Cell Autonomous and Non-Autonomous Effects of Senescent Cells in the Skin

Marco Demaria\(^1\), Pierre Yves Desprez\(^{1,2}\), Judith Campisi\(^{1,3}\) and Michael C. Velarde\(^1\)

Human and mouse skin accumulate senescent cells in both the epidermis and dermis during aging. When chronically present, senescent cells are thought to enhance the age-dependent deterioration of the skin during extrinsic and intrinsic aging. However, when transiently present, senescent cells promote optimal wound healing. Here, we review recent studies on how senescent cells and the senescence-associated secretory phenotype contribute to different physiological and pathophysiological conditions in the skin with a focus on some of the cell autonomous and non-autonomous functions of senescent cells in the context of skin aging and wound healing.

INTRODUCTION

Cellular senescence is a complex stress response that renders cells incapable of cell division, even in the presence of growth stimuli (Campisi, 2013). Senescent cells are distinct from quiescent cells, which retain the ability to proliferate in response to appropriate stimuli. Senescent cells are also distinct from post-mitotic cells and terminally differentiated cells, which generally lose the ability to divide as a consequence of developmental, as opposed to stress-activated, programs.

A senescence response is typically induced by cellular damage (often nuclear DNA damage or mitochondrial dysfunction; von Zglinicki et al., 2005; Ziegler et al., 2015). As part of the senescence response, senescent cells express a number of non-exclusive markers, including the cell cycle inhibitor p16\(^{INK4A}\) and elevated levels of a lysosomal enzyme, termed as senescence-associated β-galactosidase (Rodier and Campisi, 2011). Many senescent cells also secrete several cytokines, growth factors, and matrix metalloproteinases (MMPs), collectively termed as the senescence-associated secretory phenotype (SASP; Coppe et al., 2008), which differ from those secreted by non-senescent quiescent, post-mitotic, and/or differentiated cells.

Senescent cells can alter tissue homeostasis and promote age-related diseases, including degenerative pathologies and cancers (Campisi, 2013; van Deursen, 2014). The inability of senescent cells to proliferate can impair tissue regeneration after injury, causing prolonged or permanent tissue damage with age. In addition, the SASP factors that are secreted by senescent cells can alter tissue microenvironments through their paracrine effects and promote age-related phenotypes (Coppe et al., 2008). Indeed, removal of senescent cells in a premature aging mouse model reduced selected age-related pathologies, such as sarcopenia, cataracts, and loss of subdermal adipose tissue (Baker et al., 2011).

Although cellular senescence is often viewed as a negative contributor to tissue function during the aging process, senescent cells, and particularly the SASP, can also have beneficial effects, such as the promotion of proper wound healing. This aspect of senescent cells could explain why cellular senescence evolved and has been preserved during evolution, even though it contributes to age-related phenotypes later in life. Here, we discuss how cellular senescence can be both beneficial and detrimental during skin aging and wound healing, and how the contrasting cell autonomous and non-cell autonomous effects of senescent cells can depend on the physiological context. On the one hand, senescent cells can accelerate aging phenotypes through the loss of tissue homeostasis by promoting chronic inflammation, persistent degradation of the extracellular matrix, and stem cell exhaustion. On the other hand, senescent cells can also have essential roles during wound healing by limiting excessive proliferation and fibrosis and promoting the formation of granulation tissue.

CELLULAR SENESCENCE AND SKIN AGING

Skin aging is caused by both intrinsic and extrinsic factors. Intrinsic aging, sometimes termed as chronologic aging, refers mainly to sun-protected areas of the skin. Intrinsic aging is associated with morphological changes primarily in the epidermal layer, manifest as marked thinning and loss of undulation (flattening of the dermo–epidermal junction; Makrantonaki and Zouboulis, 2007). Intrinsic aging also reduces subcutaneous fat and dermal thickness with an accompanying loss of cellularity and vascularity (Farage et al., 2013). In contrast, extrinsic aging, particularly photoaging (sun exposure), markedly affects both the epidermal and dermal layers, with the latter showing a striking loss of collagen and extracellular matrix (Quan et al., 2004, 2010).
There is also accumulation of abnormal elastic tissues (Bernstein et al., 1994; Mitchell, 1967), which are due to formation of structurally different elastic fibers (Watson et al., 2001).

Senescent cells increase with age in both the epidermis and dermis, as determined by elevated levels of senescence-associated β-galactosidase activity and p16INK4A expression (Dimri et al., 1995; Krishnamurthy et al., 2004; Ressler et al., 2006; Waaijer et al., 2012). Because senescent cells cannot proliferate, their presence in aged skin can potentially impair tissue homeostasis, regeneration, and youthful tissue structure/function (Campisi, 2013; Signer and Morrison, 2013). For example, in a three-dimensional organotypic culture model using neonatal dermal fibroblasts and epidermal keratinocytes from human donors of varying ages, increasing the expression of p16INK4A in keratinocytes isolated from young (30–40 years) donors yielded a thin epidermal layer similar to that formed by keratinocytes from elderly (53–66 years) donors; decreasing the expression of p16INK4A in keratinocytes from elderly donors transformed the aged skin phenotype of a thin epidermal layer into a thicker epidermis, similar to that formed by keratinocytes from young donors (Adamus et al., 2014).

Aside from the cell autonomous effects of non-proliferating senescent cells on skin homeostasis, SASP factors secreted by senescent cells are also thought to contribute to skin aging phenotypes in a cell non-autonomous manner. SASP factors, especially the MMPs, become elevated with age and can alter the tissue microenvironment and accelerate skin aging phenotypes (Table 1). MMPs can degrade collagens, including type I collagen, which is the most abundant protein in the dermal extracellular matrix. Loss of collagen is associated with several clinical manifestations of aging skin, including wrinkles, sagging, and laxity (Jariashvili et al., 2012; Quan et al., 2010; Shuster et al., 1975). Hence, increased expression and activity of MMPs during aging can decrease the amount of collagen in the skin (Varani et al., 2004), diminish fibroblast-collagen interactions, and reduce mechanical tension, explaining the wrinkling phenotype observed in aged skin (Varani et al., 2006). Another hypothesis for facial wrinkling is the enhanced elastase activity upon UVB stimuli, which is associated with a reduction in the elastic properties of the skin (lmokawa, 2009). The role of cellular senescence in promoting changes in the elastic tissue has not been addressed yet but represents an important avenue for future clinical approaches.

Although it is still unclear which specific stimuli are responsible for inducing cellular senescence during aging, both intrinsic and extrinsic aging have been linked to the age-related increase in the number of senescent cells in the skin. For example, the hereditary disorders, the Werner syndrome, xeroderma pigmentosum, and the Hutchinson–Gilford progeria syndrome, which are due to defects in DNA damage repair or nuclear organization, are associated with increased cellular senescence and accelerated age-related phenotypes in the skin (Davis et al., 2007; Harada et al., 1999; Liu et al., 2006). Extrinsic factors, such as X-rays, UV light, and cigarette smoke, also can induce cellular senescence, as well as age-related phenotypes in the skin (Shin et al., 2012; Velarde et al., 2012; Yang et al., 2013).

UV light can induce photoaging via direct damage to extracellular matrix components, such as collagen and fibrillin fibers (Jariashvili et al., 2012; Menter et al., 2001; Sherratt et al., 2010), or indirect damage through mitochondrial dysfunction. Indeed, mitochondrial dysfunction is suggested to have a role in both intrinsic and extrinsic aging and may potentially serve as a common link between the two (Krutmann and Schroeder, 2009). UV radiation–induced photoaging of human skin is associated with large-scale deletions in mitochondrial genomes (mitochondrial DNA (mtDNA); Berneburg et al., 1997; Birch-Machin et al., 1998). Intra-individual studies have revealed that the frequency of a 4,977 bp deletion, also defined as “common deletion”, is increased up to 10-fold in photoaged skin compared with sun-protected skin (Berneburg et al., 1997). The majority of these deletions are detectable in the dermis of human skin exposed to physiological doses of UVA (Berneburg et al., 2005). UV radiation also induces this common deletion in cultured skin fibroblasts and decreases mitochondrial function (Berneburg et al., 2005). Because mitochondrial damage and dysfunction induces cellular senescence in culture and in vivo (Passos et al., 2006; Velarde et al., 2012), and UV light also promotes mitochondrial damage and cellular senescence, it would be interesting to test whether the UV-induced common deletion contributes to skin aging through mitochondrial dysfunction–associated senescence.

### Table 1. List of MMPs involved in skin aging, cellular senescence, and wound healing

| MMP expression | References |
|----------------|------------|
| Skin aging     | Elevated expression of MMP1, MMP3, and MMP9 | Quan et al., 2009 |
| Cellar senescence | Elevated expression of MMP1, MMP3, MMP8, MMP10, MMP12, and MMP13 | Coppe et al., 2010; Freund et al., 2011 |
| Wound healing   | Temporal upregulation of MMP1, MMP2, MMP9, MMP3, MMP10, MMP14, MMP8, MMP12, MMP13, MMP19, MMP26, MMP28 | Martins et al., 2013 |

Abbreviation: MMP, matrix metalloproteinase.

### CELLULAR SENESCENCE AND WOUND HEALING

Wound healing is a complex process by which the skin repairs itself after injury. This process is classically divided into four distinct but overlapping phases (Singer and Clark, 1999): (i) hemostasis, (ii) inflammation, (iii) proliferation, and (iv) remodeling. During the first two phases, platelets promote coagulation and begin an inflammatory cascade by secreting a variety of cytokines and chemokines to attract macrophages and neutrophils (Fuhrman et al., 1991; Kim et al., 2008; Shallo et al., 2003). Before the inflammatory phase ends, fibroblasts are recruited to the wound site and endothelial cells mature from progenitor cells to reestablish vascularization (Chen et al., 2008; Postlethwaite et al., 1987;
Sunderkotter et al., 1994). The proliferative phase begins with the formation of granulation tissue and collagen deposition, and the wound closes by epithelialization and the contraction of differentiated myofibroblasts, which are specialized contractile fibroblasts (Guo and Dipietro, 2010). The final remodeling phase initiates when a stable ratio of collagen production and degradation is reached and ends when the tissue acquires a mature organization and tensile strength after replacing transiently expressed collagen III with collagen I (Madden and Peacock, 1971; Tomasek et al., 2002).

Recent findings using mouse models show that senescent cells are transiently induced in the granulation tissue during the proliferative phase of wound healing and are efficiently removed during the transition to the remodeling phase (Demaria et al., 2014). Wound contraction is important for wound closure during the proliferative phase (Midwood et al., 2004) and proceeds through the formation of newly synthesized granulation tissue and the activation of contraction in myofibroblasts (Tomasek et al., 2002). Thus, the presence of senescent cells within this window may be essential for proper wound healing. Indeed, the elimination of senescent cells in young mice bearing cutaneous wounds leads to poor formation of granulation tissue and a marked reduction in the number of myofibroblasts, with consequent delayed wound closure (Demaria et al., 2014). Notably, this phenotype can be rescued in senescence-free mice by topical application of the SASP factor platelet-derived growth factor AA, which promotes the differentiation and maturation of myofibroblasts. Senescence-free wounds were also more fibrotic during the remodeling phase, but topical platelet-derived growth factor AA was unable to limit this excessive fibrosis. These findings illustrate the complex and diverse roles played by senescent cells during wound healing and suggest that other SASP factors in addition to platelet-derived growth factor AA are important for optimal wound healing.

As indicated above, another important contribution of senescent fibroblasts during tissue repair is to limit fibrosis, which is commonly observed in chronic wounds and is characterized by excessive collagen deposition (Telgenhoff and Shroot, 2005). Several MMPs, including MMP2, MMP3, and MMP9, are part of the SASP (Table 1; Coppe et al., 2010; Coppe et al., 2008) and can degrade excess collagen and maintain tissue homeostasis during wound healing (Jun and Lau, 2010). Indeed, failure to induce senescence during wound healing causes fibrosis in the skin and liver (Jun and Lau, 2010; Kim et al., 2013; Krizhanovsky et al., 2008). Overall, these results indicate that senescent cells can promote tissue repair through cell non-autonomous mechanisms.

The irreversible growth arrest of senescent cells may restrict proliferation during wound healing as a means to protect against aberrant cell proliferation. This cell autonomous effect of senescent cells is in keeping with a fundamental role for cellular senescence in tumor suppression (Campisi, 2001). Cells from mice lacking the p16INK4a and p21WAF1/CIP1 genes are incapable of undergoing cellular senescence and highly susceptible to skin carcinogenesis upon 7,12-dimethylbenz[a]anthracene/12-O-tetradecanoylphorbol-13-acetate treatment due to their inability to arrest cell proliferation (Takeuchi et al., 2010). Hence, the absence of cellular senescence may transform a wound into a hyperplastic or premalignant phenotype characterized by unregulated cell proliferation. Because wound healing and cancer share several molecular and cellular events (Dvorak, 1986; Feng et al., 2010), senescent cells may have an essential role in promoting wound healing while preventing cancer initiation.

Although a lack of senescent cells impairs wound healing and can promote tumorigenesis, the persistent presence of senescent cells may exacerbate pathological diseases in the skin. For example, chronic wounds are characterized by the persistent presence of senescent cells in the wound areas (Mendez et al., 1998; Vande Berg and Robson, 2003; Vande Berg et al., 2005). Because chronic wounds fail to progress through the different stages of the wound-healing process (Sen et al., 2009), an excessive number of senescent cells may restrict cell proliferation and disrupt paracrine signaling cascades, thereby retarding the ability of wounds to resolve after injury. Moreover, some of the SASP factors that are important for wound healing seem to also promote cancer progression through cell non-autonomous mechanisms. For example, certain MMPs that are anti-fibrotic in wounds can also promote tumor cell invasion during the progression of skin cancers (Woenne et al., 2010).

**THE BALANCE BETWEEN CELL AUTONOMOUS AND NON-AUTONOMOUS EFFECTS IN SKIN HOMEOSTASIS**

The complex role of senescent cells in the skin includes cell autonomous and non-autonomous functions, which may be beneficial during wound healing but deleterious during aging (Figure 1). What determines the phenotype of senescent cells, and whether their effects on the tissue microenvironment are positive or negative? One hypothesis is that both the cell autonomous and non-autonomous properties of senescent cells are highly dependent on age and time. First, the induction of an irreversible growth arrest might be an essential mechanism during wound healing that limits the number of...
highly proliferative cells, which are at risk for acquiring premalignant or malignant mutations. However, with time and age, this mechanism can exhaust the pool of proliferation-competent stem or progenitor cells, which contribute to tissue turnover and regeneration. Second, the slow accumulation of senescent cells in the skin due to increased number and/or defective clearance might create chronic inflammation and promote age-associated skin pathologies—for example, through the chronic production of MMPs. Third, the SASP may be a malleable phenotype and change over time and with age. Thus, harmful cytokines, chemokines, and other inflammatory factors may be secreted by senescent cells only when they are persistently present in the skin.

CONCLUSION
The elimination of senescent cells is an attractive avenue for developing new interventions to treat age-related pathologies, and several laboratories are searching for small molecules that might be of potential interest for future clinical studies (see Dorr et al., 2013, for an example). In the skin, the different roles of senescent cells in promoting both physiological and pathophysiological conditions are still in early phases of discovery. More experiments need to be conducted to determine how senescent cells can tip the balance between efficient and chronic wound healing. It also remains to be proven whether the presence of long-lived versus short-lived senescent cells has a major contributory factor to this difference. Thus, whether and how an anti-senescent approach will help maintain healthy skin awaits future experimentation. Although the elimination of senescent cells might reduce age-related chronic inflammation and collagen degradation, this strategy could fail to restore youthful skin phenotypes that depend on adequate stem cell numbers. Finding ways to replenish these stem cells may be necessary in order to rescue age-related skin defects after the elimination of senescent cells. Furthermore, the continuous removal of senescent cells in the skin, particularly in the elderly, could impede wound healing and increase tissue scarring, which are of bigger concerns than having a youthful looking skin. Hence, a better understanding of the complexity of the cell autonomous and non-autonomous functions of senescent cells, and the mechanisms that lead to their induction, will be essential in order to develop specific therapeutic approaches with minimal side effects to treat age-related skin phenotypes and pathologies.

CONFLICT OF INTEREST
The authors state no conflict of interest.

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