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Opinion

Skin senescence: mechanisms and impact on whole-body aging

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The skin is the largest organ and has a key protective role. Similar to any other tissue, the skin is influenced not only by intrinsic/chronological aging, but also by extrinsic aging, triggered by environmental factors that contribute to accelerating the skin aging process. Aged skin shows structural, cellular, and molecular changes and accumulation of senescent cells. These senescent cells can induce or accelerate the age-related dysfunction of other nearby cells from the skin, or from different origins. However, the extent and underlying mechanisms remain unknown. In this opinion, we discuss the possible relevant role of skin senescence in the induction of aging phenotypes to other organs/tissues, contributing to whole-body aging. Moreover, we suggest that topical administration of senolytics/senotherapeutics could counteract the overall whole-body aging phenotype.

Highlights

With age, senescent cells accumulate in the skin and spread the aging phenotype to neighboring cells, resulting in decreased thickness, regenerative capacity, and a barrier effect in the skin.

Aging and cellular senescence phenotypes in the skin were found to correlate with immunosenescence, longevity, or cardiovascular disease risk.

Skin aging, induced by ultraviolet radiation, has an impact in the brain, by decreasing hippocampal neurogenesis and activating the central hypothalamic–pituitary–adrenal axis.

Senolytics, such as dasatinib and fisetin, are drugs that selectively eliminate senescent cells and are already topically administered to the skin, showing potential antiaging effects.

Skin senescence as a systemic aging trigger

Aging is defined as a progressive process of physiological decline, leading to frailty, age-related conditions, and ultimately to death. Cellular senescence, a defense mechanism in response to damaging stimuli, was highlighted as one of the hallmarks of aging, contributing to a decline in tissue functionality with old age [1].

Senescent cells cease to proliferate while remaining metabolically active, secreting factors known as the **senescence-associated secretory phenotype** (SASP; see Glossary). These factors contribute to inducing senescence in otherwise normal cells [2]. Skin senescent cells accumulate progressively with age and, as result of its different mechanisms of aging [3], impact directly on skin structure and function.

The skin incorporates cells from several different systems of the organism, namely nervous, immune, circulatory, and endocrine systems; a cutaneous neuroendocrine system sustains the communication between the skin and the brain [4]. Interestingly, some evidence associates skin senescence with organismal aging and age-related dysfunction [5–8].

Understanding the impact of skin senescence on promoting systemic aging could result in new approaches to delay whole-body aging and age-related disorders, which could delay organismal aging by targeting skin senescent cells, using, for example, topic senolytic drugs. In this opinion, we discuss whether skin senescence is a key mechanism to accelerate the aging phenotypes of other organs/tissues and contribute to whole-body aging.

Skin aging and senescence

The skin is the biggest organ of the human body and provides a physical barrier against the environment and, thus, is permanently exposed to environmental aggressors (Box 1). During the human lifetime, the skin shows relevant changes that enable differences to be recognized

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Box 1. Skin structure and function as an environmental sensor

The skin is organized into three structural layers: the epidermis, dermis, and subcutaneous fat layer [72]. The epidermis is a stratified epithelium with permanent proliferation and renewal, comprising morphological and functionally different layers. The bottom layer is generally one-cell thick composed of proliferative cells that terminally differentiate as they move toward the outermost layer of the epidermis, which comprises anuclear dead cells termed corneocytes [72]. The most prevalent cell type of this layer are keratinocytes, although other cell types are found in the epidermis, such as Langerhans cells (antigen-presenting cells), Merkel cells (mechanosensitive cells), and melanocytes [73]. Epidermal melanin is produced in the melanosomes of melanocytes and has key photoprotective roles. Briefly, melanin biosynthesis generally begins with hydroxylation of the amino acid L-tyrosine into L-dihydroxyphenylalanine (L-DOPA) by the key regulatory enzyme of this process, tyrosinase. L-DOPA is further oxidated into a precursor dopaquinone, which can be transformed into eumelanin (black/brown color) or pheomelanin (yellow-reddish color) [74]. Melanocytes transfer mature melanosomes to epidermal keratinocytes, which form a protective cap in the supranuclear location of the cell [75].

Melanogenesis is mainly regulated by MSH-α and ACTH, which originate from POMC cleavage, activate the melanocortin receptor MC1-R, and stimulate melanotropic activity. UVR is the most relevant regulator of melanogenesis, increasing epidermal melanin synthesis and, therefore, conferring photoprotection [75]. UVR promotes the increased proliferation and recruitment of melanocytes, an increased number of dendrites, and melanosome transfer to keratinocytes [75].

The dermis mainly comprises ECM, with two main types of protein fiber (collagen and elastin) and glycosaminoglycans, whereas the cellular components of the dermis include fibroblasts, dermal dendrocytes, and mast cells [73]. The subcutaneous adipose tissue is not considered to be part of the skin. However, it has important functions in thermoregulation and energy storage, and providing cushion and skin stability [72].

The skin is the interface between the internal and external environments [76]. Given its location, the skin recognizes and integrates environmental cues and orchestrates biological responses once a critical threshold of a certain stimulus exists [76,77]. Skin response to stress is mediated by its cutaneous neuroendocrine system. Specifically, the skin has all the molecular components of the systemic HPA [4] and skin-resident cells are able to synthesize and exhibit receptors of several neuroendocrine mediators/hormones, including POMC, ACTH, β-endorphins, CRH, urocortin, among others [78]. Moreover, the skin is involved in steroidogenesis and sexual hormone conversion [77]. Glucocorticoids, including cortisol or corticosterone, are synthesized in the skin, in a process regulated by environmental factors [4].

Depending on the type and intensity of the stimulus, skin can activate the central HPA system either by direct neural transmission or through humoral skin-derived factors (e.g., cytokines or hormones) to the central nervous system [77].

Although these systems are present in both human and rodent skin, differences can be identified, especially regarding CRH. In contrast to human skin, CRH mRNA is expressed at very low levels in the mouse, suggesting neural delivery of the protein CRH to the skin. Human and mouse skin also exhibit the opposite expression of CRH receptors (CRH-R1 and CRH-R2). While scarcely expressed in human skin, CRH-R2 is preferentially expressed in mouse skin; These differences could have an evolutionary explanation related to the presence of fur and nocturnal behavior of mice, which drastically decrease skin exposure to UVR and the consequent need for a stress system, such as the CRH system [79]. Thus, the skin is more than just a barrier, being a dynamic organ with a crucial role in maintaining organismal homeostasis. (see Outstanding questions).

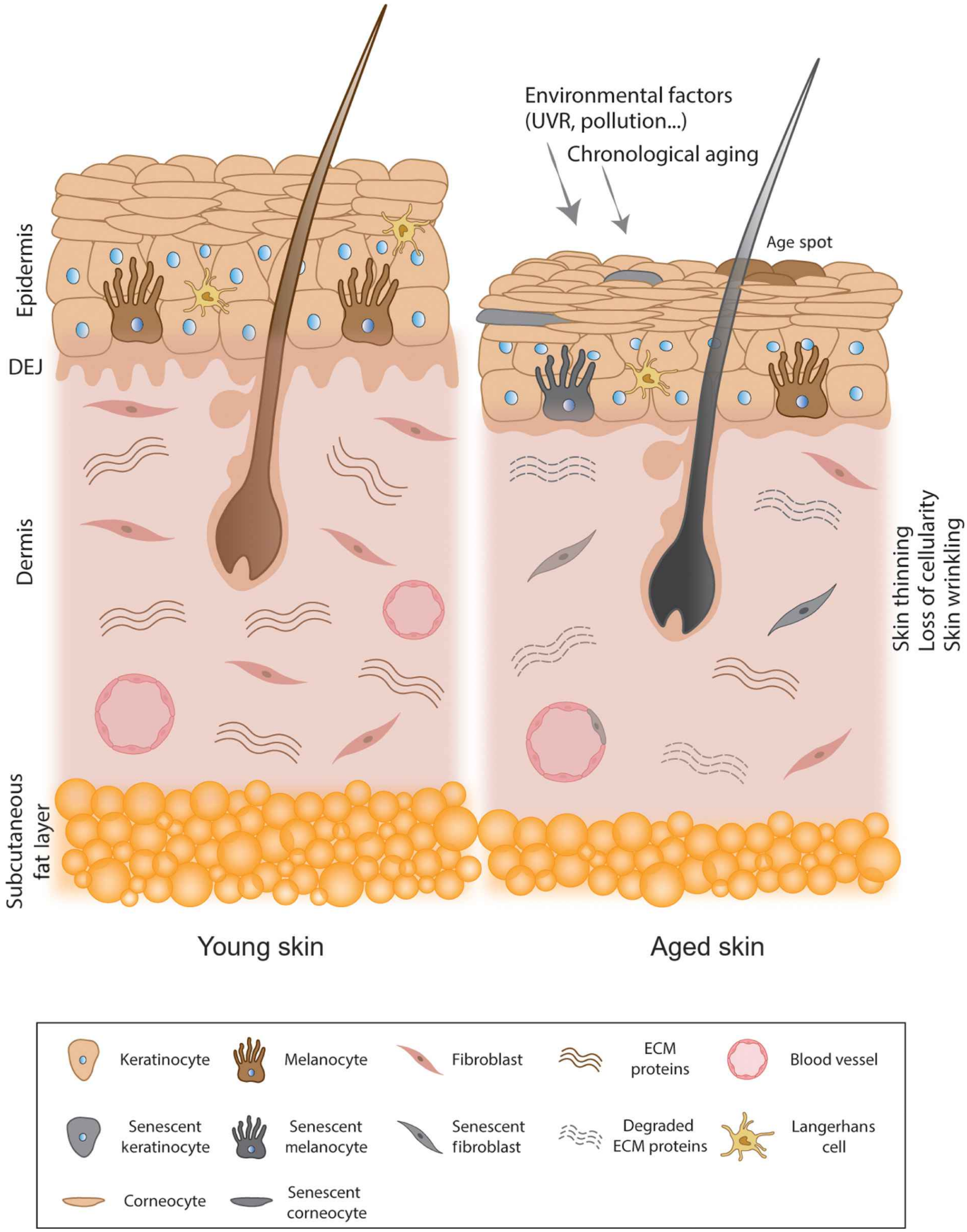
between the skin from a child or from an older person (Figure 1). Skin aging is induced by chronological aging, also known as **intrinsic aging**, or by environmental factors, such as air pollution, smoking, poor nutrition, and ultraviolet (UV) light, also known as **extrinsic aging.**

Intrinsic aging is chronologically determined, resulting in the accumulation of cellular damage [9], and is characterized by skin thinning and fine lines [9]. The loss of thickness can be caused by decreased cell proliferation and by significant changes that occur with age to dermal components [10]. The extracellular matrix (ECM) constituents (collagens, elastin, glycosaminoglycans, among others) are significantly reduced with intrinsic skin aging [11]. Moreover, oxidative stress contributes to intrinsic skin aging, not only by the increase in reactive oxygen species (ROS) generation (by mitochondrial leakage, inflammation, or others), but also by age-related decreases in cellular repair capacity [11].

With aging, senescent cells accumulate in the skin, due, in part, to the presence of several cell types with high mitotic capacity [3,12,13]. The role of cellular senescence in the skin is primarily beneficial since it promotes optimal wound healing and prevents the development of neoplasic lesions. In fact, activation of cell cycle arrest-related pathways (Box 2) is crucial to prevent skin

Glossary

Extracellular vesicles (EVs): small lipid bilayer structures, deliberately secreted by cells into the extracellular space, that can enclose nucleic acids, proteins, or lipids. EVs can be taken up by recipient cells, with various effects on that target cell.
Extrinsic aging: type of skin aging caused by exposure to hazardous environmental factors and lifestyle.
Hypothalamic–pituitary–adrenal (HPA) axis: a neuroendocrine unit comprising the hypothalamus, pituitary gland, and adrenal glands, which, by integrating physiological and endocrine signals, has a central role in body homeostasis and response to stress.
Immunosenescence: progressive dysfunction and decline in immune function, generally associated with aging or age-related diseases.
Inflammaging: state of chronic low-grade inflammation associated with progressive age.
Intrinsic aging: type of genetically programmed aging, caused by the natural passage of time; also known as chronological aging.
Neurogenesis: process of the generation of new neurons in the brain through differentiation from stem cells.
Paracrine senescence: cellular senescence caused by the secretome of primary senescent cells.
Photoaging: type of extrinsic skin aging caused by exposure to UVR from sunlight.
Secretome: entire set of proteins secreted by a given cell.
Senescence-associated secretory phenotype (SASP): set of proinflammatory, proangiogenic, and growth stimulatory molecular agents secreted by senescent cells, which influences the microenvironment and surrounding cells.
Senolytics: class of drugs that selectively eliminate senescent cells, therefore targeting the deleterious effects of senescent cells within tissues.



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Box 2. General characteristics of cellular senescence

Cellular senescence was first described by Hayflick and Moorhead during the 1960s following the observation that cells cultured *in vitro* ceased proliferation after a limited number of replication rounds [80]. The authors described a phenomenon now referred to replicative senescence, which is known to be associated with telomere attrition [81].

Cellular senescence is characterized by a stable form of cell cycle arrest. This is established by the activation of either one of two major tumor suppression pathways, p53/21 and p16/pRB. Mitogenic signals, and genomic or epigenomic stress can lead to activation of these pathways [82]. p16 is an inhibitor of the cyclin-dependent kinase inhibitors (CDKIs) CDK4 and CDK6 [83], while the tumour suppressor protein p53 mediates cell cycle arrest by directly inducing the transactivation of p21 [82]. The cell cycle inhibitor p21, in turn, represses CDK2. CDKIs are responsible for the phosphorylation of the retinoblastoma (RB) family, which represses E2F family transcription factor activity [84]. E2F, in return, is required for cell cycle progression, and its repression results in the permanent cell cycle arrest characteristic of senescent cells [84,85]. E2F inhibition is related to a reorganization of chromatin typical of senescent cells, termed 'senescence-associated heterochromatin foci' (SAHFs) [84–86].

Senescent cells exhibit several markers, namely: telomere [87–89] and mitochondrial [90,91] dysfunction; a permanent DNA damage response [92,93]; formation of SAHFs, which are responsible for the silencing of proliferation-promoting genes [94]; enlarged morphology [95]; apoptosis resistance (upregulation of BCL-2) [37,57]; altered metabolism, among others [2,86].

Senescent cells remain metabolically active and influence their environment by secreting SASPs [2], which comprise immune modulators (inflammatory cytokines and chemokines), EVs, enzymes that degrade extracellular matrix (matrix metalloproteinases; MMPs), and growth factors [20,96]. SASP genes are upregulated during senescence, with their master regulators being the transcription factors NF-κB and C/EBP β [97]. However, others, such as **miRNAs** or the mechanistic target of rapamycin (mTOR) pathway, also have a role in the regulation of SASP [3].

SASP has relevant functions, such as activating immune responses or wound healing [98]. By contrast, it is mainly known to induce senescence of surrounding cells in a paracrine manner and to contribute to persistent chronic inflammation (known as **inflammaging**), leading to tissue dysfunction and development of an aging phenotype [99].

In addition, several other agents can promote cellular senescence, as detailed in Table I.

Table I. Examples of Different Types of Cellular Senescence and Inducers

Designation/origin	Inducer	Refs
Replicative senescence	Telomere attrition	[80,87]
Stress-induced premature senescence	DNA damage, ROS[a], proteotoxic stress, irradiation	[17,32,100,101]
Oncogene induced senescence	Oncogene activation	[102,103]
Mitochondrial dysfunction-associated senescence	Mitochondrial damage	[90,91]
Paracrine senescence	Secretome of a primary senescent cell	[15,104]

[a]ROS, reactive oxygen species.

cancer progression [13]. Stimuli that induce neoplasic events are common to those that induce cellular senescent in the skin, such as UV light.

Although senescence is primarily activated to protect the skin from insults, skin senescent cells accumulate with aging, promoting tissue dysfunction through SASP, which induces senescence in neighboring cells by a process termed **paracrine senescence** [1,13–17]. Interestingly, evidence shows that skin aging mirrors and predicts the age-related dysfunction of other organs

Figure 1. Illustration of young and aged skin. Schematic representation of young (left) and aged skin (right). Skin ages with the passage of time (chronological aging) and by exposure to environmental factors (extrinsic aging). Aged skin is generally characterized by skin atrophy resulting from the reduced proliferative capacity of skin cells and a decrease/degradation of extracellular matrix proteins, such as collagen or elastin. Simultaneously, a flattening of the dermal–epidermal junction (DEJ) occurs, which is responsible for loss of skin integrity and development of skin wrinkles, a major hallmark of skin aging. Alterations in pigmentation, not only in the skin but also in hair, are common during aging due to dysfunctional activity of melanocytes. Exposure to internal and environmental insults contributes to the accumulation of senescent cells in the skin, which adds to a decline in skin function with age. Abbreviations: ECM, extracellular matrix; UVR, ultraviolet radiation.

[5–7] (discussed in the following text), suggesting that senescent skin contributes to accelerating aging of other tissues. The **secretome** of intrinsically aged dermal fibroblasts was found to display a unique protein pattern referred to as 'skin aging-associated secreted proteins', or SAASP, which differ from the classical SASP [18]. SAASP were associated with the presence of DNA-segments with chromatin alterations reinforcing senescence (DNA-SCARS), which correspond to nuclear foci positive for p53 binding protein 1 and promyelocytic leukaemia protein 1. Similar to traditional SASP, SAASP were enriched in matrix metalloproteinases (MMPs) and proinflammatory mediators. However, other distinct proteins conferred a unique pattern of secreted proteins that differ from SASP and highlight the distinctiveness of the skin aging process [18].

Extrinsic skin aging is associated with lifestyle and results from exposure to aging-promoting environmental factors, such as UV radiation (UVR), pollution, stress, tobacco smoke, among others [19].

Photoaging refers to UVR-induced skin aging, the most studied form of extrinsic skin aging [20,21]. Besides being mostly known for inducing skin dysfunction (e.g., sunburn or its carcinogenic properties), UV-provided energy has been fundamental to life on earth and evolution [22]. One of the beneficial roles of UVR is the production of vitamin D3 in the skin (Box 3).

UVR spectra, comprising UVA (320–400 nm), UVB (280–320 nm), and UVC (100–280 nm), is a strong environmental oxidizing agent and a mutagen responsible for most skin damage and aging. In fact, 80% of visible signs of skin aging are considered a result of UVR exposure [23]. Most UVC is absorbed by the ozone layer, whereas UVB and UVA rays penetrate the epidermal layer or the epidermal and dermal layers, respectively of the skin [21].

Box 3. Melatonin and vitamin D as skin photoprotectors and antiaging molecules

Melatonin, also known as the 'hormone of darkness', is the only known hormonal product of the pineal gland. This hormone is released by nightfall and, by interacting with the suprachiasmatic nuclei of the hypothalamus, exerts its well-described sleep-promotion functions and synchronizes circadian rhythm [105]. Nonetheless, melatonin has systemic pleiotropic functions, including in the skin. The skin contains elements from the enzymatic machinery of this pathway and can synthesize melatonin on site [106]. Melatonin also confers skin photoprotection. Incubation of HaCaT cells with melatonin before UV irradiation promoted cell viability by attenuating apoptosis [107], particularly by maintaining mitochondrial membrane potential and inhibiting the activation of caspases 9, 3, and 7 [108]. This protective role is supported by the antioxidant- and radical-scavenging properties of melatonin [106]. In particular, melatonin was reported to confer protection against DNA damage and to prevent UV-mediated reduction of antioxidant enzymatic defenses (catalase, superoxide dismutase, and glutathione peroxidase) [109]. Moreover, some studies suggest that melatonin has other important roles in skin processes, including the regulation of barrier function by increasing keratinocyte proliferation and the expression of epidermal macromolecules, such as involucrin, keratin-10 and 14 [110], attenuation of skin melanogenesis, thermoregulation, among others [106].

Vitamin D is produced in the skin during UVB exposure. Direct photolysis of 7-dehydrocholesterol by UVB results in the production of pre-vitamin D3. This is further transformed into three photoisomers: vitamin D3, tachysterol, and lumisterol (L3).

Vitamin D3 is converted into its active forms 25-hydroxyvitamin D3 [25(OH)D3] and then to 1,25(OH)2D3/ calcitriol. The vitamin D active metabolite 1,25(OH)2D3 and vitamin D receptor (VDR) activation in the skin improves terminal differentiation and epidermal barrier effects (increasing the expression of molecules such as involucrin, loricrin, and filaggrin), and decreases keratinocyte proliferation, with tumor suppression activity [111,112]. Moreover, L3-hydroxiderivates, the products of L3 catalysis by CYP11A1, can also interact with VDRs [113] and liver X receptors (LXRs) [114]. LXRs have important functions, such as the regulation of lipid/sterol homeostasis, suggesting that L3 compounds have broader mechanisms of action and biological functions [114]. Hydroxylumisterols were also reported to mediate photoprotection by inducing free radical scavenging, preventing DNA damage [115], exerting anti-inflammatory activity (suppressing NF-κB and, consequently, the expression of inflammatory cytokines) and promoting epidermal differentiation of keratinocytes irradiated with UVB [116].

These data suggest that both melatonin and vitamin D derivates are strong photoprotective agents and could be promising strategies to promote skin homeostasis and prevent damage from environmental stressors, such as UVR, delaying skin aging.

UVB, a small fraction of solar energy, has lower penetration and induces more biological effects compared with UVA [22]. In fact, compared with UVA, UVB is preferentially absorbed by chromophores, structurally transforming them to initiate chemical interactions between UVA or with other molecules, exerting biological functions [22,24]. Chromophores include UVR-absorbing molecules, such as aromatic amino acids, DNA, unsaturated lipids, among others [24]. For example, absorption of UVB by DNA forms pyrimidine dimers. These UVR-induced photoproducts can give rise to mutations and initiate skin carcinogenesis [24].

By contrast, by promoting oxidative damage, UVA radiation is indirectly responsible for DNA damage by increasing ROS levels [23,25]. Structurally, photoaged skin appears thicker, with deep wrinkles and aberrant pigmentation spots [3]. UVR increases the expression of MMPs and, thus, photodamaged skin is often associated with dermal connective tissue alterations, including accumulation of abnormal elastic fibers (termed 'solar elastosis') along with disorganization and fragmentation of collagen fibers [26]. ECM degradation by MMPs contributes to skin wrinkling, a major hallmark of skin aging [27]. Moreover, chronic UVR exposure is known to trigger cellular senescence in skin cells [28,29].

Markers of skin senescence

Skin senescent cells exhibit the classic markers of cellular senescence (Box 2). The expression of SA-β-galactosidase in skin cells has long been identified both *in vitro* and *in vivo* [30]. This marker is one of the most widely used markers of senescent cells. However, not only is its activity lost in fixed tissue samples, but the technique also lacks specificity, since its activity has been reported in non-senescent cells [31]. In addition, cell cycle inhibitor upregulation, chromatin reorganization, DNA damage, and telomere damage foci are also biomarkers present in senescent skin cells [7,16,32–34].

Another marker of aged skin is the deletion of 4977 base pairs in mitochondrial DNA (mtDNA), known as the 'common deletion'. This mutation is considered to be caused by UVA-induced oxidative stress damage; thus, although it has been found in sun-protected tissues, its presence in skin is associated with UVR exposure [35,36]. In addition, the number of mtDNA deletions correlates with individual age [35].

Skin senescence can also be detected by the loss of Lamin B1 expression, a protein that belongs to the family of nuclear laminas and, together with the Lamin A and C, comprises the nuclear lamina. Such loss occurs both *in vitro* and *in vivo* and in both types of aging.

Impact of cellular senescence on skin aging

Growing evidence shows that senescent cells accumulate and contribute to skin aging [30]. Skin from older donors had increased melanocyte p16 expression, and the senescent phenotype of these cells is mainly acquired by length-independent telomere damage [16]. Moreover, melanocyte telomere damage foci were positively correlated with age-related skin features, such as flattening of the epidermal–dermal junction (EDJ). Additionally, the authors showed that SASP from senescent melanocytes induced telomere dysfunction in a paracrine manner and impaired keratinocyte proliferative capacity via mitochondrial ROS [16]; the clearance of these senescent melanocytes using a senolytic drug (ABT737) suppressed this effect. Interestingly, a previous study highlighted that clearance of senescent cells from the epidermis using the same senolytic drug increased hair-follicle stem cell proliferation [37]. The senescence biomarker p16 was shown not only to increase in skin with age in the epidermal and dermal compartments *in vivo* [38], but also to correlate with defects in elastic fiber morphology, increased skin wrinkling, and perceived age [39]. Together, these data suggest that senescent cells in the skin negatively influence epidermal cell proliferative capacity, hair growth, and other skin aging features.

Excessive accumulation of senescent cells in the skin leads to suppression of macrophage-dependent clearance functions via SASP, thus causing the increased accumulation of senescent cells in the skin, contributing to skin aging [40].

SASP comprises not only soluble factors, but also **extracellular vesicles (**EVs). It was shown that senescent dermal fibroblasts secrete more EVs compared with non-senescent fibroblasts, which in return attenuate the dermal effect on keratinocyte differentiation and barrier function and increase proinflammatory cytokine IL-6 secretion [33]. This supports the intercellular communication role of the SASP, via not only soluble factors, but also EVs, in aging and related pathology [41].

Another study demonstrated that a human organotypic skin culture model constructed with increasing amounts of stress-induced premature senescent fibroblasts within a collagen matrix presented hallmarks of skin aging, including decreased epidermal thickness, impaired proliferation, defects in barrier effect, and changed surface properties [17]. All these data show that senescent skin cells promote skin aging.

Impact of skin senescence on whole-body aging

Evidence suggests that skin senescence propagates the aging phenotype to other tissues or organs (Figure 2). Interestingly, different studies suggest that the skin mirrors health status, mortality risk, and longevity [4–8,42–44]. In fact, studies that examined whether skin wrinkling in sun-protected areas and/or facial appearance correlated with familial longevity, disease risk, and mortality showed that reduced skin wrinkling in sun-protected areas was significantly correlated with longevity [5] and a significant link was identified between perceived age, survival [6], and cardiovascular disease risk in women [5]. Moreover, skin senescence is also correlated with organismal aging. The frequency of p16-positive cells in the skin positively correlated with CD4+ T- cell **immunosenescence** markers and biological age [7,8]. In return, the skin microbiome was found to accurately predict chronological age [44]. However, although interesting, these studies are based on correlations and the mechanisms underlying these correlations have not yet been investigated (see Outstanding questions).

The skin is sensitive to environmental stimuli, raising appropriate local responses and secreting hormones, neuropeptides, neurotransmitters, and their corresponding receptors [45,46]. This is mediated by the cutaneous neuroendocrine system: skin locally expresses elements of the **hypothalamic–pituitary–adrenal (HPA) axis**, particularly the corticotropin-releasing hormone (CRH) system, proopiomelanocortin (POMC), and the enzymatic machinery involved in steroidogenesis [45] (Box 1). The activation of the central HPA axis increases the production and release of CRH in the hypothalamus, a brain region with a crucial role in systemic aging (Box 4) [22,42]. Interestingly, UVR activates the HPA system according to wavelengths/doses, with these effects being more pronounced in response to UVC and UVB rather than to UVA [47]. Accordingly, UVB irradiation in mouse skin not only increased the brain/plasma levels of several neuropeptides (CRH, urocortin, ACTH, and β-endorphin) and corticosterone (CORT), but also promoted immunosuppression [48]. UVR also stimulates skin steroid production [49]. Moreover, UVB and UVC, more than UVA, increased 11β-hydroxysteroid dehydrogenase (an enzyme that regulates cortisol availability) and cortisol production, while reducing epidermal glucocorticoid receptor expression in human skin *ex vivo* [49].

Another study showed that UVR in mouse skin leads to a stress response affecting the hippocampus, impairing **neurogenesis** and decreasing synaptic protein expression, suggesting that

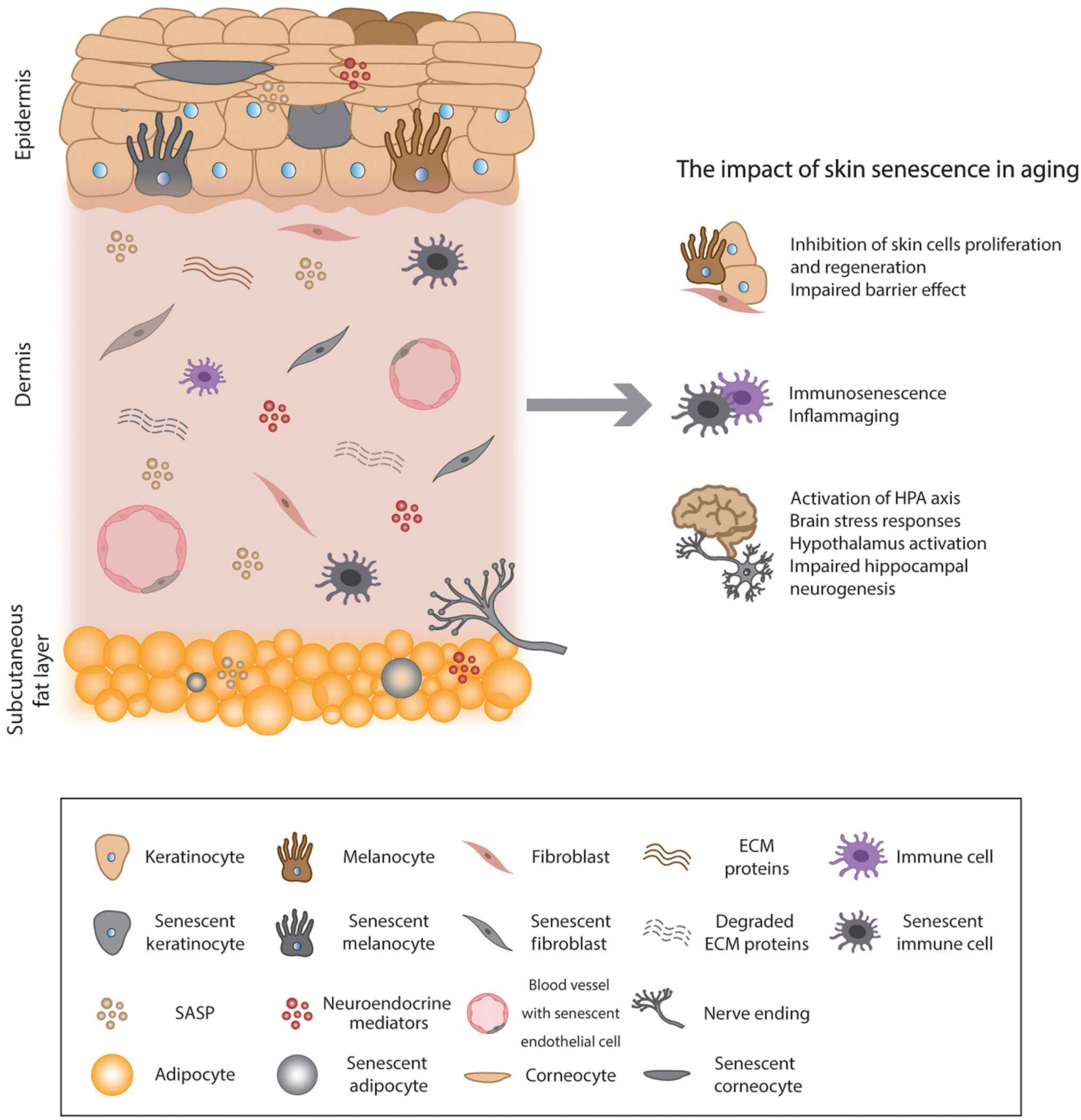

Figure 2. The role of skin senescence in whole-body aging. Senescent cells occur in the skin with aging or from exposure to environmental factors. These cells (in gray) exhibit stable cell cycle arrest and secretion of the senescence-associated secretory phenotype (SASP), which includes cytokines and matrix metalloproteinases. SASP induces dysfunction and propagates senescence to nearby cells, which can be skin cells, or other cell types, such as immune, endothelial, or nervous cells. Moreover, the skin has a cutaneous neuroendocrine system, which can be activated by environmental or endogenous stressors, and produce on-site neuroendocrine mediators. This crosstalk between different cells and molecules within the skin can contribute to aging: skin senescent cells contribute to a decline in skin function, including regeneration and proliferative capacity; the senescent phenotype might contribute to immunosenescence and to a chronic low-grade inflammatory state; furthermore, skin stress can promote brain stress responses and dysfunction due to communication maintained via the hypothalamic–pituitary–adrenal axis. Abbreviations: DEJ, dermal–epidermal junction; ECM, extracellular matrix.

Box 4. The hypothalamus as a regulator of organismal aging

The hypothalamus is a brain region that regulates the most basic life-supporting functions, such as metabolism, development, sleep, food intake, growth, and reproduction. Moreover, it maintains body homeostasis by integrating environmental, hormonal, metabolic, and neuronal signals from the periphery.

The hypothalamus is also involved in longevity/lifespan regulation through the somatotropic axis [GHRH, growth hormone (GH), and insulin-like growth factor-1 (IGF-1)], which declines with age by a process known as 'somatopause' [117]. The age-related decline in GH levels is well documented among several mammal species, primarily due to a decrease in hypothalamic GHRH levels [117].

In fact, in recent years, the hypothalamus has emerged as a critical regulator of systemic aging, although the mechanisms are still not fully elucidated [118–120]. One of the key studies that suggested a role of the hypothalamus in mice systemic aging showed that hypothalamic immunity mediated by IκB kinase-β (IKK-β), NF-κB and related microglia–neuron immune crosstalk inhibits gonadotropin-releasing hormone (GnRH), which triggers aging-related hypothalamic GnRH decline. Interestingly, using a brain-specific IKK-β-knockout model, the authors observed amelioration on skin atrophy of aged mice, supporting the crosstalk between the skin and the hypothalamus. The authors proposed immune inhibition or GnRH treatment as potential strategies to deaccelerate aging [119].

Recently, it was also shown that hypothalamic stem cell loss is a cause of aging in mouse models [121]. In a mouse model that expresses senescent-like hypothalamic stem cells (by SOX2 and BMI1 silencing), age-related alterations were accelerated and lifespan was reduced. These hypothalamic stem cells release exosomal miRNAs to the cerebrospinal fluid and their levels decline with age. These data suggest that a senescent-like phenotype in hypothalamic stem cells contributes to aging, partially through the release of exosomal miRNAs [121].

Emerging evidence supports the existence of communication axes between distant organs, such as the gut–brain axis, or skin–brain axis [122,123]. The brain–skin circuit, mediated by neuroimmune endocrine factors, underlies many allergies and inflammatory skin pathologies [123]. For instance, psychological stress was reported to promote skin dysfunction by inhibiting cutaneous barrier function, hair growth, and epidermal Langerhans cell frequency [124–127]. Hence, this brain–skin crosstalk could support the hypothesis that skin damage contributes to hypothalamic dysfunction during aging [128].

Clinician's corner

Skin aging is a health challenge, not only for its aesthetics implications, such as the appearance of wrinkles, age spots, loss of elasticity, among others, but also for the loss of function and increased risk of skin cancer.

Current approaches to counteract skin aging are based on the use of topical cosmetics, including sunscreen and ingredients, such as retinoids or resveratrol. However, the relationship between these products and their efficacy toward skin senescence is not yet fully understood.

The topical application of senolytics could be a potential antiaging approach since these compounds showed anti-inflammatory and promelanogenic features, useful for increasing skin protection against carcinogenesis and to prevent aging and age-related disorders.

The safety and effectiveness of senolytics for topical use require clinical trials before taking these agents into dermatological practice in the clinic.

skin communicates with the hippocampus via CORT [43]. The cutaneous HPA increases the levels of CORT after UVR exposure, triggering stress alterations in the hippocampus. Additionally, chronic UVR in the skin promoted a depression-like behavior in mice, suggesting that skin impacts brain function [43]. In line with these data, we hypothesize that, given the intimate communication between the skin and the brain, skin senescence (mainly via its associated secretome) contributes to hippocampal and hypothalamic dysfunction and the consequent decline in organismal function, leading to aging. However, the impact of skin senescence on hypothalamic function has not yet been fully addressed.

Does eliminating skin senescent cells by using topical senolytic drugs delay whole-body aging?

Emergent strategies to counteract aging include senescent cell elimination by using senolytic drugs [50,51]. The senolytic drugs dasatinib (D) and quercetin (Q) were shown to effectively induce apoptosis in senescent cells [52,53]. D is an inhibitor of multiple tyrosine kinases and is used for treating cancers [53], whereas Q is a flavonoid that targets BCL-2/BCL-XL, PI3K/AKT, and p53/ p21/serpine SCAPs [54]. A recent study showed that transplantation of a small number of senescent cells was sufficient to induce senescent markers in normal host cells and cause persistent physical dysfunction in young mice. In addition, the administration of D+Q alleviated physical dysfunction and increased survival in mice [55].

The drug combination D+Q is in a Phase II clinical randomized clinical trial (NCT02848131) in individuals with diabetic kidney disease, recruited by invitation. The primary outcome of this study was the alteration of the senescent cell burden. By the end of Phase I, a significant decrease was observed in senescent markers in adipose tissue and skin biopsies and SASP plasma levels. Statistical analysis involved data counts, percentages, means, and standard deviations of quantitative data. No serious adverse events were reported [52]. Moreover, the authors claimed that this combination of drugs was the most beneficial in terms of targeting cellular senescence in chronic diseases due to its highest specificity [52]. In fact, other senolytics, such as navitoclax (ABT-263) or fisetin (a low-toxicity natural flavonoid [56]), which target the BCL-2 pathway, were found to be senolytic in some but not all senescent cells [57]. Fisetin and D have been topically administered to murine skin [58,59], and showed a benefit by reducing UV-induced inflammation and increasing melanogenesis in the skin [60].

Senomorphic drugs, such as metformin and rapamycin, target senescent cells by inhibiting SASP [61,62]. Metformin, an antidiabetic drug, was shown to alleviate several age-related disorders and to increase survival in humans [63–65]. Rapamycin and analogs, which inhibit mechanistic target of rapamycin (mTOR), are US Food and Drug Administration (FDA)-approved therapeutic strategies for several conditions and were found to also ameliorate immunosenescence in humans [66,67]. In addition, they were reported to delay aging and extend lifespan in mice [68,69]. Both metformin and rapamycin have already been administered topically to human skin [70,71]. Rapamycin significantly decreased the levels of p16 and increased collagen VII and showed an overall improvement in the visible skin structure [70]. Most of these studies were performed using cellular or rodent animal models exposed to artificial light sources; thus, more human studies are required to better elucidate the efficacy of these compounds on skin aging. However, the translation of these therapies to target skin senescence and its potential impact on organismal aging could contribute to novel efficient antiaging therapies (see Clinician's corner and Outstanding questions).

Outstanding questions

Do senescent skin cells trigger accelerated age-related dysfunction in other tissues/organs?

Does skin senescence contribute to systemic aging through the hypothalamus?

Does skin senescence impair the HPA axis?

Could topical application of senolytics be effective antiaging strategies to prevent or delay aging?

Concluding remarks

Given its location, the skin is permanently exposed to environmental aggressors. Via its neuroendocrine system, the skin has a key role in sensing signals from the environment and orchestrating the appropriate responses to maintain organismal homeostasis.

Skin senescence occurs with age or in response to exposure to environmental aggressors, such as UVR, and can impact systemic aging by spreading the aging phenotype via SAPS from skin to other tissues and organs. Thus, we hypothesize that, because the skin is permanently subjected to senescence-promoting factors and given its communication with several other organs, including the brain, skin senescence might promote age-related dysfunction in other tissues/organs. We suggest that targeting skin senescence by topical administration of senolytics/senotherapeutics might contribute to the development of novel antiaging strategies and to delaying whole-body aging and the onset of age-related diseases. Nevertheless, more extensive research is required to better elucidate the role of skin senescence in whole-body aging.

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Declaration of interests

None declared by authors.

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