions and future perspectives

The adipose tissue of obese individuals exhibits several of the hallmarks of aging, including mitochondrial dysfunction, cellular senescence, and chronic inflammation. Therefore, interventions that target these processes should also influence adipose tissue physiology and mitigate further damage. Therapies targeting the fundamental aging mechanism of the adipose tissue described in this review could be used to prevent, manage, and ultimately treat obesity and obesity-associated comorbidities, in addition to providing further information about the aging process itself.

Declaration of Competing Interest

The authors have no competing interests to declare.

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