Molecular and Cellular Endocrinology xxx (2016) 1–10

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

Targeting metabolism in cellular senescence, a role for intervention

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ARTICLE INFO

Article history:
Received 30 April 2016
Received in revised form
29 July 2016
Accepted 30 August 2016
Available online xxx

Keywords:
Senescence
Metabolism
Aging
mTOR
Mitochondria
Rapamycin
Methionine restriction
Lifespan

ABSTRACT

Cellular senescence has gained much attention as a contributor to aging and susceptibility to disease. Senescent cells undergo a stable cell cycle arrest and produce pro-inflammatory cytokines. However, an additional feature of the senescence phenotype is an altered metabolic state. Despite maintaining a non-dividing state, senescent cells display a high metabolic rate. Metabolic changes characteristic of replicative senescence include altered mitochondrial function and perturbations in growth signaling pathways, such as the mTORC1-signaling pathway. Recent evidence has raised the possibility that these metabolic changes may be essential for the induction and maintenance of the senescent state. Interventions such as rapamycin treatment and methionine restriction impact key aspects of metabolism and delay cellular senescence to extend cellular lifespan. Here, we review the metabolic changes and potential metabolic regulators of the senescence program. In addition, we will discuss how lifespan-extending regimens prevent metabolic stress that accompanies and potentially regulates the senescence program.

1. Introduction

Aging is characterized by a reduction in the ability to maintain homeostasis in multiple tissues. This inability to maintain homeostasis is evident at the cellular level and is reflected by a loss in capacity for self repair and renewal, and the appearance of senescent cells. These widespread effects of cellular dysfunction and aging may be due to common cellular and molecular mechanisms. Senescent cells have long been recognized as metabolically active and significant producers of pro-inflammatory cytokines. Less well recognized are the metabolic changes that occur in senescent cells. Interestingly, there is evidence that these metabolic changes may not only be downstream consequences of senescence but also drivers of the senescence arrest. This review will explore these possibilities and provide an overview of the metabolic state of the senescent cell.

Several evolutionary theories of aging, including the antagonistic pleiotropy and mutation accumulation theories, propose that age-related decline has been allowed to occur during evolution because natural selection optimizes for reproductive fitness and declines in post-reproductive years (Kirkwood and Austad, 2000). The low selective pressure during post-reproductive years permits the development of the phenotypes of aging. Possible drivers of aging that would be allowed by natural selection are genes that exhibit antagonistic pleiotropy (providing benefit in early life while being detrimental late in life). Despite the late-acting deleterious effects, these genes are positively selected because they benefit reproductive fitness. Potential examples of genes exhibiting antagonistic pleiotropy are genes encoding for proteins in the insulin-like growth factor type 1 (IGF-I) pathway (linked in mammals to the action of growth hormone) which is a powerful stimulator of cell proliferation and a suppressor of apoptosis. Increased levels of IGF-1 lead to an increase in body size and increased fertility, yet a reduction in activity of this pathway extends lifespan in multiple organisms (Bartke, 2011,Junnila et al., 2013). A direct relationship between reduced IGF-1 and lifespan appears to exist in invertebrates but there is increased complexity in vertebrates due to the evolution of the growth hormone axis, which serves as a key regulator of IGF-1 levels both in the circulation and in a tissue specific manner. It appears that a reduction in both IGF-1 and growth hormone may be required for lifespan extension in mammals (Lorenzini et al., 2014,Sell, 2015). A key intracellular target of the IGF-1 pathway is the serine/threonine kinase mechanistic target of rapamycin complex (mTORC), which is responsive to nutrient availability as well as growth factor signaling. The mTOR complex exists in at least 2 distinct complexes, mTORC1 and

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http://dx.doi.org/10.1016/j.mce.2016.08.049
0303-7207/

mTORC2 which are distinguished primarily by the presence of the scaffold proteins Raptor (in the case of mTORC1) or Rictor (in the case of mTORC2) (Laplante and Sabatini, 2012). A reduction in mTORC1 activity either through reduced IGF-1 signaling or through direct inhibition by the macrolide rapamycin extends lifespan in multiple organisms (Fontana et al., 2010; Johnson et al., 2013a).

Cellular responses may also act in a pleiotropic manner, acting as a protective mechanism in one setting but potentially contributing to aging in another setting. Cellular senescence appears to be such a response, initially by serving as a tumor suppressive response, however, the accumulation of senescent cells over time may contribute to aging and age-related diseases (Campisi, 2003; Giaimo and d'Adda di Fagagna, 2012). In addition to limiting the regenerative capacity of tissues, senescent cells disrupt tissue microenvironment through the senescence-associated secretory phenotype (SASP), a unique secretory pattern that stimulates inflammation (Campisi and Robert, 2014,Childs et al., 2015). Numerous studies have identified the molecular effectors that mediate stable cell cycle arrest and secretory function of senescent cells, and while it is recognized that senescent cells maintain a viable and metabolically active state, studies have not fully defined metabolism during the senescence program nor whether changes in metabolism play a functional role in the senescent phenotype. This review will focus on the key metabolic effectors and alterations in cellular aging and senescence. Emphasis will be placed on key metabolic stressors that drive cellular aging including mitochondrial dysfunction and aberrant mTORC1-signaling. We will discuss the role of lifespan-extending regimens in interfering with metabolic stress that may be necessary for the senescence program.

2. Molecular program of cellular senescence

Cellular senescence was initially defined by Hayflick and Moorhead as a cellular aging process that limits the number of cell divisions that somatic cells can undergo in culture (Hayflick and Moorhead, 1961). Over 30 years later, a primary driver of replicative senescence was identified as the progressive telomere shortening during cell division *in vitro*. However, it has become clear in the past two decades that senescence is also a stress response pathway parallel to apoptosis, that can be activated by multiple stressors including oxidative stress, genotoxic stress, telomere attrition, oncogene conversion (Campisi, 2013), and mitochondrial stress (Nacarelli et al., 2016a; Wiley et al., 2016). Evidence for the importance of senescence in the aging process has accumulated with the identification of senescent cells in multiple tissues as a function of age (Herbig et al., 2006; Jeyapalan and Sedivy), and targeting senescent cells has been reported to provide protection in both progeroid models (Baker et al., 2011) and during normal aging (Baker et al., 2016).

Key regulators of the senescence program are $p53/p21^{CIP1/WAF1}$ and the $p16^{INK4A}$/Rb pathway, which are required to both establish and to maintain the senescence arrest (Herbig et al., 2004,Stein et al., 1999). Activation of $p53/p21^{CIP1/WAF1}$ during senescence has classically been attributed to a DNA damage response (DDR) caused by sustained, unresolved DNA damage through the activation of the Ataxia Telangiectasia Mutant (ATM) kinase (Herbig et al., 2004). However, $p53/p21^{CIP1/WAF1}$ activation leading to senescence may also occur due to other types of stress. Central to this review is the impact of mitochondrial function and metabolism on senescence and the changes that occur in metabolism as a consequence of senescence (summarized in Fig. 1). Several excellent reviews have recently been published describing the mechanisms of the senescence program, chromatin associated changes during senescence (Parry and Narita, 2016), and the relationship between mitochondria and the aging process (Childs et al., 2015,Sun et al., 2016). These references can be consulted for a more complete description of the fundamentals of cellular senescence and the relationship between mitochondrial function and aging.

3. Metabolic alterations in cellular aging and senescence

3.1. Changes in glucose metabolism in cellular senescence

Although in a state of stable growth arrest, senescent cells exhibit a highly active metabolism that may be essential to the senescent phenotype. Seminal studies on the metabolism of cellular senescence show that both glucose consumption and lactate production are elevated during replicative aging and senescence (Bittles and Harper, 1984,Goldstein et al., 1982). Elevated glycolysis during senescence in response to several senescence triggers including; oncogene-induced senescence (Moiseeva et al., 2009), genotoxic stress-induced senescence (Dorr et al., 2013,Liao et al., 2014,Wang et al., 2016), and replicative senescence (James et al., 2015,Takebayashi et al., 2015). Elevated glycolysis corresponded with increased extracellular acidification, which is primarily due to increased production of lactate (Mookerjee et al., 2015). In the case of replication stress-induced senescence, cells restricted glucose and glutamate metabolism in an ATM-dependent manner. During replicaton stress deoxyribonucleotide triphosphate (dNTP) become limiting and ATM prevented compensatory increases in the pentose phosphate pathway by activating p53 and destabilizing myc (Aird et al., 2015). Indeed, suppression of nucleotide metabolism combined with aberrant stimulation of DNA replication underlies oncogene-induced senescence, and knocking down ATM or overexpressing ribonucleotide reductase subunit M2, a rate-limiting component of ribonucleotide reductase that synthesizes dNTPs, bypasses replication stress-induced and oncogene-induced senescence, respectively (Aird et al., 2013, 2015). Several studies suggest that glycolysis is elevated during cellular senescence due to upregulation of key glycolytic enzymes (Dorr et al., 2013,James et al., 2015). It appears that the specific signaling events that lead to the upregulation of glycolytic genes during cellular senescence depends on the stimulus. For example, irradiation activated and required AMPK and NF-κB signaling to stimulate glycolysis and induce cellular senescence (Takebayashi et al., 2015). This response was coupled with increased activity of lactate dehydrogenase A and expression of monocarboxylate transporter 1 (Liao et al., 2014). In contrast, oncogene-induced senescence relies on retinoblastoma to transcriptionally upregulate a series of glycolytic enzymes that elevate glycolysis and increase extracellular acidification (Takebayashi et al., 2015). Both glycolysis and elevated lactate each have been shown to activate the NF-κB pathway, forming a positive feedback loop. Since NF-κB signaling transcriptionally upregulates many SASP genes, it is possible that senescent cells elevate glycolysis to activate pro-inflammatory signaling. Alternatively, the secretion of lactate may contribute to the ability of the senescent cells to evade immune cells (Haas et al., 2015) and promote wound healing and tumorigenesis (Capparelli et al., 2012,Hirschhaeuser et al., 2011).

Data opposing elevated glycolysis as a feature of cellular senescence has also been reported. A proteomics analysis revealed that oncogene-induced senescence was accompanied by an “anti-Warburg” effect involving the downregulation of glycolytic enzymes, but an upregulation of mitochondrial proteins, particularly genes related to pyruvate metabolism and oxidative phosphorylation (Li et al., 2013).

3.2. Changes in mitochondrial function during aging

Depending upon the stimulus, somatic cells are triggered to

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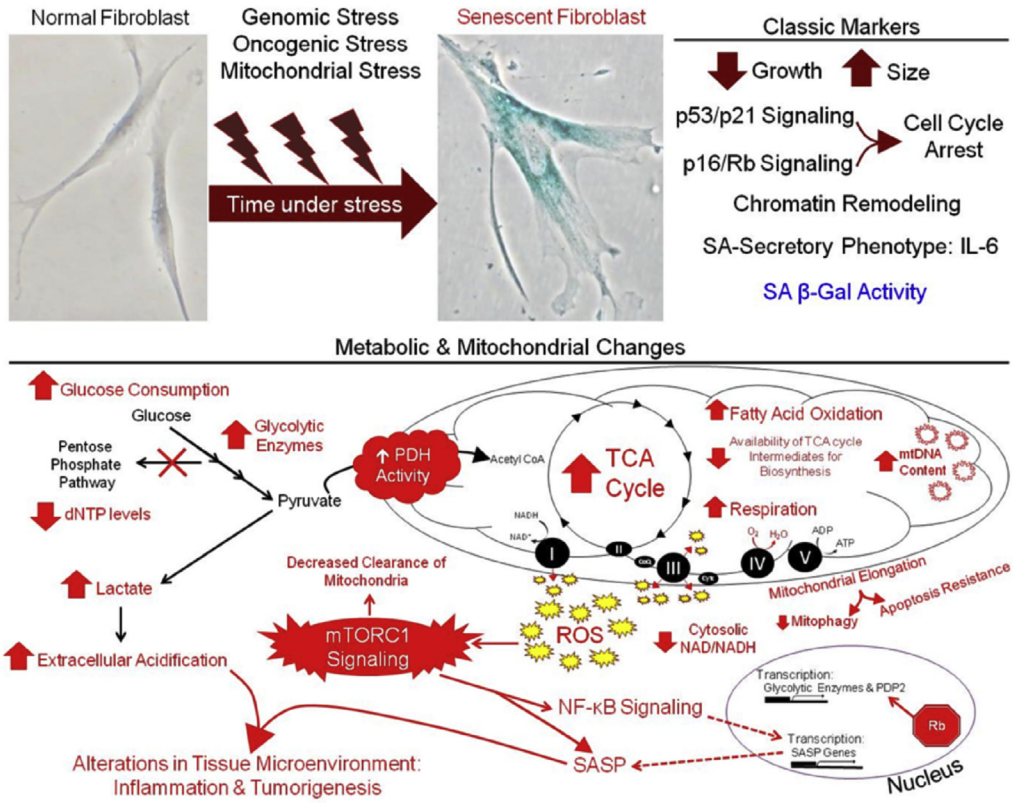

Fig. 1. Metabolic and mitochondrial changes in cellular senescence.

undergo cell fate decisions which include cell division or cell cycle arrest and differentiation, and stress responses, such as apoptosis and senescence. These cell fate decisions are modulated by both extrinsic and intrinsic modulators. Extrinsic modulators include cell-cell and cell-matrix contacts, growth factor and hormonal stimulation while intrinsic modulators include genomic integrity, DNA damage, ATP levels, and appropriate availability of metabolic precursors. A large number of these intrinsic modulators rely on mitochondrial function. For example, changes in mitochondrial activity are especially important, if not required, in the metabolic alterations which are present in cancer and apoptotic cells (Mason and Rathmell, 2011,Wallace, 2012). Mitochondria control a range of cellular processes including aerobic metabolism for the production of ATP and critical metabolic intermediates, calcium homeostasis, apoptotic signaling, beta-oxidation, and regulations of redox status. Cellular signals or altered status are also relayed by the mitochondria communicating to the nucleus to alter gene expression through retrograde signaling which is vital not only for adapting cellular energy status, but also for maintaining mitochondrial quality control (Quiros et al., 2016).

Beyond supporting proliferation by supplying the necessary levels of ATP, the mitochondria achieve a balance of catabolic and anabolic reactions that maintains the redox state, recycles the reduced-energy equivalents NADH and $FADH_2$, and also produce biosynthetic precursors for nucleotides, amino acids, and fatty acids (DeBerardinis et al., 2008,Mailloux, 2015). These metabolic reactions within the mitochondria are mediated by the tricarboxylic acid (TCA) cycle that oxidizes acetyl CoA into carbon dioxide. The primary carbon source that fuels the TCA cycle is pyruvate derived from glucose through glycolysis. However, other carbon sources such as amino acids, particularly glutamine, and fatty acids also fuel the TCA cycle. The cofactors produced during the TCA cycle are recycled after donating their electrons into the electron transport chain (ETC) to drive respiration and oxidative phosphorylation. In addition, reducing equivalents produced by the TCA cycle can impact the cytoplasmic NAD^+/NADH ratios, through the malate-aspartate and glycerol-3-phosphate shuttles, influencing NAD^+/NADH homeostasis and the activity of metabolic enzymes (Canto et al., 2015,Stein and Imai, 2012). Decreased NAD^+/NADH ratio following ETC dysfunction has been recently shown to impair cell proliferation by restricting the biosynthesis of aspartate and orotate that are critical biosynthetic precursors for amino acids and nucleotides. Proliferation was rescued following ETC dysfunction by culturing cells with a supra-physiological concentration of pyruvate that restored the NAD^+/NADH ratio and the biosynthesis of aspartate (Birsoy et al., 2015,Sullivan et al., 2015). The TCA cycle intermediates also play an epigenetic role by altering DNA and histone methylation and histone acetylation (Salminen et al., 2014). The mitochondria use these metabolic activities to coordinate energy status, epigenetic alterations, and biosynthetic potential to influence the proliferative state of cells.

Cellular dysfunction during aging is characterized by mitochondrial defects in which the most prominent features include diminished function, structural disorganization, and increased mitochondrial DNA (mtDNA) mutations. These alterations are common in aged tissues and are associated with age-related pathologies (Bratic and Larsson, 2013,Cagin and Enriquez, 2015). For example, respiratory function declines during aging in skeletal muscle (Porter et al., 2015) and contributes to weakened aerobic fitness and increased fatigue in humans (Coen et al., 2013,Santanasto et al., 2015). Cellular dysfunction during aging is characterized by mitochondrial defects in which the most prominent features include diminished function, structural disorganization, and increased mitochondrial DNA (mtDNA) mutations. These

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alterations are common in aged tissues and are associated with age-related pathologies (Bratic and Larsson, 2013,Cagin and Enriquez, 2015). For example, respiratory function declines during aging in skeletal muscle (Porter et al., 2015) and contributes to weakened aerobic fitness and increased fatigue in humans (Coen et al., 2013,Santanasto et al., 2015). Despite these observations, it is possible that mitochondrial dysfunction is an ancillary or adaptive change derived from a separate underlying primary driver of aging. Denham Harman proposed that the driving force of aging is mitochondrial ROS that accumulates and causes cellular damage (Harman, 1972). Indeed, mitochondria can generate pathologic levels of ROS from complexes I and III of the ETC, starting with superoxide anion (Brand, 2010,Suski et al., 2012). While it is thought that mitochondrial oxidative stress promotes aging and pathologies, it is not understood how this mechanistically impairs cell proliferation and maintenance (Dai et al., 2014a; Nacarelli et al., 2016b). It is also possible that elevated ROS reflects impaired mitochondrial function but is not the main driver for cellular dysfunction.

Insight into how mitochondrial dysfunction contributes towards the aging process *in vivo* comes from the analysis of mice overexpressing a ROS-scavenging mitochondrial-targeted catalase (mCAT) and 'mutator mice' harboring an exonuclease proofreading-deficient mitochondrial DNA polymerase gamma. The mCAT mice, with reduced mitochondrial oxidative damage and mtDNA mutations and deletions, exhibit increased lifespan (Schriner et al., 2005), as well as resistance to a number of age-related pathologies (Dai et al., 2009; Ge et al., 2015; Treuting et al., 2008) and the pathologic effects of a high-fat diet (Ryan et al., 2016). 'Mutator mice' are susceptible to mtDNA mutations and deletions (Vermulst et al., 2008) and exhibit an accelerated aging phenotype, attributed to cardiomyopathy and muscular atrophy (Kujoth et al., 2005,Mito et al., 2015). Analysis of heart and skeletal muscle tissue revealed increased markers of senescence, including p16, p21 and GADD45B (Dai et al., 2010; Safdar et al., 2015). Initial results confirmed that oxidative phosphorylation is defective in skeletal muscle, but were not associated with increased mitochondrial ROS production and oxidative damage (Kujoth et al., 2005). However, newer studies using more advanced approaches detected elevated mitochondrial ROS and oxidative damage in skeletal muscle and heart tissues (Kolesar et al., 2014,Logan et al., 2014) and overexpression of mCAT alleviated mtDNA deletions, mitochondrial oxidative damage, and cardiomyopathy as well as a reduction in p16 expression (Dai et al., 2010), suggesting that senescent cells may have as a result of mitochondrial dysfunction, potentially contributing to the cardiomyopathy observed in these animals. The protective effects, slowing aging and relieving pathologic features, of elevated mCAT expression may result from a preservation of mitochondrial function and resistance to age-associated decline in energy metabolism that promotes cellular dysfunction and senescence (Lee et al., 2010). A more simple intervention, endurance exercise that stimulates mitochondrial biogenesis and preserves mitochondrial function, also ameliorated oxidative stress-induced senescence and the pathologic effects in the "mutator mice" (Safdar et al., 2015), however, a caveat of the 'mutator mice' model is that mitochondrial dysfunction may not reach this intensity during normal physiological aging.

3.3. Mitochondrial alterations in cellular senescence

An increase in mitochondrial processes, including pyruvate oxidation, TCA cycle, and respiration has been observed in senescence induced through oncogene activation (Kaplon et al., 2013,Quijano et al., 2012), genotoxic stress (Wang et al., 2016), mitochondrial stress (Nacarelli et al., 2016a), and in replicative senescence (Nacarelli et al., 2016b; Takebayashi et al., 2015). Transcriptomic profiling in the replicative aging and senescence of *Saccharomyces cerevisiae* revealed elevated transcripts involved in glycolysis and TCA cycle (Kamei et al., 2014). Increased mitochondrial TCA cycle activity, respiration, and ROS levels in oncogene-induced senescence was found to be the result of elevated mitochondrial PDH activity through increased expression of its positive regulator, pyruvate dehydrogenase phosphatase 2 (PDP2). PDH was not only required for oncogene-induced senescence but also sufficient to induce cellular senescence in human fibroblasts when activated through targeting the negative regulator pyruvate dehydrogenase kinase-1 (Kaplon et al., 2013). Increased mitochondrial respiration during cellular senescence has also been suspected to be a consequence of an elevated metabolic flow stemming from increased glycolysis. In addition to upregulating glycolytic genes, retinoblastoma also targets PDP2 in response to oncogene-induced senescence. This may explain how PDP2 is upregulated and promotes PDH activity to increase mitochondrial oxidative processes during cellular senescence (Takebayashi et al., 2015). It is suspected that respiration is elevated to support mitochondrial fatty acid oxidation that drives the SASP during oncogene-induced senescence. Inhibiting fatty acid oxidation using a CPT-1 inhibitor significantly reduced respiration and the secretion of a range of cytokines that comprise the SASP (Quijano et al., 2012,Takebayashi et al., 2015).

Mitochondria are dynamic organelles that alter their morphology and organization by continually undergoing fusion and fission events. These processes maintain quality of the mitochondria along with mtDNA and help facilitate degradation of dysfunctional mitochondrial through autophagy (Westermann, 2012). Mitochondrial morphology is altered mitochondrial mass and mtDNA copy number is increased in oncogene-induced senescence (Moiseeva et al., 2009), genotoxic stress-induced senescence (Correia-Melo et al., 2016), mitochondrial stress-induced senescence (Nacarelli et al., 2016a), and replicative senescence (Hwang et al., 2009,Passos et al., 2007). The appearance of aberrantly fused and elongated mitochondria in replicative senescence was found to be the result of decreased expression of the mitochondrial fission factors fission protein 1 (Fis-1) and dynamin-related protein 1 (Mai et al., 2010). A study using dynamic sensitivity analysis of genotoxic stress-induced senescence also showed that fission was reduced, leading to decreased mitophagy and the accumulation of dysfunctional mitochondria (Dalle Pezze et al., 2014). Reciprocally, cellular senescence can be induced by aberrantly increasing mitochondrial mass and elongating the mitochondrial network, caused from inhibiting mitochondrial fission by deferoxamine treatment (Yoon et al., 2006), and knocking down Fis-1 (Lee et al., 2007) or the mitochondrial E3 ubiquitin ligase March5 (Park et al., 2010). These studies show that this altered mitochondrial morphology is accompanied by increased ROS production, suggesting that oxidative stress aids in cellular senescence under these conditions. In support of this idea, it was found that treatment with a mitochondrial-targeted antioxidant ameliorated cigarette smoke extract-induced cellular senescence, where cigarette smoke extract impaired mitochondrial clearance and led to the accumulation of aberrantly elongated mitochondria (Ahmad et al., 2015,Ito et al., 2015). Aberrantly fused and elongated mitochondria may support the senescence program beyond promoting oxidative stress, but also by altering metabolic state and signaling. In response to a variety of stressors, including starvation (Gomes et al., 2011) and genomic stress (Tondera et al., 2009), studies showed that mitochondria fuse and stimulate ATP synthase activity to resist cellular stress. A recent study showed that mitochondrial fusion dictated the metabolic state of T cells, resulting in the differentiation of dormant memory T cells that exhibit

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increased mitochondrial respiration, ATP synthesis, and fatty acid oxidation (Buck et al., 2016). Likewise, mitochondrial fusion may influence the metabolic activity of senescent cells, resulting in increased mitochondrial respiration and fatty acid oxidation that aids in driving the SASP. Mitochondrial fusion also provides resistance to apoptotic stimuli, including oxidative (Mai et al., 2010) and genomic stresses (Lee et al., 2004), whereas mitochondrial fission is associated with apoptosis (Youle and Karbowski, 2005). It is possible that altered mitochondrial morphology contributes toward apoptosis resistance of senescent cells (Childs et al., 2014).

3.4. The pro-oxidant role of mitochondria in cellular senescence

While it is clear that the mitochondria are involved in cellular senescence, the relationship between mitochondrial function and the senescence program has not been completely elaborated and it appears there may be a reciprocal relationship in that senescence induces mitochondrial dysfunction and mitochondrial dysfunction can trigger senescence. A mechanistic link that has been proposed entails cross talk between mitochondrial ROS and the DDR. Mitochondria generate a physiological level of ROS that signals to maintain redox homeostasis. For instance, mitochondrial-derived ROS can activate the nuclear factor erythroid 2-like 2 (NRF2) pathway to increase expression of genes encoding antioxidant and mitochondrial biogenesis proteins (Dinkova-Kostova and Abramov, 2015,Monaghan and Whitmarsh, 2015). Activation of this pathway has been shown to provide resistance against replicative (Atamna et al., 2015) and oxidative stress-induced cellular senescence (Volonte et al., 2013,Yang et al., 2013). However, ROS levels that exceed a physiological threshold due to progressive mitochondrial stress induce cellular senescence. A severe mitochondrial insult, such as pharmacological uncoupling, can generate sufficient levels of ROS to cause DNA damage that can accelerate telomere attrition and subsequently cellular senescence (Stockl et al., 2007). Similarly, pharmacological inhibitors of the ETC also generate mitochondrial ROS and cellular senescence. However, the inability of ROS-quenching antioxidants to prevent cellular senescence in response to such ETC inhibition suggests that mitochondrial dysfunction promotes senescence beyond the production of ROS or the effect of ROS is not an essential component of the senescence program (Stockl et al., 2006). It has been suggested that the stochastic variation of cellular senescence observed in cell culture is due to mitochondrial dysfunction, possibly through mitochondrial ROS-mediated telomere damage (Moiseeva et al., 2009,Velarde et al., 2012). Alternatively, mild uncoupling of the ETC (Passos et al., 2007) or addition of a mitochondrial ROS scavenger (Saretzki et al., 2003) reduces ROS levels and attenuates telomere shortening, delaying cellular senescence and extending replicative lifespan. Similar approaches can reduce oxidative damage within various tissues and in some cases extend lifespan in mice (Caldeira da Silva et al., 2008; Dai et al., 2014b). Mitochondrial uncoupling also has been identified as part of an adaptive response to protect against both cardiomyopathy and shortened lifespan in the 'mutator mice.' However, this protective effect was not related to altered mitochondrial oxidative stress, but enhanced fatty acid oxidation (Kukat et al., 2014).

Mitochondrial ROS may also reinforce the senescence phenotype in response to genomic damage. As a result of irradiation or replicative exhaustion, cells may activate the DDR and p21 signaling to induce mitochondrial dysfunction in a TGFβ-dependent manner, which is thought to stabilize the DDR, forming a positive feedback loop that maintains cell cycle arrest to induce cellular senescence (Passos et al., 2010). Additional signaling has been recently found to contribute to this positive feedback loop, where ATM of the DDR activates AKT and mTORC1 signaling that promotes the expansion of dysfunctional mitochondria. In this study, depleting cells of mitochondria through uncoupling-stimulated mitochondrial clearance allows cells to resist cellular senescence stimuli, ranging from genotoxic to oncogenic stressors (Correia-Melo et al., 2016). A similar positive feedback loop has been proposed in oncogene-induced cellular senescence where p53 and retinoblastoma mediate mitochondrial dysfunction to promote genomic damage and the DDR. A key observation in this study was that this response was accompanied by the accumulation of dysfunctional mitochondria around the nucleus (Moiseeva et al., 2009). In addition, p53 both transcriptionally represses mitochondrial manganese superoxide dismutase (Dhar et al., 2006), and reduces its activity (Zhao et al., 2005). p53 can also impair mitochondrial antioxidant defenses by decreasing transcription of the $NAD(P)^+$-dependent mitochondrial malic enzyme (ME2) that replenishes the NADPH pool (Jiang et al., 2013) that is required by endogenous mitochondrial antioxidants (Korge et al., 2015). While it is unlikely that mitochondrial ROS can directly damage nuclear DNA, it is important to keep in mind that mitochondrial dysfunction could elevate cellular ROS levels by activating other ROS-producing pathways, such as the NAD(P)H oxidase pathway (Dikalov, 2011,Mistry et al., 2013).

3.5. Mitochondrial metabolite-induced signaling in cellular senescence

In addition to elevated levels of mitochondrial ROS, cellular senescence is also characterized by reduced NAD^+ levels and NAD^+/NADH ratio (Han et al., 2016,Lee et al., 2012), and reduced ATP levels and increased AMP/ATP ratio (Moiseeva et al., 2009,Wang et al., 2003). Studies are emerging that suggest mitochondrial dysfunction signals in a retrograde manner to trigger cellular senescence, without initiating the DDR. Interestingly, impaired levels of key metabolites as a result of mitochondrial stress stimulate metabolic signaling that activate effectors of the senescence program.

Elevated AMP levels from ATP depletion activates the energy sensor AMP-activated protein kinase (AMPK) which has tumor suppressor functions (Lee et al., 2015,Li et al., 2015). AMPK stimulates adaptation to a metabolic stress by activating mitochondrial biogenesis and catabolic pathways, such as autophagy and fatty acid oxidation (Burkewitz et al., 2014). Acute activation of AMPK has been shown to stimulate autophagy and NAD^+ biosynthesis providing resistance to oxidative stress-induced cellular senescence (Han et al., 2016). However in other settings, chronic activation of AMPK activated p53 and cell cycle arrest to induce cellular senescence (Jones et al., 2005,Wang et al., 2003), and simply raising AMP levels to activate AMPK by culturing cells with exogenous AMP or oligomycin to inhibit the mitochondrial ATP synthase induces cellular senescence (Stockl et al., 2006,Zwerschke et al., 2003). Similarly, silencing the mitochondrial malic enzyme induced oxidative stress and AMPK signaling to trigger cellular senescence in a p53-dependent manner, and this effect was blocked by antioxidant treatment (Jiang et al., 2013). Reduced NAD^+/NADH ratio as a result of a mitochondrial dysfunction has also been shown to activate AMPK signaling to induce cellular senescence. In this study, mitochondrial function was impaired after knocking down mitochondrial sirtuin 3, inhibiting the electron transport chain, or depleting mitochondrial DNA. Cellular senescence was ameliorated in response to these mitochondrial challenges by culturing cells in the presence of the electron acceptors pyruvate or potassium ferricyanide that restore NAD^+ levels, highlighting reduced NAD^+/NADH ratio as a stress signal derived from mitochondrial dysfunction. Interestingly, this cellular senescence response was accompanied by a distinct secretory profile mediated through

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AMPK-mediated p53 activation and suppression of nuclear factor-kappa B (NF-κB) activity (Wiley et al., 2016). Diminished NAD^+ levels are also observed in aged *Caenorhabditis elegans* (Copes et al., 2015) and mice, several age-related pathologies in mice, and disease mouse models (Clark-Matott et al., 2015,Yoshino et al., 2011), while some pathologic features of aged mice (Gomes et al., 2013,Mouchiroud et al., 2013) and several disease mouse models are alleviated by restoring NAD^+ levels to improve mitochondrial function (Cerutti et al., 2014,Pirinen et al., 2014).

3.6. Mitochondrial dysfunction and mTORC1 signaling in cellular senescence

Unlike severe mitochondrial dysfunction induced by gene ablation or high concentrations of ETC inhibitors, gradual mitochondria stress is more likely during cellular aging and senescence. Indeed, our laboratory has observed that replicative aging and senescence are accompanied by the accumulation of dysfunctional mitochondria and elevated levels of mitochondrial ROS. Reducing mitochondrial ROS by improving mitochondrial homeostasis through activating autophagy following treatment with a nanomolar concentration of rapamycin extends replicative lifespan, delays cellular senescence (Lerner et al., 2013), and provides protection against mitochondrial stress. Our laboratory confirmed mitochondrial ROS as a senescence-inducing factor by showing treatment with the mitochondrial-targeted antioxidant MitoQ also provided resistance to mitochondrial stress-induced senescence (Nacarelli et al., 2014, 2016b). Other laboratories have also found that rapamycin treatment delays cellular senescence, including oncogene-induced (Kolesnichenko et al., 2012), oxidative stress-induced (Han et al., 2016), and replicative senescence (Demidenko et al., 2009,Pospelova et al., 2012).

Interestingly, elevated mTOR activity has emerged as a feature of aging and age-related pathologies. At the cellular level, mTORC1 signaling is elevated during replicative senescence in human fibroblasts independently of growth factor stimulation (Zhang et al., 2000), and studies have shown that oncogene (Herranz et al., 2015), genotoxic (Correia-Melo et al., 2016,Laberge et al., 2015), and mitochondrial and oxidative stress-induced cellular senescence exhibit elevated mTORC1 signaling (Nacarelli et al., 2016a; Zhuo et al., 2009). It appears that under the senescent state, mTORC1 promotes SASP by enhancing translation of interleukin-1α (Laberge et al., 2015) and MAPKAPK2 (Herranz et al., 2015) that activate pro-inflammatory signaling. mTORC1 was also found to promote the SASP during cellular senescence through forming a TOR-autophagy spatial coupling compartment (TASCC) where mTORC1 localizes to autolysosomes and maintains synthesis of secretory proteins, including interleukin-6 and 8 (Narita et al., 2011). However, less is known regarding how mTORC1 may respond to and possibly promote stress, providing a cellular environment that is conducive for cellular aging and senescence.

Elevation of mTOR activity is found in age-related disease states. For example, aberrant activation of mTORC1 has been reported in multiple tissues during aging (Dai et al., 2014a; Leontieva et al., 2014; Zhuo et al., 2009) and in various age-diseases, ranging from Alzheimer's disease to diabetes, while several disease mouse models also show evidence of elevated mTORC1 activity, including diabetic (Helman et al., 2016), Hutchinson-Gilford progeria syndrome (Ramos et al., 2012) and the mitochondrial disease models Leigh syndrome (Johnson et al., 2013b) and focal-segmental glomerulosclerosis renal disease (Peng et al., 2015). Rapamycin treatment is known to extend organismal lifespan and protect against the pathologic effects in disease mouse models of Leigh syndrome, cardiovascular disease, Alzheimer's disease, and Parkinsons's disease (Nacarelli et al., 2015). However, the mechanisms by which rapamycin extends lifespan are still unclear. The lifespan extension by rapamycin appears to require functional autophagy in yeast (Alvers et al., 2009) and invertebrates (Bjedov et al., 2010,Hansen et al., 2008). Supporting increased autophagy and altered protein synthesis as potentially important changes, studies show that rapamycin treatment reduces protein damage and improves protein homeostasis in the heart (Dai et al., 2014b) and liver tissue of mice (Karunadharma et al., 2015), and metabolic profiling in aged mice hearts revealed that rapamycin treatment stimulated mitochondrial biogenesis and reversed the age-related reduction in mitochondrial metabolic pathways, including fatty acid oxidation (Chiao et al., 2016). These changes following rapamycin treatment were concomitant with increased mitochondrial and TCA cycle metabolites that suggest enhanced mitochondrial substrate utilization and anaplerosis (Chiao et al., 2016). Beneficial effects of rapamycin on metabolism have also been observed in the mitochondrial disease mouse model of Leigh Syndrome (Johnson et al., 2013a). Improved mitochondrial homeostasis following rapamycin treatment may confer better adaptation to metabolic stress that accompanies replicative aging *in vitro* or exogenous insults. This adaptation entails enhanced mitochondrial carbon oxidation that maintains ATP levels and redox state to meet the bioenergetic demand for cellular maintenance and proliferation. It is possible that rapamycin treatment serves as a metabolic intervention that prevents metabolic catastrophe during cellular aging that aids in the induction of cellular senescence.

Top: Bright field micrographs of non-senescent and senescent human cardiac fibroblasts that were stained for senescence-associated beta-galactosidase (SA-β-Gal) activity, along with an indication of the classic markers of cellular senescence. Bottom: Synthesis of alterations in metabolic and signaling pathways that are a part of the cellular senescence program.

4. Metabolic interventions & future direction

Cellular aging and senescence are characterized by a loss a proliferative potential. Rather than a parallel reduction in metabolism, senescent cells exhibit elevated activity of several metabolic processes that may be necessary for the induction of cellular senescence. Acute senescence stimuli, including oncogenic (Kaplon et al., 2013) and genotoxic stressors (Correia-Melo et al., 2016), activate mitochondrial processes that are required for and stabilize the senescence phenotype. Our laboratory has shown that a low level of chronic mitochondrial stress elevates metabolic processes and activates mTORC1 signaling which mediates growth arrest and cellular senescence. These findings were recapitulated during replicative senescence where there is stochastic mitochondrial stress, as evidenced by the accumulation of dysfunctional mitochondria during cellular aging (Nacarelli et al., 2016a). Mitochondrial status also appeared to influence mTORC1 signaling following genotoxic stress-induced senescence, where stimulating mitochondrial clearance reduced mTORC1 signaling along with senescent features (Correia-Melo et al., 2016) (Figs. 1 and 2).

Mitochondria dysfunction impairs metabolism not only by depleting ATP levels, but also through the loss of biosynthetic precursor pools and an inability to maintain redox state. Given the evidence, it seems probable that under the proper conditions, somatic cells undergo a metabolic catastrophe due to an imbalance in metabolic intermediates, a stress that may be relayed through metabolic signaling, as a trigger for cellular senescence. This may represent yet another metabolic/mitochondrial path to senescence (summarized in Fig. 1).

In addition, specific metabolic alterations appear to be associated with senescence, as evidenced by the fact that mitochondrial oxidative processes are elevated during cellular senescence. These

Please cite this article in press as: Nacarelli, T., Sell, C., Targeting metabolism in cellular senescence, a role for intervention, Molecular and Cellular Endocrinology (2016), http://dx.doi.org/10.1016/j.mce.2016.08.049

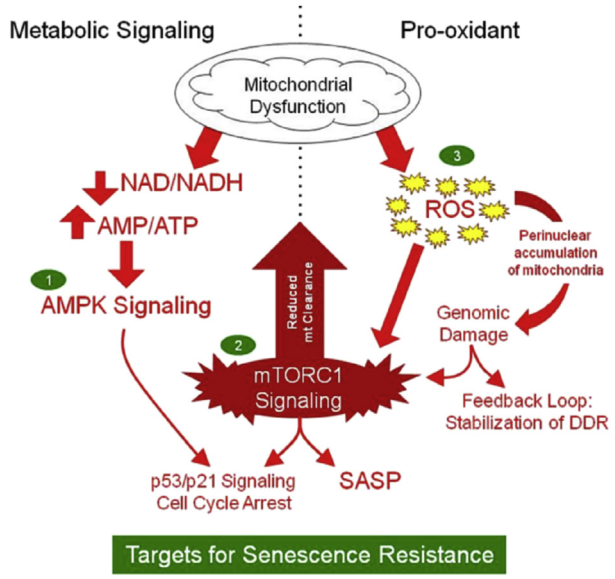

Fig. 2. Mechanisms of mitochondrial dysfunction-induced senescence.

metabolic changes may support activities of the senescent state, such as the SASP and acidification of the tissue microenvironment to modulate immune response. For instance, activated retinoblastoma not only mediates cell cycle exit, but also stimulates mitochondrial oxidative processes and respiration to promote the SASP (Takebayashi et al., 2015). Similarly, during senescence, instead of promoting growth, mTORC1 signaling promotes retention of dysfunctional mitochondria (Correia-Melo et al., 2016) and stimulates pro-inflammatory signaling to maintain the SASP (Laberge et al., 2015). When one considers mTORC1 as a node for stress signaling, an elevation in mTORC1 signaling may not seem paradoxical during cellular aging and senescence.

The majority of lifespan-extending regimens impact nutrient signaling and metabolism that essentially control cellular maintenance and growth. Although it is not clear how longevity is assured, a possible mechanism of these interventions involves establishing an efficient coordination between cellular growth with maintenance and bioenergetics, which rely on the mitochondria. Thus, improving mitochondrial homeostasis may be an approach to delay cellular aging and senescence. Our laboratory previously demonstrated that culturing cells with a nanomolar concentration of rapamycin improves mitochondrial homeostasis through autophagy and retrograde signaling (Lerner et al., 2013), while rapamycin treatment has been shown to protect against mitochondrial stress (Nacarelli et al., 2016b) and various other stressors (Han et al., 2016,Kolesnichenko et al., 2012) that induce cellular senescence. We found that rapamycin treatment slows the deterioration in mitochondrial function and retains the ability to maintain bioenergetics, which may reflect the ability of the mitochondria to maintain biosynthetic precursor pools and proper NAD^+/NADH ratio that are necessary for proliferation. There is evidence *in vivo* supporting that a therapeutic benefit of rapamycin treatment is improved metabolism (Chiao et al., 2016; Johnson et al., 2013a; Karunadharma et al., 2015). Beneficial metabolic responses *in vivo* are also observed in rodents whose lifespan is extended by methionine restriction. Indeed, methionine restriction in human fibroblasts delays cellular senescence and extends replicative lifespan. This response is coupled with improved mitochondrial homeostasis, resulting in similar features of reduced mitochondrial respiration and ROS production as in rapamycin-treated human fibroblasts (Koziel et al., 2014; Sanchez-Roman and Barja, 2013). Culturing cells chronically in the presence of rapamycin or under methionine restriction may also provide stress resistance by maintaining proteostasis and preventing unbalanced growth through curtailing translation. Simply inhibiting cytoplasmic translation using cycloheximide resists genotoxic stress-induced and replicative senescence, but additionally inhibiting mitochondrial translation negated this resistance (Takauji et al., 2016). In addition to suppressing cellular stress and the development of senescent cells, rapamycin treatment also has potential to intervene with the phenotype of established senescent cells. For instance, rapamycin treatment can inhibit mTORC1 signaling that stimulates translational (Herranz et al., 2015,Laberge et al., 2015), mitochondrial ROS-mediated (Correia-Melo et al., 2016), and TASCC-forming (Narita et al., 2011) activities that support the SASP. Rapamycin treatment may also interfere with the SASP by stimulating autophagic degradation of GATA4, a transcription factor that is activated in response cellular senescence stimuli that stimulates pro-inflammatory signaling (Kang et al., 2015).

Depiction of mitochondrial dysfunction-induced metabolic signaling (Left side) and pro-oxidant effects (Right side) that induce cellular senescence. The mTORC1 complex is impacted by mitochondrial dysfunction to drive senescence rather than proliferation. Targets for interventions (Green) that have been shown to delay or prevent cellular senescence include 1) acute AMPK activation, 2) Inhibition of mTORC1 by rapamycin treatment, and 3) Reducing mitochondrial-derived ROS using a mitochondrial-targeted antioxidant or mild uncoupling.

5. Conclusion

With the prospect of intervening with cellular aging and tissue deterioration, research is further unfolding the mechanisms that underlie cellular senescence and the pro-aging effects of senescent cells. Classic markers of cellular senescence include phenotypic changes and activation of pathways that mediate stable growth arrest (Fig. 1,Top). Over three decades ago, studies emerged demonstrating that senescent cells exhibit an altered metabolism, but the functional significance remained unclear. By uncovering distinct changes in metabolic and mitochondrial activities, studies now suggest that senescent cells may be metabolically reprogrammed (Fig. 1, Bottom). This reprogramming appears to support and, in some cases, be required for aspects of the senescence phenotype, including growth arrest and the SASP. Reciprocally, mitochondrial dysfunction and metabolic stress activate pathways that induce cellular senescence, even independent of genomic stress and the DDR. Given this background, improving mitochondrial homeostasis and alleviating metabolic stress appears to be an approach to delay cellular senescence and extend replicative lifespan (Fig. 2). However, further research is needed to clarify the complex relationship between metabolism and cellular senescence, in order to fully explore the opportunities to intervene with the development and effects of senescent cells.

Acknowledgements

This work was supported by grants AG039799 to CS. TN was supported by a fellowship from the Drexel Aging Initiative.

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Please cite this article in press as: Nacarelli, T., Sell, C., Targeting metabolism in cellular senescence, a role for intervention, Molecular and Cellular Endocrinology (2016), http://dx.doi.org/10.1016/j.mce.2016.08.049

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Please cite this article in press as: Nacarelli, T., Sell, C., Targeting metabolism in cellular senescence, a role for intervention, Molecular and Cellular Endocrinology (2016), http://dx.doi.org/10.1016/j.mce.2016.08.049

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Please cite this article in press as: Nacarelli, T., Sell, C., Targeting metabolism in cellular senescence, a role for intervention, Molecular and Cellular Endocrinology (2016), http://dx.doi.org/10.1016/j.mce.2016.08.049