

The regulation of cutaneous immunity and pathology by cellular senescence

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Abstract

Skin diseases affect nearly one quarter of the global population, with prevalence rising sharply among older adults. By 2050, the number of individuals over 60 years will double, making age-related dermatological conditions an increasing public health concern. A central process underlying aging is cellular senescence, a stable form of growth arrest induced by diverse stressors, including DNA damage, telomere attrition, and oncogenic signaling. Senescent keratinocytes, fibroblasts, melanocytes, and immune cells accumulate in the skin with age and secrete a pro-inflammatory senescence-associated secretory phenotype (SASP) that actively shapes the cutaneous immune landscape. Although senescence can promote tissue repair and tumour suppression, the persistence of senescent cells drives inflammation, impairs immunity function, and contributes to pathology, a concept now termed senopathy. In this review, we first examine the crosstalk between senescent stromal and immune cells in human skin. Then we discuss how SASP from senescent fibroblasts inhibits the function of resident T cell, while senescent T cells adopt a paradoxical state, hyperfunctional yet non-proliferative, that can accelerate tissue damage. We further highlight the immune evasion strategies which enable senescent cells to persist and drive inflammaging. Insights from patients with Familial Melanoma Syndrome (germline *CDKN2A* mutations) illustrate how defective senescence pathways across multiple cell types impair cutaneous immunosurveillance and increase melanoma risk. Finally, we explore evidence for stromal- and immune-mediated cutaneous senopathies, including psoriasis, lupus, vitiligo, and leishmaniasis, where senescent cells actively drive the diseases' progression. Based on the analysis, we propose that the skin represents a powerful and accessible model for investigating the interplay between senescent immune and non-immune cells across the lifespan, with therapeutic implications for aging and age-related pathologies.

Keywords: Cellular senescence, immunosenescence, immunity, skin, melanocyte, fibroblast, T cell, p16

1. Introduction

At any given time, nearly a quarter of the global population is living with skin diseases^[1]. The conditions span from inflammatory and infectious disorders to malignancies, affecting individuals at all stages of life. The skin undergoes profound structural and immunological changes during aging; after the age of 65 years, the prevalence of skin diseases rises sharply, with 50-80% of older adults affected by at least one dermatological disease^[2,3]. By 2050, the number of people over 60 is expected to double and those over 80 years to triple^[1]. Therefore, the burden of skin diseases will increase dramatically in the future, underscoring an urgent need to elucidate mechanisms that underpin declines in skin health.

Cellular senescence is central to the process of skin aging. It represents a stable form of cell cycle arrest in multiple cell types triggered by various intrinsic and extrinsic stressors, including DNA damage, telomere attrition, oxidative stress, and oncogenic signaling^[4,5]. Initially considered a tumour-suppressive mechanism, cellular senescence is now recognized as a dynamic regulator of tissue homeostasis^[6]. In the skin, senescent keratinocytes, fibroblasts, melanocytes, and immune cells increase with age^[7,8]. These senescent cells can influence immune cell recruitment^[9,10], tissue remodelling^[11] and inflammatory signaling^[9,12] through the secretion of a mixture of cytokines, chemokines, proteases and growth factors, collectively referred to as the senescence-associated secretory phenotype (SASP)^[13]. As such, the accumulation of diverse senescent cells actively shapes the immune landscape of the

skin^[14-17]. It also raises key questions on whether these cells are beneficial (promote repair) or detrimental (drive chronic inflammation). Furthermore, clarification is needed on whether senescent stromal cells influence the function and fate of aging immune cells in this tissue, and vice versa.

Recent work suggests that senescent structural cells in the skin are not merely remnants of damage, but actively contribute to immune regulation by creating an inflammatory environment that inhibits cutaneous immunity^[9,12]. In addition, our study of skin from individuals having heterozygous defects in the *CDKN2A* gene that encodes the senescence associated protein p16^{Ink4a}, has provided valuable insights into the regulation of cellular senescence across different cell types within the same human skin samples. In this review, we will explore how cellular senescence influences cutaneous immunity and its role in cutaneous ‘senopathy’ (i.e., dermatopathology caused by the accumulation of senescent cells).

2. Senescence: Physiology and Detection

Cellular senescence was originally described by Hayflick and Moorhead in the context of replicative exhaustion^[18]. Senescent cells are characterized by the cessation of proliferation, resistance to apoptosis and a highly secretory nature^[13]. These physiologic alterations are induced by metabolic reprogramming, including enhanced glycolytic flux, mitochondrial dysfunction, altered lipid metabolism and disrupted autophagy^[19]. These cells also exhibit numerous features that facilitate their identification, including enlarged cell size, increased expression of cyclin-dependent kinase inhibitors (such as p16^{Ink4a} and p21^{CIP1}^[10,20], persistent DNA damage response foci (e.g., γ H2AX)^[21,22], epigenetic changes^[23], expression of senescence-associated β -galactosidase (SA- β -Gal)^[24], and altered mitochondrial dynamics^[25].

The potential role of these cells in organ dysfunction and disease emphasizes the critical importance of their identification for ongoing research. At present, no single marker or combination of markers can detect senescence with complete sensitivity and specificity across all cell types in tissues and experimental approaches. The consensus is for multi-parameter profiling using cytoplasmic, nuclear and SASP/cell-type-specific markers for detection in all cell/tissue types including skin^[26]. However, many conventional senescence markers have inherent limitations. For instance, cell cycle inhibitors can be upregulated in both quiescent and senescent cells^[5,27], and marker expression varies depending on the employed senescence stimulus^[10]. As demonstrated in Table 1, studies have reported variable, and sometimes opposing senescence marker expressions within the same cell type. This may reflect differences in experimental protocols, including senescence modality, technological advancements and experimental limitations. Moreover, the most widely used markers for identification (enlarged cell size, permanent cell cycle arrest, SA- β -Gal expression) are largely restricted to cells studied *in vitro*. Detection of senescent cells in the skin follows the same above-mentioned limitations^[5,26]. Table 1 summarises both *in vitro* and *in vivo* senescence markers in human cutaneous research.

Table 1. Senescence markers for stromal cells in human skin.

Senescence Marker	Keratinocyte	Melanocyte	Fibroblast	Endothelial Cells
p16 ^{Ink4a}	Increased ^[28,29] Not detected ^[30,31]	Increased ^[10,31-34]	Increased ^[22,35-37,38]	Increased ^[39-42]
p21 ^{CIP1}	Increased ^[30,31,43] Reduced ^[28]	Increased ^[33] Unchanged ^[10,31,32]	Increased ^[36-38]	Increased ^[40-42]
p53	Reduced ^[28]	Increased ^[33,44] Not detected ^[10]	Increased ^[36,37,45]	Increased ^[42] Unchanged ^[40]
SA- β -Gal	Increased ^[24,30,46-48]	Increased ^[31,33,34]	Increased ^[10,22,24,36,37,49,50]	Increased ^[39,42,51]
Lamin B1	Reduced ^[47,52]	Reduced ^[53] Not detected ^[10]	Reduced ^[52-54]	Unknown
HMGB1	Reduced ^[31]	Reduced ^[10,31]	Reduced ^[49,55]	Unknown
TAF (telomere associated DNA damage foci)	Increased ^[31]	Increased ^[31]	Increased ^[22]	Unknown
Ki67	Reduced ^[48,56]	Reduced ^[22,33]	Reduced ^[10,22,49]	Unknown
Lipofuscin	Unknown	Unknown	Increased ^[38,57]	Increased ^[39,51]
Proliferation assay	Reduced ^[24,31,46]	Reduced ^[31]	Reduced ^[10,36,37,50]	Reduced ^[51]
SASP	Increased ^[48]	Increased ^[31,58,59] Unchanged ^[10]	Increased ^[10,13,22,60-62]	Unknown

SASP: senescence-associated secretory phenotype; SA- β -Gal: senescence-associated β -galactosidase.

Several machine learning tools have recently been developed to define senescence-associated signatures. For instance, SENESCopedia identifies common transcriptomic profiles of senescent cancer cells^[63], while SenPred is an emerging machine learning tool that utilizes single-cell transcriptomics to detect *in vitro* replicative senescence in human dermal fibroblasts^[64,65]. SenMayo offers a gene set for identifying senescence across multiple *in vitro* cell types^[66]. However, the generalizability of these tools across diverse cell types, tissues, and experimental platforms has yet to be fully validated. In 2021, the SenNet Consortium was launched with the goal of mapping senescent cells and their associated SASP across 18 healthy human tissues throughout the lifespan. By integrating genomic, proteomic and lipidomic data, it aims to build a comprehensive senescent cell atlas^[67]. Although it remains uncertain whether a universal method for senescence detection will emerge, such an atlas would provide a valuable resource for tailoring senescence detection approaches to specific experimental contexts.

Despite the limitations, two methods have been successfully used to detect senescent non-lymphoid cells in human skin, namely the expression of p16^{INK4a}, and the expression of telomere associated DNA damage (TAF)^[22]. Both these methods correlate strongly with each other and indicate that senescent cells, particularly fibroblasts, increase in the skin with age^[22]. The reliability of these methods was further supported by studies in individuals heterozygous for defects in the *CDKN2A* gene encoding p16^{INK4a}, who show significantly reduced expression of both p16^{INK4a} and TAF expressing cells in the skin^[10]. The functional consequences of altered cellular senescence in different populations of skin-derived cells from these individuals will be discussed more detailed below.

2.1 Immune senescence

In addition to structural cells such as fibroblasts, immune cells can also become senescent. These changes are most extensively characterized in T cells^[68-72], but are increasingly being studied in other immune cell subsets, including macrophages^[73,74] and B cells^[75]. In humans, senescent T cells can be identified by a wide range of cell surface markers, including loss of co-stimulatory receptors such as CD28 and CD27, and upregulation of CD57 and KLRG1^[68,76]. Functionally, these cells exhibit shortened telomeres, reduced telomerase activity, and profound deficits in antigen responsiveness, including reduced TCR signaling, defective calcium flux, and impaired synapse formation and proliferation after activation^[68,77-79]. They rely on glycolysis for energy and display mitochondrial dysfunction with increased reactive oxygen species production^[80]. They also exhibit persistent DNA damage signaling, often accompanied by upregulation of p16^{INK4a} and p21^{CIP1}^[80]. This led to earlier assumptions that senescent T cells were dysfunctional^[81]. However, despite their impaired proliferative capacity, senescent T cells still secrete high levels of IFN- γ and TNF- α upon activation, and express numerous cytotoxic molecules such as granzyme B and perforin. This paradoxical non-proliferative but hyper-functional profile is considered a unique SASP signature of senescent T cells^[68,76]. Table 2 outlines the markers commonly used to detect senescent T cells in blood and skin. While certain cell surface markers, such as KLRG1 and CD57, can identify these cells in resting peripheral blood of healthy individuals, they are not reliable for detecting those in the skin^[89]. In contrast, in patients with inflammatory conditions such as cutaneous leishmaniasis, where large numbers of T cells infiltrate the tissue, these markers can identify senescent populations. For this reason, senescence markers detecting senescent cells across cell types (p16, p21, γ H2AX; Table 2), are used to detect senescent T cells in the skin.

Table 2. Human T cell senescence markers in blood and skin.

Senescence Marker	Senescent Peripheral T Cells	Senescent Cutaneous T Cells
p16 ^{INK4a}	Increased ^[82-85]	Increased ^[86,87]
p21 ^{CIP1}	Increased ^[82,85]	Increased ^[86,87]
CD27	Absent ^[68,88]	Absent ^[88,89]
CD28	Absent ^[69,88]	Unknown
CD45RA	Increased ^[69]	Increased ^[88,89]
TCR-mediated proliferation	Reduced ^[79,80,90]	Unknown
CCR7	Reduced ^[91-94]	Unknown
CD62L	Reduced ^[95]	Unknown
CD57	Increased ^[96]	Increased ^[88,96,97]
KLRG1	Increased ^[90,94,98]	Increased ^[87]
NKG2A/C	Increased ^[78,87,99]	Increased ^[88]
NKG2D	Increased ^[79,99,100]	Increased ^[88]

DAP12	Increased ^[79]	Unknown
Proliferative capacity	Reduced ^[69]	Unknown
Telomere length	Reduced ^[101]	Unknown
Telomerase	Reduced ^[101]	Unknown
BCL-2	Reduced ^[93,102,103]	Unknown
yH2AX	Increased ^[104,105]	Unknown
DDR	Increased ^[76,79]	Increased ^[87]
Sestrins	Increased ^[78,79]	Increased ^[87]
P38MAPK	Increased ^[76,79,80]	Increased ^[87]
SASP	Increased ^[76]	Increased ^[87]
Cytotoxic granules (perforin, granzyme)	Increased ^[91]	Increased ^[88] Reduced ^[89]

SASP: senescence-associated secretory phenotype.

Recent studies have shown that senescent human T cells express a group of stress-sensing molecules known as sestrins, which regulate their reduced proliferative capacity and senescence characteristics^[78,79]. Notably, senescent CD8⁺ T cells exhibit a sestrin-dependent shift toward natural killer (NK) receptor expression (e.g., NKG2D, NKG2C) and MHC-unrestricted cytotoxicity against NK target cells, such as the K562 cell line^[79]. CD8⁺ T cells can recognize and eliminate senescent non-lymphoid cells expressing MICA/B, the ligand for the activating NK receptor NKG2D^[22]. Therefore, beyond their established role in eradicating malignant and infected cells, NK and CD8⁺ T cells can also recognize and eliminate senescent non-lymphoid cells, thus identifying a novel form of immunosurveillance *in vivo*. Altered interactions between senescent immune and non-immune cells in different tissue compartments during aging or in inflammatory diseases, may contribute to the disease pathophysiology^[22,72].

2.2 The accumulation of senescent lymphoid and non-lymphoid cells in the skin during aging

The skin is anatomically divided into three principal tissue compartments: the epidermis, dermis, and subcutis (or hypodermis). Each layer contains distinct populations of structural and immune cells, and provides a unique microenvironment in which cellular senescence can arise and exert context-dependent effects.

The epidermis, composed primarily of keratinocytes, serves as the frontline barrier against environmental insults. Immunologically, it hosts resident Langerhans cells and a population of skin-homing memory T cells^[106,107]. The dermis beneath is rich in fibroblasts, vascular and lymphatic endothelial cells, macrophages, mast cells and dermal T cells, functioning as a connective tissue and an immunological interface^[106,107]. The subcutis, consisting of adipocytes, blood vessels, and a diffuse population of immune cells, is increasingly recognized as a critical regulator of the metabolic environment for leukocytes. This role is highlighted by studies showing that how adipokines (cytokines derived from adipocytes) influence immune cell metabolism and systemic metabolic outcomes such as thermogenesis^[108-111].

Several studies have quantified the proportion of senescent cells in the skin, but the values are markedly different due to experimental differences, markers employed, and units used to quantitate. For instance, in the epidermis, Victorelli *et al.* identified 6% of senescent cells based on the p21 expression but 30% based on TAF^[31]. Another study showed 4% p16-positive cells and 6% p21-positive cells in the aged epidermis^[112]. In the dermis, Ressler *et al.* reported a mean of seven p16-positive senescent cells per visual field in aged skin^[20], while Pereira *et al.* observed 20-65% TAF-positive senescent cells per visual field in aged dermis^[22]. Despite the variations in markers, methods and quantification, a consistent finding is the accumulation of senescent cells in the skin with age.

Senescent cells have been identified in all these compartments of aged skin^[20,22,31,112]. Melanocytes and fibroblasts, in particular, exhibit clear hallmarks of senescence in response to replicative stress, ultraviolet (UV) radiation, pollution and inflammation^[113]. These cells adopt a SASP that can profoundly alter the local immune landscape by recruiting, activating, or even dysregulating immune cells. Senescence has been best characterized in fibroblasts, and senescent dermal fibroblasts actually remodel the extracellular matrix, impair fibroblast-keratinocyte crosstalk, and secrete SASP factors that drive chronic low-grade inflammation and matrix degradation^[114]. These changes contribute to hallmark features of cutaneous aging, such as dermal thinning, wrinkle formation, delayed wound healing, and reduced tensile strength. Melanocytes similarly undergo senescence with age^[31,115].

While the classic regulators of senescence are the p53/p21 and p16/Rb pathways, melanocyte senescence appears to be at least partially distinct from other studied cell types, more dependent on p16 relative to the other pathways^[10,32,116]. Melanocytes secrete

melanin, which protects the skin from the UV-induced damage by mitigating reactive oxygen species production^[117,118]. Indeed melanocytes accumulate more DNA damage than dermal fibroblasts *in vivo*^[10], and after UVA irradiation *in vitro*^[117]. Few studies have explored the nature of melanocyte SASP. Gene-level analyses have revealed the upregulation of inflammatory and SASP signatures in a model of oncogene-induced melanocyte senescence, including TGF β regulators, MMP7 and VEGF^[58]. Senescent melanocyte-derived IP-10 can induce paracrine senescence in neighbouring keratinocytes, contributing to epidermal thinning^[31], a key feature of aged skin. Although melanin is actively secreted via extracellular vesicles, it does not seem to constitute a component of the SASP. In fact, senescent melanocytes display impaired melanin secretion^[115].

Senescent stromal-immune interactions in the skin under normal homeostatic conditions remain poorly understood. Tissue-resident memory T cells, having growing proportions with age, can adopt a dysfunctional, pro-inflammatory phenotype, secreting IFN- γ and TNF- α while exhibiting reduced proliferation and antigen-specific capacity^[17,119,120]. The shift promotes an inflammatory microenvironment that is no longer protective but exhaustive and maladaptive. Despite this, long-lived resident memory T-cells (Trm) are not obviously “senescent” in healthy human skin. For instance, CD8 Trm cells typically show low CD57/KLRG1 and lack immediate cytotoxicity^[89]. Aging changes the Trm functional diversity rather than abundance, resulting in an age-related shift toward cytotoxicity through CD49a⁺ expression in CD8 Trm^[17]. Evidence of classically defined senescent T-cells, characterized by expression of p16/p21⁺ and SASP-like features, remains scarce. This contrasts with the evidence in human blood, where a sharp rise in such T-cells is observed in a steady state during aging^[121]. Nevertheless, increased numbers of senescent T cells defined by loss of CD28⁺ and gain of CD57⁺ expression are found in the skin of patients with systemic sclerosis^[122]; psoriasis^[123] and cutaneous infections such as leishmaniasis^[124].

2.3 Immune evasion by senescent cells in tissues

It is paradoxical that despite the immune system’s capacity to eliminate senescent cells^[125,126] the cells accumulate in many tissues during aging. This is because senescent cells can evade the immune system by expressing inhibitory NK ligands such as HLA-E and PD-ligand 1 (PD-L1) on their surface *in vitro* and *in vivo*^[22,127]. HLA-E binds to the inhibitory NK receptor NKG2A on NK and senescent CD8⁺ T cells, thereby inhibiting their cytotoxic activity^[22], while PD-L1 engages PD1 on T cells to inhibit their functions^[22,128,129]. Senescent cells can also employ other strategies to evade the immune system, including the secretion of soluble MICA/B, the ligand for the activating NK receptor NKG2D expressed on NK and T cells^[130].

Similarly, protease/exosome-mediated loss of NKG2D ligands can occur in the context of cellular stress and senescence, with MICA/B lost in an ADAM10/17-dependent manner due to its metalloproteinase activity. The loss of NK/T-cell activating ligands results in clearance-evasion in specific microenvironmental contexts^[131].

In a human skin model, it was shown that senescent fibroblasts recruit inflammatory monocytes that produce prostaglandin E₂, which subsequently suppresses tissue T-cell responses to antigen-recall challenge in a p38MAPK-dependent manner^[9]. Likewise, in senescence-rich tumours, tumour-associated macrophages expressing CD73, drive adenosine accumulation, thus inhibiting NK/T-cell activity via A2A receptors^[132].

More recently, ganglioside-mediated immune checkpoints have been found to be upregulated on senescent cells and can hence inhibit NK cytotoxicity^[130,133,134]. Collectively, these evasion strategies may enable senescent cells to persist in tissues during aging, and contribute to increased inflammation with deleterious consequences.

2.4 Senescent non-lymphoid cells regulate decreased cutaneous immune responses during aging

The lack of suitable human models for investigating immunity *in vivo* prompted the development of an experimental system, where recall antigens were injected into the skin of volunteers, followed by the biopsy of the injection site^[120,135–138]. The biopsied tissue was then investigated using immunohistological and transcriptional platforms, while leukocytes and other cell types were also isolated for functional analyses *in vitro*^[12,120,138,139]. These studies demonstrated that older adults respond significantly weaker to cutaneous challenge with bacterial (tuberculin PPD), fungal (candida albicans) and viral (varicella-zoster virus; VZV) recall antigens^[9,12,120]. This was not attributable to diminished immune memory, since the responses to these antigens by T cells in the peripheral blood were similar to those in both young (> 40 years) and older (> 65 years old) subjects^[120]. Furthermore, the number of skin resident T cells and their responses to recall antigen after isolation were similar across both age groups^[139]. This suggested that the factors within the skin environment during antigen challenge inhibited the local response to the challenge.

Elevated baseline inflammation in the skin of older individuals was found to be strongly correlated with the diminished responsiveness to recall antigen challenge^[9,12]. The inflammation arose from the recruitment of inflammatory myeloid cells by senescent fibroblasts, driven by their secretion of monocyte chemoattractant molecules such as CCL2^[9]. Therefore, the fibroblast-derived SASP creates an inflammatory environment that inhibits resident memory T cell responses^[9]. As senescent cells, particularly fibroblasts, accumulate in the skin and other organs during aging^[22,114,140–144], they may contribute to broader age-associated immune decline by promoting sterile inflammatory responses, a manifestation of inflammaging^[145,146]. As proof of this regulatory axis, the inhibition of the cutaneous SASP in older adults using an oral p38 MAP kinase inhibitor (Losmapimod) for 4 days

in vivo significantly enhanced the recall responses to antigen challenge in these subjects^[9,12]. Accordingly, the accumulation of senescent stromal cells can inhibit resident memory T cell activation in the skin and may exert similar effects in other organs.

However, resident memory CD8⁺ T cells themselves can also become senescent and studies in mice demonstrated that these cells can accelerate tissue aging and contribute to physiological decline^[147,148]. Although senescent non-lymphoid cells generate inflammatory, immunosuppressive environments, senescent T cells, via their NK-like cytotoxic functions, can directly induce tissue damage^[72,148]. In support of this contention, senescent T cells have been identified in the skin of humans and mice with systemic lupus erythematosus^[72,149] and psoriasis^[87] based on the expression of p16^{Ink4a} and p21^{CIP1}. The use of a topical Bcl-2 inhibitor (senolytic therapy) reduces the numbers of these senescent T cells in mice, reducing disease severity^[72,87,149]. Senescence in both lymphoid and non-lymphoid cells may occur simultaneously, and their interactions may synergistically induce pathology in aging and inflamed tissue^[72]. Therefore, it is crucial to understand the co-evolution of senescence across different cellular compartments, as this may be induced by a shared mechanism that leads to pathology in inflamed and aging tissues.

2.5 A skin model of crosstalk between senescent immune and non-immune cells: Familial Melanoma Syndrome (FMS)

Our understanding of cellular senescence remains compartmentalized, focusing on isolated cell types, individual signaling pathways, or specific SASP components^[113,150]. However, senescence in human tissue is a multi-cellular, spatially integrated process, shaped by the dynamic interactions among structural cells, immune populations, and the aged tissue microenvironment. An integrated overview of senescence in both immune and non-immune compartments of the skin has emerged from analyses of skin and blood samples of patients with the FMS^[10]. These patients carry autosomal dominant heterozygous germline mutations in the *CDKN2A* gene, which encodes the tumour suppressor p16^{INK4a}^[10]. Despite surviving to adulthood, they exhibit phenotypic features, including multiple atypical melanocytic naevi, increased susceptibility to melanoma, often developing early and repeatedly, and, less commonly, pancreatic cancer^[151]. Their tissues offer a unique window into how defective senescence pathways shape cutaneous immunity and tumour risk prior to overt tumour development.

Both melanocytes and fibroblasts in FMS patients fail to undergo normal p16-mediated senescence^[10,152]. Notably, melanocytes in these patients are particularly vulnerable to the loss of p16 as they do not upregulate p21 during senescence induction to compensate for this deficit, while senescent fibroblasts can upregulate both p16 and p21 (Figure 1A,D)^[10]. In addition to this intrinsic senescence defect in melanocytes, senescent dermal fibroblasts in FMS patients exhibit attenuated SASP secretion, which is associated with a marked reduction in resident memory CD4⁺ and CD8⁺ T cell populations in the skin (Figure 1C,F)^[10]. This increased risk of melanoma in *CDKN2A*-deficient individuals may result from the reliance of senescent melanocytes on p16 for growth arrest after DNA damage, rendering them susceptible to malignant transformation. This susceptibility is further exacerbated by senescence-related defects in fibroblasts, especially reduced SASP secretion, which hinders recruitment of T cells^[10].

When either melanocytes^[10,152] or fibroblasts^[10] were isolated from the skin of FMS patients and cultured continuously toward replicative senescence *in vitro*, further evidence of senescence-associated defect in these cells was observed. These cell types showed substantially increased replicative capacity before reaching senescence compared to age- and sex-matched controls (Figure 1B,E)^[10]. Of note, pre-senescent fibroblasts from FMS patients could proliferate despite harboring DNA damage, ultimately developing abnormal nuclei upon entry into replicative senescence (Figure 1E)^[10]. The study of FMS patients has thus enabled the simultaneous assessment of the integrated dysregulation of senescence across multiple cell types in the skin of humans *in vivo*. Consequently, the susceptibility of these patients to melanoma is multi-faceted.

2.6 Senopathy: when senescence causes disease

The term “senopathy” has emerged to describe a class of diseases where the accumulation and persistence of senescent cells actively contribute to pathology^[153]. Senescence can play a beneficial role in processes such as wound healing^[11], tumour suppression^[154-156] and tissue remodelling^[157]. In contrast, senopathy is a maladaptive state where senescent cells are not effectively cleared and instead exert chronic effects on their surrounding environment. These effects are primarily mediated by the SASP that disrupts local tissue homeostasis^[158], promotes secondary senescence in neighbouring cells^[159], and fosters a microenvironment conducive to inflammation^[13], fibrosis^[160], and degeneration^[161]. Therefore, senescent cells can act as active drivers of age-associated disease, with broad relevance across multiple organ systems. In the skin, we propose that senopathy reflects the establishment of a ‘stable senopathic niche’, where senescent stromal and immune cells persist within a remodelled microenvironment and fail to return to homeostasis. Across the diseases discussed below, SASP-driven inflammation, secondary senescence and impaired clearance cooperate in a self-reinforcing ‘senopathic loop’, converting transient, physiological senescence into a chronic driver of cutaneous pathology (Figure 2).

2.6.1 Non-immune-mediated cutaneous senopathy

Environmental insults, such as UV radiation^[162,163], mechanical injury^[182], infection^[164], and pollution^[165], as well as intrinsic factors such as metabolic stress, hypoxia^[167] and nutrient imbalance, are capable of driving senescence in fibroblasts, keratinocytes,

melanocytes, and endothelial cells. Senescent stromal cells have been shown to accumulate in inflammatory dermatoses, contributing to disease pathology. In psoriasis, mid and upper epidermal keratinocytes exhibit features of senescence, including elevated expression of p16 and p21 in both *in vivo* and *in vitro* studies^[173-175]. These cells also demonstrate reduced proliferation^[174], resistance to apoptosis^[176], and enhanced SASP secretion, even relative to senescent keratinocytes from non-psoriatic individuals^[174]. Though psoriasis is traditionally considered a disease of hyperproliferative keratinocytes, the presence of senescent keratinocytes within psoriatic plaques has been proposed to be protective against keratinocyte malignancies. However, this benefit is offset by increased immune activation and basal keratinocyte proliferation driven by excessive SASP secretion^[175].

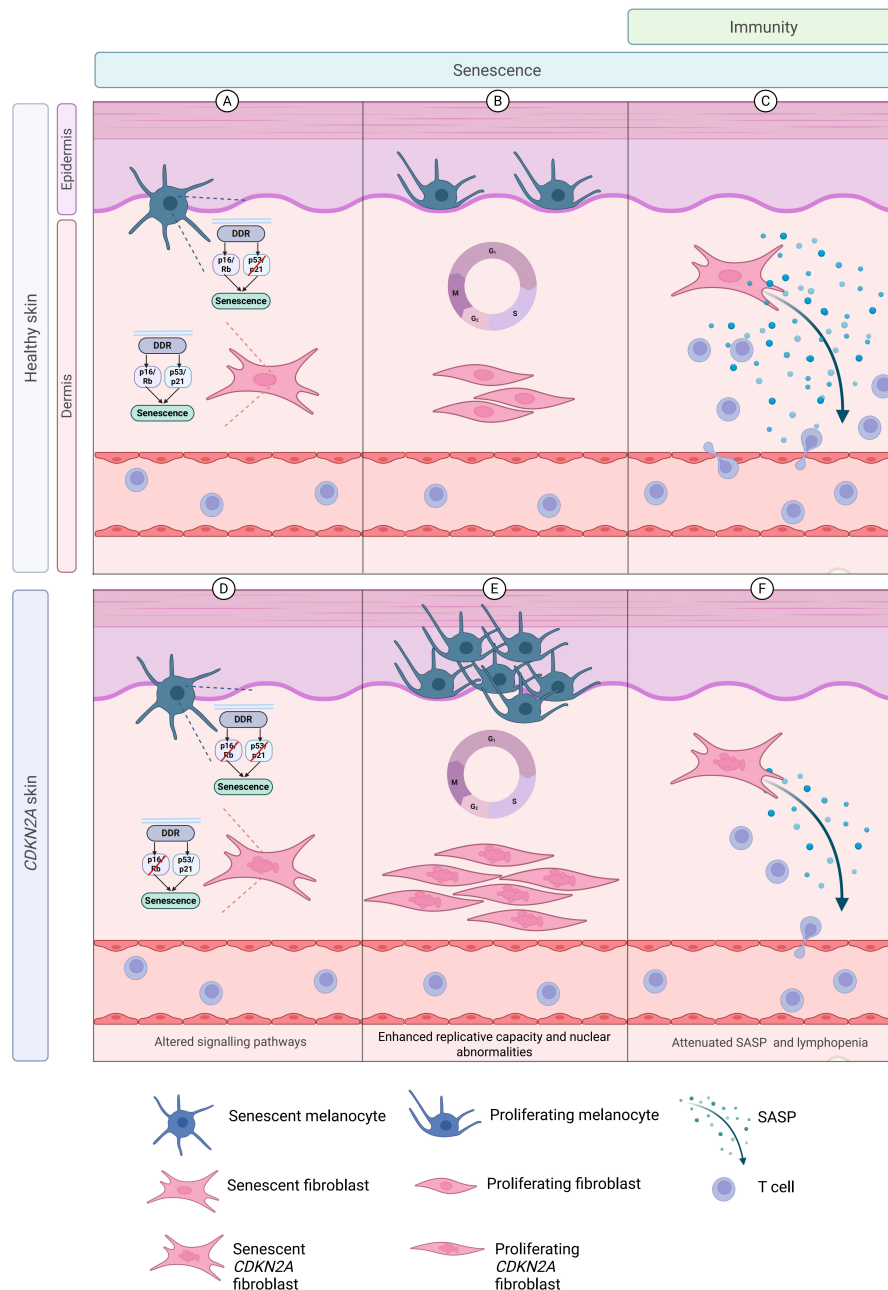


Figure 1. The germline *CDKN2A* mutation leads to multiple cutaneous abnormalities in senescence and immunity. Schematic showing alterations in the skin of individuals with the germline *CDKN2A* mutation. In skin from healthy individuals (A) Melanocytes preferentially recruit the p16 pathway to execute senescence, while fibroblasts can flexibly use both the p16 and p21 pathways; (B) Melanocytes and fibroblasts proliferate with normal nuclear architecture; (C) Senescent fibroblasts secrete a SASP rich in inflammatory proteins, chemokines and cytokines, with preserved numbers of resident memory T cells. Differences exist in baseline skin from individuals with the germline *CDKN2A* mutation in which (D) Both melanocytes and fibroblasts fail to upregulate p16 to effect senescence, while fibroblasts are able to recruit the p21 pathway in the context of p16 pathway redundancy; (E) Melanocytes and fibroblasts have increased replicative capacity, fibroblasts showing nuclear morphological abnormalities in pre-senescent and senescent states; (F) Senescent fibroblasts secrete less SASP with an associated reduction in numbers of cutaneous CD4⁺ and CD8⁺ T cells. Created in [Biorender.com](https://www.biorender.com). SASP: senescence-associated secretory phenotype.

Stromal senescence has further been implicated in cutaneous lupus erythematosus (CLE). In lesional epidermis from CLE patients, diffuse expression of p16 and p21 is observed, in contrast to unaffected skin from the same individuals^[178]. Comparisons across other inflammatory skin diseases reveal increased p16 and p21 expression in the basal epidermis, particularly in conditions characterized by dermo-epidermal junction inflammation^[178]. While direct causality has not been established, this spatial correlation between senescent cell accumulation and sites of inflammation suggests a potential mechanistic link. Similarly, senescent fibroblasts and their SASP-driven activation of innate immunity may contribute to eczema in older subjects^[180]. In vitiligo, the presence of senescent dermal fibroblasts has raised the possibility that SASP-mediated CD8⁺ T cell recruitment may play a role in melanocyte destruction^[177,179].

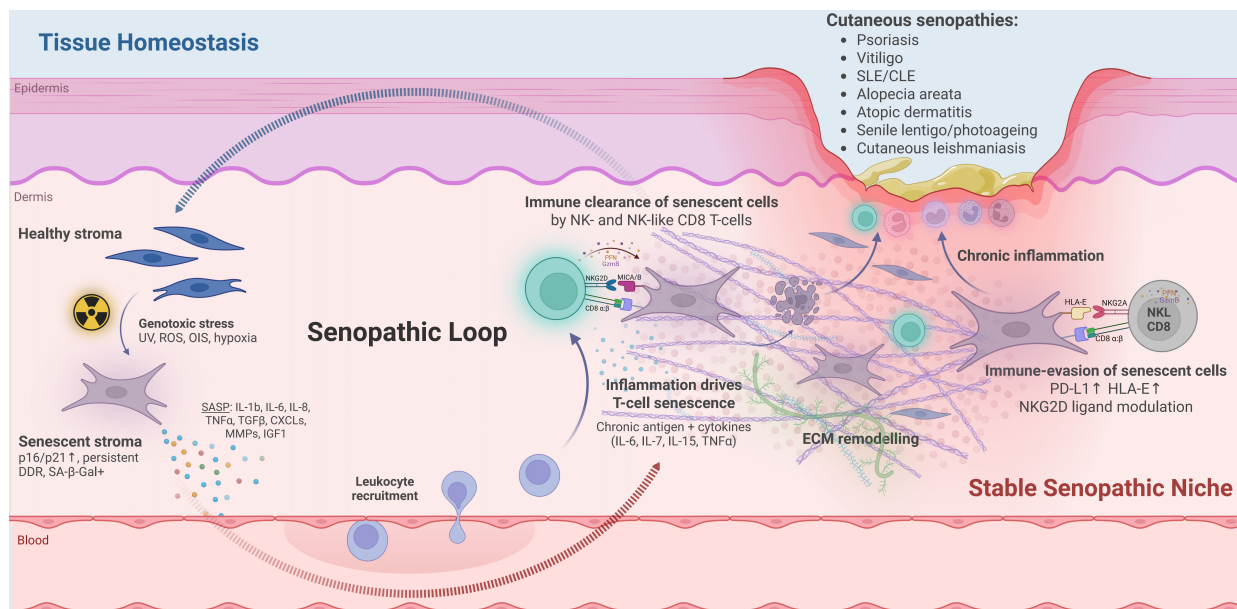


Figure 2. The senopathic loop and formation of a stable senopathic niche in human skin. Schematic cross-section of skin illustrating how cellular senescence in stromal and immune compartments regulates cutaneous immunity. **Left:** tissue homeostasis is disrupted by environmental and intrinsic genotoxic stressors—such as UV radiation, reactive oxygen species, oncogene-induced stress and hypoxia—which drive senescence in stromal cells (for example dermal fibroblasts). Reproduced from reference^[21,25,163–165]. CC BY 4.0. Reproduced with permission from reference^[162]. Copyright © 2017 Elsevier; reference^[166]. Copyright © 2006 Springer Nature. Senescent stromal cells are characterised by p16/p21 up-regulation, persistent DNA damage responses and SA-β-Gal activity. Reproduced from reference^[21,24]. CC BY 4.0. Reproduced with permission from reference^[20]. Copyright © 2006 John Wiley & Sons; reference^[35]. Copyright © 2012 John Wiley & Sons. These cells secrete a SASP rich in inflammatory cytokines, chemokines, growth factors and matrix metalloproteinases—for example IL-1β, IL-6, IL-8, IL-15, TGF-β, CXCL chemokines, MMPs and, under hypoxia, IGF-1—which recruit leukocytes from the circulation and remodel the extracellular matrix. Reproduced from reference^[45,61,62,114,168]. CC BY 4.0. Reproduced with permission from reference^[60]. Copyright © 2009 Springer Nature; reference^[167]. Copyright © 2025 American Association for Cancer Research. In human skin models, senescent dermal fibroblasts promote leukocyte recruitment and low-grade inflammation, reinforcing this loop. Reproduced from reference^[12]. CC BY 4.0. Reproduced with permission from reference^[9]. Copyright © 2021 Springer Nature. Under effective immunosurveillance, NK and NK-like CD8⁺ T cells expressing activating NK receptors such as NKG2D recognise ligands including MICA/B on senescent stromal cells and mediate their clearance, thereby returning the tissue towards homeostasis. Reproduced from reference^[22,71,124,126]. CC BY 4.0. Reproduced with permission from reference^[79]. Copyright © 2020 Springer Nature; reference^[125]. Copyright © 2025 Springer Nature. **Right:** when SASP-driven inflammation is chronic, recruited T cells themselves acquire senescent, NK-like phenotypes in response to persistent antigen and cytokine exposure (for example IL-6, IL-7, IL-15, TNF-α), amplifying tissue damage. Reproduced from reference^[22,71,76,87,169]. CC BY 4.0. Reproduced with permission from reference^[79]. Copyright © 2020 Springer Nature. Senescent stromal cells up-regulate immune checkpoint ligands such as PD-L1 and HLA-E. Reproduced from reference^[22,127,170]. CC BY 4.0. Reproduced with permission from reference^[128]. Copyright © 2023 Informa UK Limited, and senescent or stressed cells modulate NKG2D ligands—including shedding of MICA/B—creating an immunosuppressive, immune-evasive microenvironment that permits survival of both senescent stromal and lymphoid cells within a remodelled ECM. Reproduced from reference^[127,131,172]. CC BY 4.0. Reproduced with permission from reference^[125]. Copyright © 2020 Springer Nature; reference^[171]. Copyright © 2014 S. Karger AG. This self-sustaining configuration constitutes a stable senopathic niche, in which persistent senescent cells and chronic inflammation reinforce one another, and is proposed to underlie “cutaneous senopathies” such as psoriasis. Reproduced from reference^[173–176]. CC BY 4.0, vitiligo. Reproduced from reference^[177]. CC BY 4.0, systemic/cutaneous lupus erythematosus. Reproduced from reference^[178]. CC BY 4.0. Reproduced with permission from reference^[149]. Copyright © 2024 Elsevier, alopecia areata. Reproduced with permission from reference^[179]. Copyright © 2023 Springer Nature, atopic dermatitis/eczema. Reproduced with permission from reference^[180]. Copyright © 2024 Elsevier, senile lentigo/photoageing. Reproduced from reference^[141]. CC BY 4.0, and cutaneous leishmaniasis, where stromal and/or T-cell senescence are directly linked to lesion burden and tissue injury. Reproduced from reference^[124,169,181]. CC BY 4.0. Created in [Biorender.com](https://www.biorender.com). SASP: senescence-associated secretory phenotype; UV: ultraviolet; SA-β-Gal: senescence-associated β-galactosidase.

2.6.2 Immune-mediated cutaneous senopathy

Senescent T cells may play a crucial role in mediating senopathy across various dermatological diseases. In cutaneous leishmaniasis, *Leishmania braziliensis* is inoculated into human skin via sandfly bites. In untreated patients, peripheral blood shows increased senescent CD4⁺ and CD8⁺ T cells, characterised by CD57 and KLRG1 expression, along with other hallmarks of senescence, including DNA damage, elevated pp38 activity, and shortened telomeres^[181]. Peripheral blood mononuclear cells (PBMCs) from these patients exhibit a more pro-inflammatory and cytotoxic profile compared to healthy controls, with enhanced skin-homing potential due to increased expression of the CLA. Notably, the abundance of these senescent T cells positively correlates with cutaneous lesion size^[181]. At the tissue level, lesional skin is enriched with senescent CD8⁺ T lymphocytes and NK cells^[88]. The severity of cutaneous disease also links strongly to the presence of these CD8⁺ lymphocytes, independent of the low parasite burden in the skin^[70,169]. This observation has led to the hypothesis that extensive skin damage in leishmaniasis results from non-specific NK-like cytotoxicity exhibited by senescent T cells^[70,124].

A broad role of senescence in other cutaneous diseases has also been identified. In alopecia areata, a subset of highly differentiated memory CD8⁺ T cells (senescent) displays innate-like cytotoxic behaviour mediated by NKG2D^[179], which may cause hair follicle destruction. In human psoriasis patients and murine psoriasis models, numerous senescent CD4⁺ T cells are observed in both the epidermis and dermis. Topical treatment of the senolytic BCL-2 inhibitor ABT-737 in psoriatic mice significantly reduces the number of senescent CD4⁺ T cells and mitigates the inflammatory milieu, lowering the levels of key cytokines implicated in psoriasis pathogenesis, including IL-17A, IL-17F, IL-12, and IFN- γ ^[87]. Furthermore, in patients with systemic lupus erythematosus (SLE) and in SLE mouse models, increased numbers of senescent CD4⁺ CD57⁺ lymphocytes were observed in peripheral blood and skin compared with both healthy individuals and those with other rheumatological conditions^[149,180]. The abundance of these cells and the intensity of CD57 expression, correlate positively with disease activity and cutaneous involvement. Treatment with the BCL-2 inhibitor ABT-263 (navitoclax) reduces senescent T cell numbers in peripheral blood samples from SLE donors *in vitro* and in a lupus mouse model *in vivo*. This reduction is accompanied by an alleviation of lupus-like phenotype and improved renal function^[148]. Additionally, the gene expression analysis of senescent CD4⁺ lymphocytes from SLE patients highlights their proinflammatory signature, supporting the notion that these cells contribute to the inflammatory pathology of lupus.

2.7 Senotherapeutics in skin: immune or stromal modulation?

The prospect of halting or reversing age-related decline has long been a focus of interest. Pharmacological targeting of senescence, either through senolytic (cell-killing) or senomorphic (SASP-suppressing) therapies, has increasingly become viable and extensively reviewed elsewhere^[86,183,184]. There is growing interest in leveraging these approaches to treat age-related skin dysfunction and inflammatory dermatoses. Both lymphoid and non-lymphoid senescent cells contribute to cutaneous pathology, representing the potential therapeutic targets. In the skin, senescent stromal cells, notably fibroblasts, exert immune-suppressive effects by producing excessive SASP, impairing local immunity^[9,12,185]. They also induce immune checkpoint molecules on T cells and ligands on stromal cells (e.g., PD-L1, HLA-E)^[22,128], and cleave immune-stimulatory molecules^[130], collectively inhibiting their own clearance. Meanwhile, chronic inflammation upregulates activating NK ligands, such as MICA/B, on non-senescent stromal cells^[171,172,186], rendering them susceptible to NK-like cytotoxicity of senescent T cells. This duality raises a therapeutic paradox: in skin diseases, should interventions target senescent stromal cells, senescent T cells, or both?

2.7.1 Evidence for targeting stromal cells

Senolytic agents, dasatinib and quercetin, can eliminate senescent human dermal fibroblasts *in vitro* and *in vivo*, resulting in increased collagen deposition and suppressed SASP in the skin^[187]. Systemic dasatinib monotherapy in systemic sclerosis improves skin thickness in a subset of patients, accompanied by a reduction in cutaneous SASP and senescence-associated gene expression^[187,188]. Furthermore, the combined dasatinib-quercetin treatment alleviates radiation-induced cutaneous ulcers in mice through the clearance of senescent stromal cells^[189].

Several senomorphic agents have demonstrated efficacy in modulating cutaneous immunity by targeting dermal fibroblasts. The p38 MAPK inhibitors losmapimod with vitamin D3 reduces systemic inflammation, and improves cutaneous T cell infiltration and antigen-specific immunity in aged human skin by suppressing senescent dermal fibroblast SASP^[9,12]. The mTOR inhibitor rapamycin is a powerful SASP suppressor in humans^[190,191], effectively working on human dermal fibroblasts *in vitro*^[192] and reducing objective measures of human skin aging *in vivo*^[193]. Although its efficacy in dermatopathology has yet to be proven, aberrant mTOR activity has been implicated in psoriasis, eczema, and pemphigus^[194]. This suggests that rapamycin may have potential to modulate cutaneous immunity through its senomorphic activity in these conditions.

Multiple other agents have been shown to modulate senescent stromal cells in the skin, such as BCL-2 inhibitor ABT-737, which selectively removes senescent melanocytes in a 3D co-culture model, restoring epidermal thickness^[31,194]. Another BCL-2 inhibitor, navitoclax (ABT-263), eliminates senescent human fibroblasts grafted onto mice, improving collagen density of grafted skin and reducing SASP production^[195].

Numerous plant-derived extracts have exhibited senomorphic activity in human stromal cells *in vitro*. Acting on human dermal fibroblasts, flavonoids apigenin, quercetin, kaempferol and wogonin reduce SASP (Lim, Park, and Kim 2015). Ferulic acid reduces *p16*, *MMP1/3* mRNA and SA- β -Gal expression after UVA exposure^[196], while nectandin B attenuates SA- β -Gal, p21, p53 and p16 expression in aged fibroblasts^[196,197]. Reseveratrol, a SIRT1 activator, mitigates the effects of senescence in human epidermal keratinocytes *in vitro*^[198], and also modulates senescence in dermal papillae cells *in vitro*, reducing SA- β -Gal expression, SASP cytokine and cell cycle inhibitor mRNA levels, and p16/p21 protein levels^[199]. Emerging technologies such as extracellular vesicles have similarly demonstrated efficacy in mitigating human dermal fibroblast^[200-202] and epidermal keratinocyte^[200] senescence *in vitro*, and in reducing inflammatory cytokines in the skin to improve psoriasis and eczema in mouse models^[203]. Several other second-generation senotherapeutics, such as nanoparticles and drug antibody conjugates, have shown early *in vitro* potential in dermal fibroblasts^[204]. Although the impact of these interventions on cutaneous immune profile and function has not yet been evaluated, they hold potential as the basis for novel treatments of dermatoses with dysregulated cutaneous immunity.

2.7.2 Evidence for targeting T cells

Evidence supporting the targeting of senescent T cells to beneficially modulate the cutaneous environment remains limited; however, BCL-2 inhibitors have yielded encouraging results. Topical ABT-737 improves psoriasis in mice by reducing senescent dermal CD4⁺ T cells and cutaneous inflammatory cytokines^[86], and further improves histological and clinical features in a mouse model of cutaneous lupus erythematosus^[205]. Similarly, ABT-263 selectively eliminates senescent T cells *in vitro* from both healthy human and SLE patient PBMCs. These effects were replicated in a murine lupus model, with associated attenuation of lupus disease activity in multiple organs, including the skin^[205,206].

2.7.3 Dual action

Metformin directly regulates mTOR-STAT3 signaling in dermal fibroblasts *in vitro*^[206], and significantly reduces levels of inflammatory cytokines, including IL-6, IL-8, IFN- γ , TNF- α , in lesional skin explants from both hidradenitis suppurativa and psoriasis patients^[207]. Metformin improves skin fibrosis in a mouse model of scleroderma, reducing infiltration of lymphocytes and inflammatory cytokine burden in the skin^[207]. It also reduces the burden of inflammatory cytokines in patients with inflammatory skin disease^[207], directly impacting immunosenescence through the reduced numbers and IFN- γ secretion of senescent CD8⁺ T cells and increasing the frequency of naive T cells in aged humans^[208].

Metformin, a first-line diabetes medication, can increase lifespan^[209] and reduce all-cause mortality^[209,210] in diabetic patients compared with non-diabetic controls. Its dual action on senescent lymphoid and non-lymphoid compartments indicates that targeting multiple sources of senescence may not only benefit the cutaneous landscape but overall organism health.

Emerging data suggests that targeting senescence in the skin may restore immune homeostasis, particularly in diseases with combined stromal and immune dysfunction. However, interventions aimed at one cell type may exacerbate dysfunction in others. For instance, stromal senolysis could relieve immunosuppressive barriers but may also destabilize tissue structure; immune cell senolysis may reduce inflammation but impair host defense. Future therapies must carefully balance these opposing effects. This paradox underscores the necessity to better understand the immune-stromal crosstalk in health and disease.

3. Concluding Remarks

Skin acts as a window into systemic aging: as the body's largest immune-stromal organ, it is uniquely exposed to environmental and mechanical stress.

Natural human experiments provide the clearest route to causality. Cohorts carrying *CDKN2A* (familial melanoma) or TP53 (Li-Fraumeni) germline variants, alongside well-characterized progeroid paediatric syndromes, can reveal how defective senescence control shapes immunity and tissue architecture over time. In parallel, controlled human models, including standardised UV exposure, tape-stripping, suction blisters and recall-antigen challenge, can connect senescence programs to skin-organ function and immune responses *in situ*.

Successful translation depends on discrimination. We need robust biomarkers to separate physiological from pathological senescence across epidermis, dermis, and subcutis, and across ages, phototypes and anatomical sites. A composite Skin Senescence Index could integrate canonical markers (p16/p21, Lamin B1 loss), SASP/chemokine profiles, immune checkpoint ligands (HLA-E, PD-L1, sialoglycans), SCAP dependence and dermal-adipose immunometabolism, while anchoring these to patient-centered functional readouts such as barrier recovery, wound closure, infection-free days, vaccine responsiveness, thermoregulation, itch/pain and activity metrics.

Therapeutically, the goal remains to integrate senostatics/senomorphics to dampen harmful SASP (e.g., p38MAPK blockers), senolytics (e.g., BCL-2 inhibitors) to eliminate persistent senescent cells, and immune/metabolic modulators to restore surveillance and resilience (e.g., NKG2A/PD-1 or anti-sialoglycan strategies with SCAP sensitisation). Delivery should be local first (topical or intradermal) to maximise on-target effects while preserving beneficial, transient senescence elsewhere. Patient selection, dosing and

endpoints should be driven by the biomarker framework outlined above, with safety and function (not just histology) outcomes.

By treating skin as an accessible sentinel of systemic aging, we can preserve physiological senescence while selectively targeting its pathological counterpart, guided by discriminatory biomarkers. The ultimate goal is to convert descriptive maps into actionable, tissue-specific interventions that restore barrier, immunity and function. In short, this represents the beginning of precision senescence medicine for the skin.

Declarations

Authors contribution

Subramanian P: Conceptualization, investigation, data curation, writing-original draft, visualization.

Devine O: Conceptualization, writing-original draft, visualization.

Akbar AN: Conceptualization, writing-review & editing.

Conflicts of interest

Arne N. Akbar is an Editorial Board Member of *Geromedicine*. The other authors declare no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

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