



CELL BIOLOGY

Cellular senescence in normal physiology

Long associated with aging, senescent cells can promote health and have physiological roles

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The aging of the world's population has intensified interest in understanding the aging process and devising strategies and interventions to prolong a healthy life span. Cellular senescence, when cells become irreversibly growth arrested after a period of *in vitro* cell proliferation or in response to sublethal stress or oncogene expression (1, 2), plays a role in aging phenotypes and age-associated diseases (1). Increasing evidence shows that senescent cells also have essential physiological functions, such as in tumor suppression, development, wound healing, tissue remodeling, regeneration, and vasculature. This raises important questions about the similarities and differences between senescent cell types and how they function in homeostasis and pathology, and it creates additional challenges in targeting them therapeutically.

Despite the importance of cellular senescence in tumor suppression and aging phenotypes, its precise definition is still debated. Furthermore, there is no single biomarker of senescence but rather several markers—including growth arrest, senescence-associated β -galactosidase activity, telomere-associated DNA damage, and expression of the cell cycle inhibitors p16 and p21—that have been used to identify and sometimes quantify senescent cells both *in vitro* and *in vivo* (1, 2). Senescent cells have been found to secrete proinflammatory cytokines and other factors, a characteristic called the senescence-associated secretory phenotype (SASP), that may disrupt tissue homeostasis and contribute to a proinflammatory state (1). Indeed, a seminal study demonstrated that genetically eliminating senescent cells, using an inducible system that triggers apoptosis in p16-expressing cells, ameliorated signs of aging and extended the median life span of mice by 24 to 27% (3). Thus, the study and development of senolytics—drugs that selectively kill senescent cells—has gained traction in recent years (1).

Although several studies in mouse models support the hypothesis that senescent cells can trigger or contribute to age-associated phenotypes, more recent studies have revealed additional roles for senescent cells

in nonharmful and even physiological processes. Indeed, eliminating senescent cells in mice can be detrimental to health, highlighting the importance of these cells in mammalian homeostasis and physiology. For example, senescent cells become more prevalent with age, particularly in the liver, and are often vascular endothelial cells. The continuous or acute removal of these senescent cells in mice disrupted blood-tissue barriers and led to the buildup of blood-borne macromolecular waste, resulting in perivascular fibrosis in a variety of tissues and subsequent health deterioration (4). These results underscore the functional and structural roles that senescent cells play in tissues that are important for organismal health.

Another recent study using p16 as a marker identified in young mice a population of senescent fibroblasts in the basement membrane adjacent to epithelial stem cells of the lungs that monitor barrier integrity and respond to tissue inflammation to promote epithelial regeneration (5). A different study detected senescence in multiple cell types of the lungs of neonatal mice and demonstrated that reducing senescent cells either pharmacologically or genetically (by p21 deletion) disrupted lung development (6). These findings suggest that programmed senescence, which is apparently not induced as a damage response but rather associated with developmental processes, is crucial for lung development in mice. However, reduction of senescent cells once lungs were developed in 7-day-old mice attenuated hyperoxia-induced lung injury, suggesting that senescent cells can also limit tissue repair (6). Paradoxically, eliminating senescent cells might exacerbate pulmonary hypertension in mice, despite the increased presence of senescence markers in the lungs of both mice and patients with hypertension (7). Notably, a study using p16 transgenic mice also found a role for p16 and cellular senescence in promoting insulin secretion by pancreatic beta cells, which was also observed in human cells, suggesting that cellular senescence can in some contexts enhance cellular function (8).

Studies of senescence *in vivo* often use senescence-ablator mice, which are genetically engineered to allow for the selective elimination of senescent cells, typically by targeting cells expressing p16. One important consideration is that many of these

mouse models use different constructs to target p16 (3, 4). Different constructs can lead to differences in the rate and effectiveness of senescent cell elimination. As such, technical disparities might explain inconsistencies in some results and further suggest that certain proportions or types of senescent cells within a tissue could be healthy whereas other senescent cell types and amounts might be pathologic. It is also important to note that even though p16 is the most widely used marker in these experiments, it is not a universal marker of cell senescence, and senescent cells can be observed independently of p16 expression (9).

Although cellular senescence has been observed during development in mice and other organisms (1, 2), its functions in development are still being unveiled. Senescent cells and activation of senescence signaling have been observed in human placentas and were down-regulated in placentas from pregnancies with intrauterine growth restriction (9). Interestingly, senescence-deficient mice, owing to deletion of genes encoding key senescence-associated signaling proteins (p16, p21, and p53), exhibited morphological aberrations in the placenta, suggesting that cellular senescence and the underlying signaling pathways regulate placental structure and function (9). Additionally, senescent cells in mice promote hair growth, and clusters of senescent cells appear to enhance the activity of adjacent stem cells to stimulate tissue renewal (10). Thus, damage-independent programmed senescence serves various functions during the development of different mammalian tissues, and the precise functions of these senescent cells require further investigation.

The role of senescence in wound healing and repair has been recognized for several years, and it has been suggested that senescent cells, probably by means of the SASP, recruit immune cells to promote tissue repair (2). However, a broader picture is emerging regarding the role of cellular senescence in regeneration and tissue repair across different animals. In an invertebrate cnidarian (*Hydractinia symbiolongicarpus*), senescent cells can induce the reprogramming of neighboring somatic cells into stem cells, driving whole-body regeneration (11). Genetic or pharmacological inhibition of cellular senescence prevented reprogramming and regeneration, suggesting that senescent cells signal

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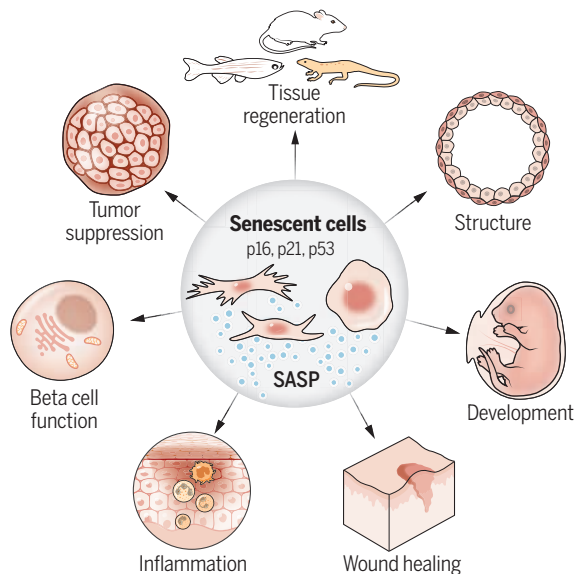
to nearby cells at an injury site to prepare for regeneration (11). Similarly, in newts (*Notophthalmus viridescens*), cellular senescence enhances limb regeneration, particularly by promoting muscle dedifferentiation and generating regenerative progenitor cells (12). In zebrafish, senescent cells appear after fin amputation, and their pharmacological removal impairs tissue regeneration (13). Although the relevance of these observations to mammals is unclear, several studies in mice have also demonstrated that senescent cells are important for tissue regeneration. For example, senescence of hepatic stellate cells is induced after liver injury, and pharmacological or genetic ablation of these senescent cells impairs liver regeneration (14).

Cellular senescence is an adaptive process; senescent cells are not aging, dysfunctional cells, they are functional cells that are important for several physiological processes (see the figure). Unfortunately, the word “senescence” implies a detrimental or nonfunctional role that is no longer accurate (15). Although the lack of universal senescence markers and of a clear definition of cellular senescence poses challenges, it is unquestionable that cells exhibiting senescence-associated markers play crucial roles in various normal physiological functions and in maintaining tissue homeostasis. Although damage and stress can induce cellular senescence, perhaps to recruit immune cells through the SASP and promote tissue repair and remodeling, cellular senescence can also arise independently of molecular damage or injury, for example, during development. Furthermore, senescence induced by injury can encourage regeneration and wound healing, and the degree of senescent cell involvement in the regeneration of different tissues is an exciting avenue for future research. Although a role for senescent cells in aging has been suggested by many studies (1–3), the recent findings that demonstrate normal physiological functions of senescent cells reveal a more complicated picture of the potential role of cellular senescence in mammalian aging.

A few limitations should be acknowledged. A growing number of pharmacological interventions, namely senolytics, have been shown to have health benefits in aging mice (1). But these drugs have off-target effects, and hence genetic manipulations, as has been the focus here, might offer a more precise way to test the role of senescent cells in health, aging, and disease. Nonetheless, several studies in mice have used both genetic and pharmacological methods to target

Functions of senescent cells

Recent evidence from mice and other model organisms has revealed that cellular senescence is important during the development of several tissues and organs, tissue regeneration in several animals, inflammation and wound healing, tumor suppression, insulin secretion in pancreatic beta cells, and has structural roles in the vascular system and placenta. There can be different types of senescent cells, which have a senescence-associated secretory phenotype (SASP), and are associated with the expression of markers such as p16 and p21.



senescent cells and shown that their elimination can impair normal physiology, such as organ development and tissue regeneration (6, 14).

Another important caveat is that most in vivo studies of cellular senescence have been conducted in mice, and its role in humans remains poorly understood. Senescent cells have been observed in the context of human age-associated diseases (2), often as part of inflammatory responses. However, whether senescent cells are protective or harmful (or both) in human pathologies remains to be established. Just as inflammation promotes tissue repair but may inadvertently contribute to tissue dysfunction, senescence is also likely pleiotropic and may be detrimental or harmful in humans, depending on context. Perhaps some types of senescent cells prevent tissue degeneration, by promoting regeneration as well as maintaining structure and function, thereby contributing to health maintenance, whereas other types—or an excessive amount—contribute to degeneration. Notably, not all senescent cells are the same. They can have different inducers, express different markers, and originate from different tissues and cell types; our understanding of the different types of senescent cells is still very limited. Many questions remain regarding the temporal dynamics of different types of senescent cells, their functions, and their clearance by the immune system.

Maybe short-term, transient cellular senescence is beneficial whereas long-term, chronic senescence becomes detrimental. Indeed, senescent cells are not only heterogeneous but perhaps dynamic, shifting with time and with changes in the tissue microenvironment. More research is needed to discriminate between healthy and pathologic senescent cells, and there are ongoing projects, such as the Cellular Senescence Network (SenNet; <https://sennetconsortium.org/>), that aim to identify, classify, and characterize senescent cells in humans and model organisms to improve understanding.

The growing number of physiological roles of senescent cells raises challenges concerning the development of senolytics and other senotherapeutics that target them. Perhaps removing certain types of senescent cells in some tissues is beneficial, whereas removing other types of senescent cells or too many of them is detrimental. As such, effective therapies will need the precision—at a certain dosage and administration—to eliminate pathologic senescent cells while sparing healthy senescent cells. Or perhaps modulators

of cellular senescence, which alter the function of senescent cells without necessarily eliminating them, need to be explored. Thus, the development of aging therapies centered on senescent cell targeting remains a promising avenue but is likely to be more complex than initially anticipated. ■

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SUPPLEMENTARY MATERIALS

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