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JMS Journal of Medical Science

Senescent cells as new pharmacological targets for age-related diseases and anti-aging therapy

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Received: 2023-08-02
Accepted: 2023-09-13
Published: 2023-09-29

How to Cite: Masternak MM. Senescent cells as new pharmacological targets for age-related diseases and anti-aging therapy. Journal of Medical Science. 2023;93(3);e907. doi:10.20883/medical.e907

DOI: https://doi.org/10.20883/medical.e907

Keywords: aging, senescence, senolytics

ABSTRACT

Aging is a natural process leading to decline in physical function, reducing ability to adjust to everyday organismal stress and increased frailty. Recent studies of the mechanism of aging have brought attention to naturally occurring senescent cells in different organs throughout the body. This natural process of senescence is caused by cell cycle arrest due to cellular damage, which protects cells from apoptosis, while stimulating the production and secretion of different senescent associated secretory phenotypes (SASPs) causing low grade chronic inflammation. Emerging studies show that by targeting and eliminating these cells with a new class of senolytic drugs in old animals we can improve a variety of health conditions including reduction of inflammation, improvement of insulin sensitivity and metabolic status, increase of bone mineral density and enhanced physical function together with extended overall longevity. Ongoing clinical trials using Desatanib and Quarcetin (D+Q) and other classes of senolytic drugs indicate high translational potentials in targeting and clearing senescent cells to cure some age-related diseases; however, more in depth studies have to be completed to incorporate these therapies in general healthy elderly populations for safe anti-aging intervention.

For centuries, people searched for the cure of aging and secrets of longevity with hopes for immortality and youthful lives. The last few decades of scientific research have established multiple theories of aging including (i) programmed aging, which contains neuroendocrine theory of aging, finite cell division, immune theory of aging, and (ii) wear and tear theory including free radicals, DNA damage, rate of living, error catastrophe and glycosylation theory. Through investigating these different topics using different biological aging models researchers found some overlapping mechanisms as well as some contradicting regulations still lacking consensus about the detailed mechanism of biological aging. Importantly, the newest trends in aging research focus on the process of cellular senescence. Cellular senescence is a defense mechanism to arrest proliferation of damaged cells. Through this mechanism potential cancerous cell stops dividing, but at the same time are protected from apoptosis. This "zombie" like cell keeps produc-

ing and secreting SASPs, mainly consisting of pro-inflammatory cytokines, chemokines, miRNAs, and variety of proteins and enzymes [1]. This pro-inflammatory activity sends localization signals attracting immune cells and activating immune response potentially suppressing tumor development and growth. Aging-associated increased accumulation of senescent cells shifts the beneficial function of these cells into a detrimental one through increased chronic inflammation, thus promoting tumor progression, tissue disfunction and acceleration in the development of varied age-related diseases. More importantly, Xu at al. showed that transplanting mice with senescent preadipocytes, thus increasing number of these cells in the organism, significantly shortens the overall survival of these mice when comparing with control animals with transplanted healthy cells [2].

Based on this knowledge, researchers are trying to develop novel senolytic therapies selectively targeting and eliminating senescent cells from human bodies in hopes to delay the aging phenotype and increase health span and lifespan [3–6]. There are several promising pharmacological agents already tested in vitro, in animal models as well as in humans [1, 7–9]. These treatments have been already reported to reduce the onset of aging-related diseases and increase the lifespan [2, 10].

One of the earliest senolytic cocktails developed and studied is the combination of dasatinib and quercetin (D + Q). This cocktail was shown to be effective in killing and eliminating senescent cells. Importantly, the study by Xu and colleagues showed that treating 20-months old mice with D+Q for 4 months significantly improved several physical functions in these old mice including maximum speed, grip strength, hanging endurance etc. However, the most significant observation was a successful lifespan extension in mice treated with D+Q [2]. However, present approaches with senolytic drugs represent hit and miss targeted therapy, which depends on providing a rather high dosage of the drug for 2–4 days with 2–4 weeks intervals. This regimen targets senescent cells in the whole body, yet there is a need to better understand possible side effects or consequences when therapy could be started too early. Based on this, scientists are trying to investigate the impact of senolytic therapy in different organs and varied diseases. The study by Saccon at al. indicated that treatment of old mice with D+Q also have a positive impact on eliminating senescent cells from intestinal tissues including the colon and cecum with a concomitant shift in intestinal and fecal microbiota promoting bacterial diversity and maintenance of good versus bad bacteria, thus reducing inflammation in the gut [4]. Unfortunately, there are some factors accelerating the accumulation of senescent cells which include high fat diet induced obesity, metabolic syndrome and diabetes. Different studies showed that obesity driven accumulation of adipose tissue is associated with increased number of senescent cells in fat tissue as well as other organs. This implies that obesity and/or metabolic associated chronic inflammation might be related to increased accumulation of senescent cells and higher production of SASPs. The study by Hanse at al. showed that obesity causes increased accumulation of these "zombie" cells in ovarian tissue potentially increasing the risk of infertility, ovarian cancer and decline of female health due to accelerated process of menopause. However, subjecting obese induced female mice to D+Q successfully targeted and cleared senescent cells from the ovaries indicating the potential of improving overall health and fertility through senolytic therapies [8]. Furthermore, other studies have demonstrated that mice exposed to irradiation damage, which caused impairment in physical capacity, had significant functional improvement after treatment with D+Q, that in an old or transgenic atherosclerosis mice model this senolytic intervention improved cardiac function [11, 12], and that D+Q senescent cell clearance improves bone health and metabolic functions by targeting adipose tissue [13, 14]. Lastly, there is also growing evidence of the role of senescent cells in brain function and Alzheimer's disease [15, 16]. However, the most critical question we can ask is the translational potential for senolytic therapies for human aging and age-related diseases. Several completed small trials or ongoing clinical testing showed potential for using senolytic therapy to eliminate senescent cells, reduce inflammation and attenuate frailty in humans. The first in human, open-label and then follow-up phase I, single-blind, randomized and placebo-controlled pilot trial demonstrated improved physical function, feasibility and toler-

ability after D+Q intervention in patients affected by idiopatic pulmonary fibrosis [7, 9]. Yet another clinical trial with D+Q showed reduced senescent cells accumulation in adipose tissue biopsies collected from patients diagnosed with diabetic kidney disease [17]. Importantly, due to high potential in targetting senescent cells in aging and age-related diseases there is growing interest in the develement of new senolytic drugs to improve efficiency and specificity thus reducing any potential toxicity to healthy cells.

However, at this point more studies and clinical trials are necessary to better understand this complex mechanism and to validate the safety and/or necessity to start senolytic therapies outside of pending clinical trials to prevent or delay aging and age-assocoiated disease in generally healthy elderly populations.

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

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