NEWS, VIEWS, AND REVIEWS

The Senile Cell: Understanding Cellular Senescence in Dermatology

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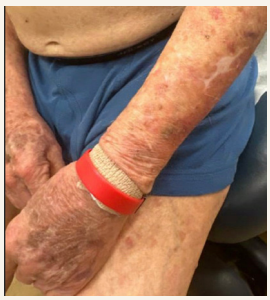
INTRODUCTION

Cellular senescence is a permanent and stable arrest of the cell cycle triggered by endogenous and exogenous stressors, such as DNA damage, oxidative stress, and telomere dysfunction.[1,2] In this state, cells are unable to proliferate despite favorable growth conditions and often exhibit increased resistance to apoptosis through upregulation of cell survival pathways.[1] Additionally, senescent cells may influence the surrounding environment through the senescence-associated secretory phenotype (SASP), which consists of inflammatory cytokines, chemokines, growth factors, and proteases.[3,4] Cellular senescence and SASP play key roles in skin aging and are thought to contribute to dermatoporosis, an age-related condition that primarily affects chronically sun-exposed areas, such as the forearms.[5] Dermatoporosis is characterized by skin atrophy and increased skin fragility, susceptibility to skin tears, secondary infection, and delayed wound healing[5-7] (Figure 1).

Figure 1. Clinical presentation of dermatoporosis of the left hand and forearm.



In response to the growing recognition of senescence-driven pathology, emerging research has focused on senotherapeutics, a field focused on targeting cellular senescence.[8] Here we review the role of cellular senescence and SASP in skin aging and examine potential senotherapeutic agents. We also discuss commonly used topical treatments, including hyaluronic acid (HA), retinoids, vitamin C, niacinamide, and alpha hydroxy acids (AHAs), to inform clinical strategies for addressing cellular senescence in skin aging.

Cellular Senescence and SASP

Cellular senescence plays a key role in both intrinsic and extrinsic skin aging. Intrinsic aging primarily occurs in sun-protected areas, resulting in epidermal thinning, loss of subcutaneous fat, and reduced dermal thickness.[2,9] Extrinsic aging is largely driven by chronic sun exposure, leading to a loss of collagen and dermal extracellular matrix.[9] Both intrinsic and extrinsic aging contribute to the accumulation of senescent cells, driving structural and functional changes in the skin.[10] Skin biopsies from older individuals reveal increased frequency of senescent cell markers, specifically $p16^{INK4A}$, a cell cycle checkpoint protein, and senescence-associated β-galactosidase (SA-βgal) expression, a lysosomal enzyme.[2,9,11]

Senescent cells also influence skin aging and tissue regeneration through paracrine signaling via SASP.[1,10] Similar to senescent cells, SASP increases with age and can alter the tissue microenvironment through collagen degradation and chronic inflammation, leading to visible features of aging such as sagging, wrinkles, and skin laxity.[8,9] Although senescent cells and SASP contribute to skin aging, they also play beneficial roles in certain physiological contexts, including embryonic development, suppressing cancer cell proliferation, and aiding in wound healing by limiting excessive cell growth, fibrosis, and granulation tissue formation.[8,9]

Senotherapeutics

Senotherapeutics, including senolytics and senomorphics, have emerged as a promising strategy for treating age-related disease and restoring skin tissue structure and function.[2,8] Senolytics are currently under investigation for their potential to induce cell death in senescent cells.[8] Several classes of senolytic compounds have been investigated, including tyrosine kinase inhibitors, B-cell lymphoma-2 (BCL-2) inhibitors, and FOXO4-DRI peptide.[8] However, many senolytic agents lack cell-type specificity, leading to off-target effects and toxicity in healthy tissues.[8] As a result, further research is needed to optimize dosing strategies and enhance tissue-specific targeting.[8]

Senomorphics modulate senescent cell behavior by suppressing or altering SASP rather than eliminating senescent cells. Examples include mammalian target of rapamycin (mTOR) inhibitors, Janus kinase (JAK) inhibitors, and nuclear factor kappa B (NF-κB) inhibitors.[8] Although senotherapeutics have promise, they are not yet approved for clinical use.[2] Potential side effects and safety profile of long-term treatment need to be evaluated prior to clinical application in dermatology.[2,8]

Over-the-Counter Topicals and Retinoids

While senotherapeutics remain experimental, several agents such as HA, retinoids, vitamin C, niacinamide, and AHAs have been studied for their effects on cellular senescence and the clinical manifestations of skin aging and dermatoporosis.

HA is the most abundant glycosaminoglycan in the skin and is a major component of the extracellular matrix.[5] However, HA and CD44 levels, a transmembrane receptor essential for HA synthesis, decline markedly in aging skin.[5] In a study of patients with dermatoporosis, reduced HA and CD44 expression were observed in both the epidermis and dermis and were accompanied by significantly increased epidermal expression of $p16^{INK4A}$.[5,6] Following one month of twice-daily topical treatment of the forearm with a combination cream containing 1% intermediate size hyaluronate fragments (HAFi) and 0.05% retinaldehyde (RAL), patients exhibited a significant reduction in $p16^{INK4A}$-positive cells in both the dermis and epidermis, along with measurable clinical improvement in skin thickness by ultrasonography.[6] Retinoids, including RAL, are vitamin A derivatives that promote epidermal barrier function, collagen synthesis, keratinocyte proliferation, and inhibit transepidermal water loss (TEWL) and matrix metalloproteinase (MMP) activity.[5] Prescription tretinoin was evaluated in a 16-week randomized, double-blind study comparing 0.1% topical tretinoin cream with a vehicle control.[12] Tretinoin significantly improved photoaging on the treated face and forearm, with histologic evidence of increased epidermal and granular layers.[12]

Vitamin C (ascorbic acid) is an antioxidant that is implicated in the treatment of aging skin by reducing reactive oxygen species, increasing dermal thickness, and downregulating MMPs responsible for collagen degradation.[5] In a double-blind, randomized study, twice daily application of 5% topical vitamin C for 12 weeks revealed clinical improvement in skin elasticity and thickness and a reduction of hemorrhagic lesions associated with dermatoporosis.[13] Ascorbic acid 2-glucoside, a vitamin C derivative, has even been shown to downregulate SA-β-gal activity.[5] Niacinamide, a vitamin B3 derivative, exhibits anti-inflammatory and antioxidant properties, reducing proinflammatory cytokines such as IL-1α, IL-6, and IL-8, which are implicated in SASP.[5] Niacinamide has also been shown to delay cellular senescence and stimulate the production of collagen, glycosaminoglycans, and other dermal matrix components.[5]

AHAs, specifically mandelic acid, have been investigated for the treatment of senescence-associated dermatoporosis.[7] In vitro studies demonstrated that concentrations of 0.05% mandelic acid and 0.005% *Centella asiatica*, a botanical extract, reduced SASP expression in keratinocytes.[7] In an ex vivo photodamaged skin model, immunofluorescence analysis demonstrated reduced $p16^{INK4A}$ expression in the papillary dermis following treatment, whereas untreated samples retained senescent cells.[7] A follow-up study evaluated twice-daily application of mandelic acid and *Centella asiatica* combination cream in 54 adults with self-reported sensitive skin and dermatoporosis.[14] At 12 weeks, treatment of both forearms and one leg, with the contralateral leg serving as an untreated control, demonstrated significantly improved hydration, increased skin thickness of the epidermal, dermal, and subdermal layers, and reduced TEWL.[14] No adverse reactions were reported, and both clinical assessment and participant reports noted improved skin texture and overall skin quality.[14]

CONCLUSION

Cellular senescence plays a key role in skin aging and age-related dermatologic conditions. Senotherapeutics represent a promising and rapidly evolving area of research, however, their clinical application in dermatology remains limited and requires further investigation to establish safety and efficacy. In contrast, several commonly used topical agents, particularly HA, retinoids, vitamin C, niacinamide, and AHAs have been studied in the context of cellular senescence and age-related cutaneous changes, specifically for preventing and managing dermatoporosis. Together, these findings highlight the role of established topical therapies as accessible, adjunctive strategies for addressing the clinical consequences of cutaneous cellular senescence while senotherapeutic approaches continue to evolve.

DISCLOSURES

NZ's work is funded through an independent research grant from Galderma. MF's work is funded through independent research grants from Incyte and Johnson & Johnson. NCA and AF have no conflicts to disclose.

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