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Targeting metabolism in cellular senescence, a role for intervention

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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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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