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Cellular Senescence in Aging, Tissue Repair and Regeneration

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Abstract

Society and our healthcare system are facing unprecedented challenges due to the expansion of the aged population. As plastic surgeons, we can improve care of our aged patients through understanding the mechanisms of aging that inevitably impact their outcomes and wellbeing. One of the major hallmarks of aging, cellular senescence, has recently become the focus of vigorous research in academia and industry. Senescent cells, which are metabolically active but in a state of stable cell cycle arrest, are implicated in causing aging and numerous age-related diseases. Further characterization of the biology of senescence revealed that it can be both detrimental and beneficial to organisms depending on tissue context and senescence chronicity. Here, we review the role of cellular senescence in aging, wound healing, tissue regeneration, and other domains relevant to plastic surgery. We also review the current state of research on therapeutics that modulate senescence to improve conditions of aging.

Keywords

senescence; aging; wound healing; regeneration; fibrosis; senolytics

Introduction

Globally, the number of aged individuals is expanding dramatically due to improved management of chronic diseases. In 2004, 461 million people were older than 65 years-of-age, and it is projected that this will reach 2 billion by 2050, leading to unprecedented challenges in planning and delivery of healthcare[1]. As aging is recognized as a major contributor to almost all chronic conditions[2], the increasing socio-economic pressure associated with the growing aged population prompted the expansion of aging research to increase efforts aimed at extending human healthspan[3]. This brought attention to the hallmarks of aging: genomic instability, telomere shortening, epigenetic changes, cellular

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senescence (CS), stem cell exhaustion, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, and altered intercellular communication[4]. Here we focus on CS and its role in aging, tissue repair, and regeneration, relevant to plastic surgery and discuss potential therapeutic strategies targeting senescence (Figure-1).

Cellular senescence

The link between senescent cell (SnC) accumulation and numerous aging-related disorders is firmly established[5,6]. CS is characterized by stable cell cycle arrest triggered by exposure to a damage or stress stimuli, while remaining metabolically active and unresponsive to mitogenic and apoptotic signals[7,8]. CS can be triggered by oxidative, mechanical, or genotoxic stress, telomere shortening, mitochondrial dysfunction, and oncogene activation[7]. DNA damage caused by oxidative stress appears to be a pivotal factor driving the accumulation of SnCs with aging and impacting other causes of senescence and hallmarks of aging[9,10]. As DNA damage increases with age, mutations accumulate resulting in genomic instability[11]. Genomic instability causes a decrease in the efficiency of DNA repair machinery, which, in turn, contributes to more DNA damage, forming a vicious cycle of cellular decline occurring with aging[11-14]. Endogenous oxidative DNA damage can drive mitochondrial dysfunction, increased abundance of reactive oxygen species, and further damage to many cellular macromolecules and organelles[15].

Although CS is a tumor-suppressive mechanism, preventing duplication of damaged cells, SnCs instigate deleterious effects on their tissue microenvironment[16,17]. SnCs influence surrounding cells via their senescence-associated secretory phenotype (SASP) characterized by secretion of proinflammatory interleukins, chemokines, cytokines, matrix metalloproteinases, and growth factors[16-18]. CS also plays a beneficial role in embryogenesis, development, and tissue regeneration. For example, transient senescence is detected during mammalian embryonic development at multiple sites, including the mesonephros, the endolymphatic sac of the inner ear[19], the apical ectodermal ridge, and the neural roof plate[20]. Embryonic senescence is dependent on $p21^{CIP1}$, but independent of DNA damage[19]. Senescence during embryogenesis is followed by clearance of SnCs by macrophages, and tissue remodeling[19], and represents a physiological programmed mechanism that plays instructive roles in development and limb patterning[20]. Fin amputation in zebrafish leads to the transient accumulation of SnCs at the site of wounding, and their removal impairs tissue regeneration[21]. In these contexts, CS is a tightly regulated and a transient process[5,22] distinct from persistent CS in aging.

The heterogeneity of senescent phenotypes

CS encompasses diverse phenotypes varying based on the stressor inducing CS, the cell type, and physiological contexts[7,23]. Biomarkers of senescence are neither absolutely sensitive nor specific, and a combination of biomarkers is required to identify SnCs [7,24]. The most commonly used CS markers include upregulation of cell cycle inhibitors (in particular, $p16^{INK4a}$, $p21^{CIP1}$, and p53) and SASP, morphological changes such as cell enlargement and flattened morphology, expanded lysosomal compartment with increased senescence-associated β-galactosidase (SA-β-Gal) activity, and characteristic chromatin and epigenetic alterations[7,8].

Multiple pathological conditions are characterized by increased abundance of SnCs. Examples include idiopathic pulmonary fibrosis[25], osteoarthritis[26], posttransplant state, inflammatory bowel disease, hepatocellular carcinoma, obesity[27], and viral infections[28]. Whether accumulation of SnCs is related to the etiology in each of these conditions or is a compensatory mechanism is yet to be elucidated. Whether elimination of SnCs in humans with these conditions could bring substantial long-term benefits also remains to be defined.

The heterogeneity of SnCs prompted the idea of classifying SnCs into “Deleterious” and “Helper” types[23]. “Helper”-SnCs promote stem cell function, wound healing, and tissue regeneration, while deleterious cells promote chronic sterile inflammation and impaired wound healing and regeneration in aging[23].

Interestingly, cells can express senescence markers temporarily. A recent study demonstrated that expression of *p16*^{Ink4a} and SA-β-Gal in macrophages is induced as part of the physiological response to immune stimuli, consistent with data that *p16*^{Ink4a} plays a role in macrophage polarization and response to stimuli[29]. These results prompt the need to discriminate helper and deleterious SnCs in health and disease, and to elucidate whether cells are truly senescent or express senescent markers transiently as a part of a physiological response.

The relevance of cellular senescence to plastic surgery

SnCs impact aging and tissue repair, areas relevant to plastic surgery. Although SnCs accumulate with aging, there is increasing evidence that senescence signaling also upregulates during tissue repair and regeneration[5,22]. Indeed, senescence signaling plays an important role in cutaneous wound healing, musculoskeletal regeneration, as well as regeneration of liver, heart, and lung, and the response of the kidney and spinal cord to injury[30,31]. These critical physiological roles of CS were established by selective genetic or pharmacological elimination of SnCs or disruption of immune clearance of SnCs leading to impaired tissue regeneration[21,30].

Facial and skin aging—Skin from older individuals has significant cellular, biomechanical, biochemical, and physiological differences compared to skin from young individuals[32]. The number of p16^{INK4a} positive cells in sun-protected human skin significantly correlates with age-associated loss of elastic fibers, increase in facial wrinkles, and higher perceived age[33]. Independent of chronological age, individuals in the lowest tertile of epidermal p16^{INK4a} cell counts appear three years younger than those in the highest tertile[33]. In particular, senescent fibroblasts are implicated in skin aging by expressing SASP containing ECM-degrading matrix metalloproteinases (MMP-2 and MMP-9) and proinflammatory interleukins (IL-6 and IL-8)[34-37]. Additionally, senescent fibroblasts produce decreased insulin-like growth factor-1 what decreases epidermal cell proliferation and collagen expression[34,38], all features of skin aging.

Acute wounds and delayed wound healing—Transient upregulation of CS plays an important role in wound healing[39,40]. Cell cycle arrest proteins (in particular p16, p21, and p53) and SASP are transiently upregulated after cutaneous wounding in both mice and humans[41,42]. This upregulation appears to be essential for the healing process, as

selective elimination of SnCs impairs wound healing in mice[41]. Wound-associated senescent fibroblast and endothelial cells express platelet derived growth factor-AA (PDGF-AA) as part of the transient SASP, and in mice, topical administration of PDGF-AA alleviates delayed wound healing in the absence of SnCs[41]. Activated macrophages, which are critical for infection control and elimination of dead cells, can transiently express CS markers *p16*^{INK4a} and SA-β-Gal[29,43].

Delayed wound healing in aging, although multifactorial[44], is also associated with an altered senescence response. Subcutaneous irradiation-induced senescent fibroblast transfer to young mice causes delayed wound healing similar to that registered in aged mice[45]. In a recent human study a punch biopsy was used to induce a cutaneous wound, and p21 and p53 were upregulated during wound healing in younger, but not older subjects[42]. Interestingly, local and transient inhibition of p21 expression by *in vivo*-delivery of a p21-targeting siRNA ameliorated the delayed wound healing in aged mice[46]. In summary, transient senescence is beneficial for wound healing and without it, delayed healing can occur. However, the persistence of SnCs can contribute to chronic wounds[47,48].

Chronic wounds—Chronic wounds are usually stalled at the inflammatory stage[49]. Senescent fibroblasts are found in venous ulcers, diabetic foot ulcers, and pressure ulcers, and their incidence decreases after healing[49,50]. Exposure to chronic wound fluid causes dermal fibroblasts to switch their secretion profile from extracellular matrix deposition to a matrix-degrading phenotype[50], analogous to SnC SASP. A fraction of SnCs greater than 15% in cells isolated from venous ulcers negatively correlates with healing rate[51]. There is also a correlation between decreased collagen area and the presence of SnCs in human venous leg ulcers, diabetic foot ulcers, and pressure ulcers[52], and collagen imaging has been proposed as a non-invasive method to predict CS and wound healing trajectory[52].

SnCs are implicated in impaired wound healing in diabetics, which has multiple pathological components analogous to delayed wound healing in aging[53]. Hyperglycemia, oxidative stress, and mitochondrial and nuclear DNA damage may act as major drivers of SnC accumulation in diabetic ulcers, and it negatively impacts wound healing[54]. One of the mechanisms through which chronic CS contributes to impaired diabetic wound healing is via the CXCR2 receptor, which when blocked promotes repair [48,55].

Pathological scarring and fibrosis—Senescent fibroblasts appear at the site of wound repair presumably as the result of oxidative stress[56]. CS controls fibrotic response during wound healing inhibiting fibroblast proliferation and extracellular matrix synthesis[56]. This process is modulated by the matricellular protein CCN1, which triggers the DNA damage response and fibroblast senescence with concomitant expression of antifibrotic genes at the site of wound repair in wild type mice. Mice with mutant CCN1, that cannot bind integrin α6β1 and cell surface heparan sulfate proteoglycans, are unable to induce CS in granulation tissue and display exacerbated wound fibrosis[57]. Therefore, CS inhibits fibroblast proliferation and extracellular matrix synthesis dampening the fibrotic response in wound healing[56].

Based on the evidence that CS could limit fibrosis, it was hypothesized that insufficient number of SnCs could result in uncontrolled proliferation in keloid formation[56]. Therefore, "pro-senescence" therapeutic approaches were proposed as a mean to control keloid onset and recurrence[58]. For example, ionizing irradiation may prevent the recurrence of keloids by decreasing fibroblast proliferation and inducing CS[59].

Conversely, there is evidence that CS promotes fibrosis and scar formation. Interestingly, both hypertrophic and keloid scars demonstrate a unique CD34−/α-SMA+/p16+ scar phenotype, with p16 positivity being greater in keloid[60].

In addition, fibrotic capsules surrounding surgically excised human breast implants contain increased numbers of interleukin 17 (IL-17)–producing T cells and senescent stromal cells. In mice, the IL-6 produced by SnCs in response to implanted synthetic material is sufficient to induce IL-17 expression in T cells. When SnCs were eliminated, IL-17 expression and fibrosis in the murine implant model were reduced[61], suggesting that SnCs contribute to capsular contracture formation. Furthermore, species capable of scar-free healing are more resistant to oxidative stress and downregulate cellular senescence[62,63].

Interestingly, fetal and newborn wounds are characterized by rapid and scarless healing[22]. As transient senescence during embryonic development is distinct from the chronic senescence associated with aging, and contributes to the tissue remodeling[19,20], deeper investigation of the developmentally programmed senescence may give cues to novel approaches to improving wound healing and cosmetic outcomes in adult population.

Nerve repair and regeneration—Schwann cell senescence is involved in decreasing axonal regeneration in acellular nerve allografts in rats [64]. Compared to short acellular nerve allografts that heal faster, longer allografts are repopulated with greater percentage of $p16^{+}$ Schwann cells and stromal cells, suggesting a role of SnCs in poor axonal regeneration of long acellular nerve allografts[65]. Similar data were obtained in a rat sciatic nerve defect model where long isografts had significantly higher expression of SA-β-Gal, p21, and p16, and distinct chromatin changes in Schwann cells compared to short isografts[66].

SnC and SASP were also discovered in the carpal tunnel synovium and subsynovial connective tissue[67].

Fracture healing—*In silico* analysis of public mRNAseq data reveal that senescence and SASP markers are increased during fracture healing[68]. Consistent with that, in a murine fracture model, a significant increase in the expression of senescence markers occurs in the fracture callus during bone healing[68]. Using mice containing a *Cdkn2a*^{Ink4a}-driven luciferase reporter, a transient *in vivo* accumulation of SnCs is detected during callus formation[68]. Treatment of young adult mice after bone fracture intermittently with the senolytics Dasatinib and quercetin, decreased senescence and SASP markers in the fracture callus and accelerated fracture healing[68]. Furthermore, senescent osteocytes are implicated in age-associated bone loss, and senolytic treatment can improve bone mass, strength, and microarchitecture[69,70] to protect from fractures and potentially improve healing.

Therapeutic strategies targeting senescence and aging

Given the growing evidence that CS impacts aging and disease, multiple efforts have been focused on manipulation of SnCs to treat age-related pathology. Senotherapeutic approaches aimed at targeting SnCs include substances that selectively kill SnCs (senolytics) and suppress the SASP (senomorphics)[71-73] (Table-1). Some of these drugs, however, have severe side effects limiting their translational potential. For example, senolytic Navitoclax causes life-threatening thrombocytopenia[74].

Removal of SnCs using senolytics dasatinib plus quercetin, which cause apoptosis of SnCs, increases lifespan and alleviates diabetes, osteoporosis, neurodegeneration, pulmonary fibrosis, and cardiovascular disease in mice[23,75,76]. Because of these promising findings, there are already multiple clinical trials targeting senescence in humans[77]. Furthermore, a recent explosion of biotechnology companies entering the field of senotherapeutics has occurred (reviewed in [78]). Chimeric antigen receptor (CAR) T-cells, that target SnCs, is another approach being used to target SnCs *in vivo*[79].

While senolytic decrease SnCs in humans[77], longitudinal studies of longer duration are needed to understand the clinical significance of these findings and long-term efficiency, safety, and side-effects. At this time, it remains unclear whether senescence modification can decrease frailty and delay aging, or if this approach should be restricted to particular pathologies or topical application only. The results demonstrating transient expression of senescence markers by macrophages suggested that improved health outcomes in animal models following eradication of $p16^{Ink4a}$-positive cells could involve elimination of $p16^{Ink4a}$/SA-β-Gal-positive macrophages. The importance of exercising careful approach when attempting to eradicate SnCs is emphasized, while acknowledging the importance of senolytic exploration[29]. Continuous or acute elimination of $p16^{High}$ SnCs in transgenic mice, leads to disruption of blood-tissue barriers resulting in liver and perivascular tissue fibrosis[80]. It has also been postulated that elimination of SnCs may accelerate aging-related decline by driving remaining cells into senescence[81]. Currently, senotherapeutics are not selective for pathologic SnCs and are anticipated to impact beneficial SnCs as well. To summarize, while senotherapeutics deserve thorough investigation, many questions remain: Will systemic elimination of SnCs bring a long-lasting improvement without side effects? Whether it is beneficial to use senolytics in very old individuals (as many cells are potentially damaged and/or senescent)? When is it optimal to initiate senolytic therapy?

In addition to systemic administration, topical approaches are being developed to target localized senescence-associated conditions. Topical approaches might alleviate conditions such as chronic wounds or fibrotic processes and are presumed to be safer than systemic administration. A pilot study in humans yielded improved wound healing in diabetic ulcers treated with nano-hydrogel embedded with the senolytic quercetin and oleic acid[82]. Topical senolytics are also being tested in pre-clinical models for treatment of carpal tunnel syndrome[67]. A proprietary topically-delivered senotherapeutic peptide reduces skin biological age and improves skin health markers in *ex vivo* human skin models[83].

Conclusion

CS elicits diverse and potent effects on aging, numerous age-related diseases, as well as tissue repair and regeneration. Thus, targeting SnCs can have a potentially profound impact on the restorative aspects of plastic surgery. The therapeutic potential of CS modification is evident in preclinical studies and is currently being pursued in clinical trials, however, with exercised caution. The development of targeted and localized delivery technologies to modulate CS may be a promising area to influence outcomes in plastic surgery. The dichotomous ability of SnCs to both facilitate and hinder tissue repair processes, means continuing research on SnC biology is essential. Efforts to both harness the benefits of transient senescence and reduce the detrimental effects of chronic senescence may have a transformative impact on wound healing and tissue repair in general. Notably, many senotherapeutics identified to date are natural products that are available over the counter (OTC). Until further clinical studies are completed, it may be prudent for surgeons to be vigilant regarding patient OTC supplementation that could influence tissue regeneration and wound healing.

The heterogeneity of SnCs is now being revealed using single-cell and spacialomics approaches[7] with the hopes of creating an atlas that fully characterizes SnC subtypes in health and disease and discover biomarkers that can distinguish between beneficial versus detrimental SnCs. This is the focus of the NIH Common Fund Initiative: Cellular Senescence Network that was initiated in 2021 to create Tissue Mapping Centers, develop novel analytics and technologies for SnC identification, and create a Consortium Organization and Data Coordinate Center (https://sennetconsortium.org/).

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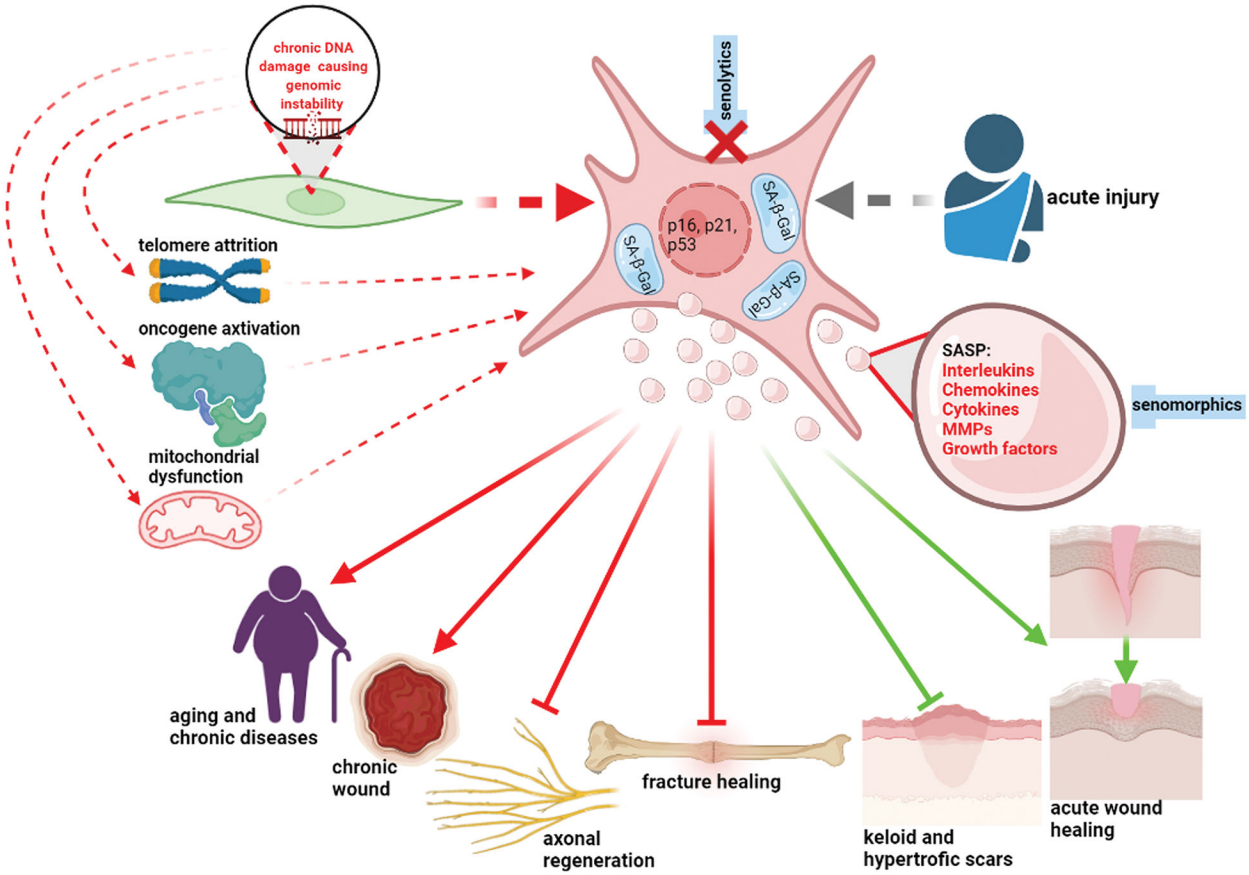

Figure 1.

Senescent cells (enlarged, hypersecretory (SASP-producing), expressing cell cycle arrest markers, with expanded lysosomal compartment containing senescence-associated β-galactosidase) accumulate with aging largely as a result of genomic stress, telomere attrition, oncogene activation, and mitochondrial dysfunction, and other external and internal stress stimuli. Upregulation of senescence also arises after acute tissue injury. The SASP influences surrounding cells affecting their function and drives chronic sterile inflammation. Chronic senescence contributes to aging, many chronic diseases, delayed wound healing and chronic wounds. Senescent cells also negatively affect axonal and bone regeneration. Sells, expressing senescence markers, however, play a positive role in wound healing after acute injury, and prevent hypertrophic and keloid scar formation. Senolytics act by eliminating senescent cells; senomorphics modulate the SASP (created in BioRender.com)

Table 1.

The list of most studied senotherapeutic molecules.

Substance	Mechanism of action	References
Senolytics – eliminate senescent cells		
Dasatinib	Tyrosine kinase inhibitor	84
Quercetin	Targets BCL-2 family Regulates NF-kß and P13K/AKT/mTOR Induces HIF-1a	85
Navitoclax (ABT-263) and ABT-737	Targets BCL-2, BCL-x(L), BCL-w	86
Fisetin	Inhibits PI3K/Akt/mTOR, MAPK, NF-κB, and ERK-MYC Targets BCL-2	87-90
FOXO4-DRI peptide	Disrupts the p53-FOXO4 interaction	91,92
Senomorphics - inhibit SASP		
Metformin	Targets NF-κB and Dicer	93,94
Rapamycin	mTOR inhibitor	95
Ruxolitinib	Targets JAK (Janus kinase) pathway	96