VIEWPOINT

SCIENTIFIC DISCOVERY AND THE FUTURE OF MEDICINE

Aging, Cell Senescence, and Chronic Disease
Emerging Therapeutic Strategies

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Age is the leading predictive factor for most of the chronic diseases that account for the majority of morbidity, hospitalizations, health costs, and mortality worldwide. These diseases include Alzheimer disease and other neurodegenerative diseases, cardiovascular disease, and most cancers. Chronological age is also the main risk factor for the geriatric syndromes, including frailty and immobility as well as decreased physical resilience, which is manifested by delayed or incomplete recovery from stressors, such as surgery, hip fracture, and pneumonia. The prevalence of these problems not only increases with age, but these conditions tend to cluster within older individuals, leading to multimorbidity. Therefore, if any single major age-related disease were cured, it would only be supplanted by others, adding little to quality or length of life and limiting the effectiveness of treating age-related chronic diseases one at a time.

The fundamental aging processes that contribute to phenotypes characteristic of advanced old age, such as muscle weakness and loss of subcutaneous fat, also appear to underlie the major chronic diseases, geriatric syndromes, and loss of physical resilience. These aging processes can be broadly classified as follows: (1) chronic, low-grade inflammation that is "sterile" (occurring in the absence of known pathogens), together with fibrosis; (2) macromolecular and cell organelle dysfunction (such as DNA damage, dysfunctional telomeres, protein aggregation and misfolding, decreased removal of damaged proteins, or mitochondrial dysfunction); (3) changes in stem cells and progenitors that lead to reduced capacity to repair or replace tissues; and (4) cellular senescence. These aging processes are frequently evident at etiologic sites of chronic diseases, for example, in the brain of patients with Alzheimer disease or in the adipose tissue of patients with type 2 diabetes. Activation of any single fundamental aging process tends to influence the others. In laboratory animals, genetic or other interventions that target a particular aging process often also target others. Thus, fundamental aging processes are an attractive target for developing interventions to delay, prevent, or alleviate age-related disorders as a group.

Cellular Senescence

Senescence involves essentially irreversible arrest of cell proliferation, increased protein production, resistance to programmed cell death (apoptosis), and altered metabolic activity.[1] Senescent cells accumulate in multiple tissues as a result of chronological aging, especially after middle age, and in tissues central to the pathogenesis of chronic diseases. For example, senescent cells accumulate in and near bone in patients with age-related osteoporosis and in blood vessel walls in patients with vascular disease.[2,3] Cells can be driven into senescence by such inducers as DNA damage or other potentially oncogenic or chronic viral infection–induced insults, metabolic stresses such as high glucose level or reactive oxygen species, repeated cell divisions, or tissue damage signals such as the presence of extracellular DNA or protein aggregates.

Some senescent cells develop a senescence-associated secretory phenotype (SASP) that entails release of proteins, bioactive lipids, nucleotides, extracellular vesicles, and other factors. The SASP contributes to inflammation and the breakdown of tissues, stem and progenitor cell dysfunction, and the spread of senescence to nonsenescent cells. The SASP, immune cells attracted and activated by the SASP, and spread of senescence contribute to profound local and systemic effects with even small numbers of senescent cells. For example, transplanting small numbers of senescent cells around knee joints in young mice leads to joint pain and pathologic changes closely resembling human osteoarthritis.[4] Transplanting senescent cells into middle-aged mice so that only 1 in 10 000 cells in the recipients is a transplanted senescent cell is sufficient to cause profound physical dysfunction within 2 months, together with early death due to accelerated onset of age-related diseases as a group, compared with transplanting nonsenescent cells.[5]

There appears to be a threshold number of senescent cells above which frailty, chronic diseases, and accelerated mortality occur. Senescent cell burden is usually low in healthy people through middle age but increases across several years after the late 60s. The number of senescent cells in adipose tissue in women in their early 70s correlates with extent of frailty and disability.[6]

Senolytics

These findings about senescent cells led to efforts to develop senolytic agents—drugs that preferentially remove senescent cells.[1] A hypothesis-driven approach was used to discover the first senolytic drugs reported in early 2015: dasatinib, a tyrosine kinase inhibitor, and quercetin, a flavonoid.[7] Because senescent cells produce factors that kill cells around them yet resist death, senescent cells must have mechanisms in place to protect themselves from their own proapoptotic SASP. With the use of bioinformatics approaches, senescent cell antiapoptotic pathways (SCAPs) were discovered. The importance of these SCAPs was verified by targeting key nodes of SCAP pathways in senescent cells by RNA interference. Cultured senescent and nonsenescent cells

were exposed to drugs and natural products known to target the identified SCAP pathway nodes. Among these were dasatinib and quercetin, which eliminated senescent but not nonsenescent cells in rodent and human cell cultures, freshly isolated human tissue explants, and old mice or mice with accelerated aging–like conditions.[1,5,7] Numerous new and increasingly effective senolytics are being developed at an accelerating pace.

Because senescent cells originating from different cell types or resulting from different inducers use different SCAPs as a form of self-defense, the senolytic drugs reported to date are effective against some but not all senescent cell types. Agents or combinations that target multiple SCAPs generally kill a broader range of senescent cell types than those with a single SCAP pathway target. Few class adverse effects have been observed in mice treated with senolytics, although agent-specific adverse effects of certain drugs with senolytic activity are known to occur.[1] For example, navitoclax commonly causes neutropenia and thrombocytopenia when used to treat cancer, whereas other senolytics, such as quercetin, do not often appear to cause similar effects. Senolytics are effective when given in a "hit-and-run" intermittent approach, for example monthly, even if the agents have elimination half-lives of only a few hours. This may be because human senescent cells take approximately a month to appear and express a SASP, at least in cell culture; therefore, unlike drugs that act by occupying a receptor or targeting an enzyme, senolytics do not need to be present continuously.

Besides targeting SCAPs, other strategies for reducing the burden of senescent cells are being explored, such as immunomodulators and vaccines to accelerate immune removal of senescent cells, agents that recognize senescent cells and deliver a toxin, and drugs that target the metabolic pathways that senescent cells depend on. Drugs that reduce damage caused by senescent cells through inhibiting the SASP are being developed. Metformin, rapamycin (sirolimus), and the JAK1/2 inhibitor ruxolitinib act in part by inhibiting the SASP. Interventions such as caloric restriction or exercise can delay development of senescent cells. Although strategies that interfere with progression of cellular senescence after its induction carry a theoretical risk of increasing cancer predisposition, ablating already-formed senescent cells that harbor potentially oncogenic mutations by using senolytics appears to delay cancer development, at least in mice.[5] Furthermore, in patients with cancer, dasatinib and navitoclax are prescribed to induce cancer cell apoptosis.

Consistent with cellular senescence being a fundamental process that drives aging and its consequences, senolytics extend life span in mice as well as health span, the period of life when individuals are independent and free of major disability. In mice equivalent to 80-year-old humans, treatment with dasatinib plus quercetin increases survival by 36% and does so without increasing the period of morbidity at the end of life.[5] Senolytics also prevented or alleviated the accelerated onset of physical dysfunction, delayed age-related chronic diseases including cancers, and prevented the decreased survival caused by transplanting senescent cells into mice.[5] In preclinical studies, senolytics delay, prevent, or alleviate multiple age- and senescence-related conditions, including frailty, age-related osteoporosis, and numerous other conditions.[1,2,5] The first report that targeting senescent cells may arrest or reverse Alzheimer and related neurodegenerative diseases was recently published: treatment with dasatinib plus quercetin reduced neuroinflammation, alleviated brain hypoperfusion, and partially reversed brain shrinkage in mice with high tau expression.[8]

A handful of clinical trials of senolytics are under way or will soon start. Some are phase 1 or phase 2 trials using repurposed drugs approved by the US Food and Drug Administration for other indications or natural products for participants with symptomatic senescence-associated disorders, such as chemotherapy-induced physical dysfunction. If senolytic drugs are effective across a range of disorders, provided they are safe, clinical trials of senolytics might move toward studies in presymptomatic individuals to delay or prevent age-related conditions. Until then, patients should be advised not to self-medicate with senolytic agents or other drugs that target fundamental aging processes in the expectation that conditions alleviated in mice will be alleviated in people. Senolytics represent a new potential treatment approach, and the adverse effects of these therapies remain to be elucidated. If senolytics are shown to be safe and effective in humans, they could transform care of older adults and patients with multiple chronic diseases that now can only be managed and have not been amenable to disease-modifying interventions. This speculation merits intensive and rapid investigation.

ARTICLE INFORMATION

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