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Review Article

Cellular Senescence: A Translational Perspective

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ABSTRACT

Cellular senescence entails essentially irreversible replicative arrest, apoptosis resistance, and frequently acquisition of a pro-inflammatory, tissue-destructive senescence-associated secretory phenotype (SASP). Senescent cells accumulate in various tissues with aging and at sites of pathogenesis in many chronic diseases and conditions. The SASP can contribute to senescence-related inflammation, metabolic dysregulation, stem cell dysfunction, aging phenotypes, chronic diseases, geriatric syndromes, and loss of resilience. Delaying senescent cell accumulation or reducing senescent cell burden is associated with delay, prevention, or alleviation of multiple senescence-associated conditions. We used a hypothesis-driven approach to discover pro-survival Senescent Cell Anti-apoptotic Pathways (SCAPs) and, based on these SCAPs, the first senolytic agents, drugs that cause senescent cells to become susceptible to their own pro-apoptotic microenvironment. Several senolytic agents, which appear to alleviate multiple senescence-related phenotypes in pre-clinical models, are beginning the process of being translated into clinical interventions that could be transformative.

Contents

1. Cellular Senescence: Causes and Consequences.

Cellular senescence is a cell fate that involves essentially irreversible replicative arrest, apoptosis resistance, and frequently increased protein synthesis, metabolic shifts with increased glycolysis, decreased fatty acid oxidation, increased reactive oxygen species generation, and acquisition of a senescence-associated secretory phenotype (SASP; Fig. 1)

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(Tchkonia et al., 2013; LeBrasseur et al., 2015). The SASP entails secretion of cytokines, bradykines, prostenoids, miRNA's, damage-associated molecular pattern proteins (DAMPs), and other pro-inflammatory mediators, chemokines that attract immune cells, factors that cause stem cell dysfunction such as activin A, hemostatic factors such as PAI-1, pressors, and extracellular matrix-damaging molecules, including proteases (Xu et al., 2015a, Xu et al., 2015b; Coppé et al., 2006). Senescence can occur in response to potentially oncogenic mutations, activated oncogenes, metabolic insults, and damage/danger signals.

2. Aging, Chronic Diseases, and Cellular Senescence

Aging is the major risk factor for most of the chronic diseases that account for the bulk of morbidity, mortality, and health costs in the developed and developing worlds (Kirkland, 2016; Goldman et al., 2013). Chronic diseases, including dementias, atherosclerosis, diabetes, blindness, kidney dysfunction, and osteoarthritis among many others, become more prevalent with increasing age and tend to cluster together within older individuals (St Sauver et al., 2015). Risk for geriatric syndromes, including frailty, immobility, mild cognitive impairment, and incontinence, increases with aging. These conditions also cluster within individuals and are associated with age-related chronic diseases. Additionally, loss of physiological resilience, the capacity to recover following stresses such as surgery or pneumonia, occurs with advancing age and tends to precede onset of chronic diseases and geriatric syndromes (Kirkland et al., 2016). Fundamental aging processes, including chronic "sterile", low-grade inflammation, macromolecular and organelle dysfunction, stem/progenitor cell dysfunction, and cellular senescence, are not only associated with development of age-related phenotypes, but are also frequently apparent at sites of pathogenesis in age-related chronic diseases (Kirkland, 2016). For example, senescent cells accumulate in adipose tissue in diabetes and with age-related metabolic dysfunction (Minamino et al., 2009; Tchkonia et al., 2010; Xu et al., 2015a), osteoarthritic joints (Xu et al., 2016), the aorta in vascular hyporeactivity and atherosclerosis (Roos et al., 2016), and the lung in idiopathic pulmonary fibrosis (Schafer et al., 2017). Indeed, transplantation of small numbers senescent cells around the knee joint can cause osteoarthritis (Xu et al., 2016). Senescent cells can be eliminated from transgenic INK-ATTAC mice by administering a drug, AP20187, that does not affect normal cells. AP20187 activates the "suicide" protein, ATTAC, which is expressed only in senescent cells due to a senescence-induced promoter, $p16^{Ink4a}$ (Baker et al., 2011). Activating ATTAC alleviates multiple phenotypes in progeroid mice, naturally-aged mice, or mice with age-related diseases (Baker et al., 2011; Xu et al., 2015a; Roos et al., 2016; Schafer et al., 2017). These include adipose tissue and metabolic dysfunction, vascular hyporeactivity and calcification, chemotherapy-induced pulmonary fibrosis, and progeria-associated cataracts, lipodystrophy, and muscle dysfunction, among others. Thus, targeting senescent cells is a promising potential approach for delaying, preventing, or alleviating multiple age- and cellular senescence-associated conditions.

3. Senescence-associated Secretory Phenotype (SASP) Inhibitors

The composition of the SASP appears to vary depending on the cell type from which senescent cells originated, how senescence was induced, hormonal *milieu*, and presence of drugs including glucocorticoids, rapamycin, metformin, or JAK1/2 inhibitors (Xu et al., 2015b, Wiley et al., 2016; Laberge et al., 2012; Moiseeva et al., 2013; Laberge et al., 2015). Thus, the SASP is modifiable. At least in the case of rapamycin in senescent cultured fibroblast strains, suppression of the SASP is segmental: not all SASP components are down-regulated.

Metformin alleviates a range of age-related disorders in experimental animals and humans, including insulin resistance, diabetes, metabolic dysfunction, cardiovascular disease, cancer development and spread, and cognitive dysfunction (Huffman et al., 2016). It may even increase 5 year survival in elderly humans (Bannister et al., 2014). Rapamycin and related agents increase lifespan in mice, delay age-related adipose tissue loss, alleviate frailty in old mice, decrease heart failure, cancers, cognitive impairment, and immune dysfunction in mouse models, and enhance antibody response to influenza vaccination in elderly humans, among other effects (Harrison et al., 2009; Li et al., 2014; Majumder et al., 2012; Wilkinson et al., 2012, Zhang et al., 2014, Mannick et al., 2014; Bitto et al., 2016). Ruxolitinib, a JAK1/2 inhibitor in human application, alleviates age-related adipose tissue dysfunction, insulin resistance, and stem cell dysfunction in old mice (Xu et al., 2015a). Importantly, ruxolitinib reduces frailty even in very old mice (Xu et al., 2015b), a circumstance once believed to be impervious to interventions. Ruxolitinib partially corrects reduced strength, body weight, and appetite, which are features of frailty, in older humans with myeloproliferative

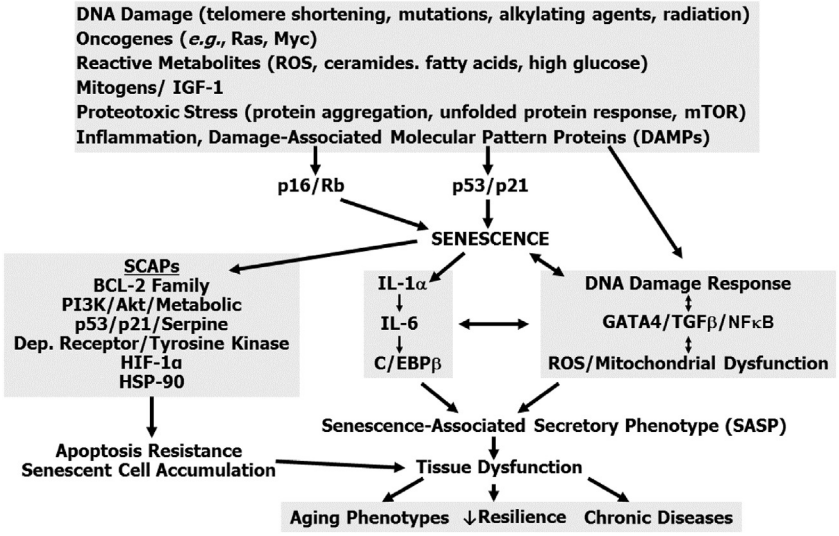

Fig. 1. Inducers, mediators, SCAPs, the SASP, and effects of senescent cells. Cellular senescence is a cell fate that, like replication, differentiation, or apoptosis, is 1) induced by a range of intra- or extracellular stimuli or combinations of them, 2) mediated by a cascade of transcriptional regulators that affect expression of multiple downstream target genes, and 3) associated with widespread changes in chromatin structure. Senescence takes days to weeks to become fully established and changes in quality over time. Senescent Cell Anti-apoptotic Pathways (SCAPs) shield senescent cells from their own pro-apoptotic SASP. These SCAPs constitute the Achilles' heel of senescent cells (Zhu et al., 2015b) that have turned out to be the critical key for developing the senolytic drugs and peptides discovered so far.

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