

# Cellular Senescence and the Biology of Aging, Disease, and Frailty

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Population aging simultaneously highlights the remarkable advances in medicine and public policy, and the formidable challenges facing society. Indeed, aging is the primary risk factor for age-related diseases and frailty, which have profound social and economic costs. Population aging also reveals an opportunity, i.e. interventions that target the underlying biology of aging, as opposed to individual diseases, have the potential to delay the onset of age-related conditions as a group. If successful, this innovative approach would have a profound impact on extending the healthy life span and dramatically compress the period of morbidity at the end of life.

There is now considerable evidence that cellular senescence is an underlying mechanism of aging and age-related conditions, including frailty. Cellular senescence is a process in which cells lose the ability to divide and enter a state of stable growth arrest. It is associated with diverse stimuli, including telomere erosion, DNA lesions, reactive oxygen species, and other mitogenic stressors [1]. The induction of 'stable' growth arrest is tied to the activation of the tumor suppressor pathways, p16<sup>INK4a</sup>/retinoblastoma protein and/or p53/p21. Correspondingly, senescence has long been viewed as a fundamental anticancer mechanism. However, the abundance of senescent cells increases in multiple tissues with chronological aging, and markers of senescence, most notably p16<sup>INK4a</sup>, are increased in the affected tissues of patients with age-related conditions, including osteoarthritis, pulmonary fibrosis, atherosclerosis, and Alzheimer's disease (extensively reviewed by Naylor et al. [2]). Senescent cells compromise the functionality and regenerative potential of a tissue, as well as damage to neighboring cells by the factors they secrete, collectively referred to as the senescence-associated secretory phenotype (SASP). SASP is composed of cytokines and chemokines, matrix-remodeling proteins and growth factors. Importantly, SASP may be a significant component of age-related inflammation, or *inflammaging*, which is recognized as a pathogenic factor in the development of conditions such as cardiovascular disease, diabetes, cancer, depression, dementia, and frailty.

In light of the growing body of data implicating senescent cells and SASP in aging, age-related disease, and frailty, a number of strategies are being considered to mitigate their deleterious effects. These include (i) preventing the cellular damage that triggers cellular senescence; (ii) selectively killing senescent cells, and (iii) suppressing SASP. As proof of concept, we designed a transgenic mouse model in which senescent cells could be inducibly eliminated through a chain of events that triggers apoptosis of p16<sup>Ink4a</sup>-positive cells. Recently, we demonstrated that in a progeroid (rapid aging) mouse background, *INK-ATTAC* removes p16<sup>Ink4a</sup>-positive senescent cells upon drug treatment [3]. In tissues –such as adipose tissue, skeletal muscle, and eye – in which p16<sup>Ink4a</sup> contributes to the acquisition of age-related pathologies, life-long removal of p16<sup>Ink4a</sup>-expressing cells delayed the onset of these phenotypes and improved physical function. Furthermore, late-life clearance attenuated progression of already established age-related disorders. The translation of these findings to humans is contingent upon the ability to specifically target senescent cells using biological or small molecule ‘senolytic’ therapies. Frailty offers a unique clinical opportunity to test the effectiveness of pharmacological interventions to remove senescent cells or diminish SASP. If, in fact, patients with high compared to low senescent cell burden experience worse short-term outcomes (e.g. more complications, higher incidence of delirium or longer length of stay) and longer-term outcomes (more readmissions, greater dependence in activities of daily living, delayed recovery of function or higher institutionalization) following a medical intervention, then the efficacy of senolytics at improving these clinically important and patient-centered metrics could be evaluated. While the search is on for pharmacological strategies to delay aging, significant work is still needed to further understand the biology of cellular senescence and its mechanistic role in the pathogenesis of age-related diseases and frailty.

## References

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- 3 Baker DJ, Wijshake T, Tchkonja T, et al: Clearance of p16<sup>Ink4a</sup>-positive senescent cells delays ageing-associated disorders. *Nature* 2011;479:232–236.