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Skin health and biological aging

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Accumulating evidence indicates that biological aging can be accelerated by environmental exposures, collectively called the 'exposome'. The skin, as the largest and most exposed organ, can be viewed as a 'window' for the deep exploration of the exposome and its effects on systemic aging. The complex interplay across hallmarks of aging in the skin and systemic biological aging suggests that physiological processes associated with skin aging influence, and are influenced by, systemic hallmarks of aging. This bidirectional relationship provides potential avenues for the prevention of accelerated biological aging and the identification of therapeutic targets. We provide a review of the interactions between skin exposure, aging hallmarks in the skin and associated systemic changes, and their implications in treatment and disease. We also discuss key questions that need to be addressed to maintain skin and overall health, highlighting the need for the development of precise biomarkers and advanced skin models.

Aging and disease are the result of a gradual functional decline of an organism's physiology. The common denominators of aging in different organisms were defined in 2013 as the 'hallmarks of biological aging'[1]. An updated and expanded version of these 'hallmarks of aging' incorporated the knowledge gained in the field over the past decade[2], resulting in 12 tightly interconnected hallmarks of aging, emphasizing the holistic nature of the aging process and the imperative to study these as a whole (the 'geroscience' theory). Human skin, being the largest organ of the body and the most exposed to the environment, suffers from both intrinsic and extrinsic pro-aging factors (such as pollution[3] and ultraviolet radiation (UVR)[4]), that regulate the expression of a wide variety of genes governing cell function. The skin consists of three layers: the outer epidermis, the underlying dermis and the deeper hypodermis. The epidermis, composed primarily of keratinocytes, forms a self-renewing, waterproof barrier. The dermis contains fibroblasts, extracellular matrix (ECM) components such as collagen and elastin, vasculature, nerves and skin appendages. The hypodermis is rich in connective and adipose tissue, providing mechanical cushioning and insulation. Skin aging leads to multiple structural and functional alterations, including epidermal thinning, degradation of the dermal ECM, loss of pigment regularity, impaired barrier recovery and reduced immune surveillance. These changes contribute to wrinkles, laxity and overall loss of skin integrity[5]. Figure 1 illustrates the age-related changes in skin through the lens of 12 hallmarks of aging. Understanding these changes at the molecular, cellular and tissue levels provides clues on how to maintain skin quality and health. It is likely that histogenetically distinct skin cell types share core hallmarks of aging but also exhibit important differences in how these hallmarks manifest. In this Review, we place particular emphasis on keratinocytes and hair follicle stem cells, given their critical roles in barrier function and tissue renewal, and the centrality of stem cell exhaustion as a hallmark of aging. For in-depth analyses of aging in other key skin cell types, including melanocytes, fibroblasts and immune cells, we refer the reader to specialized reviews[6–8].

Given accumulating evidence that the aging skin can have a direct impact on systemic biological aging, the maintenance of skin health is proposed to have a positive effect on systemic aging and in the prevention of age-associated diseases[9]. We provide an overview of the relationship between human skin health and function in the context of the 12 hallmarks of aging: genomic instability, telomere attrition, epigenetic

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alterations, loss of proteostasis, disabled autophagy, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation and dysbiosis (Fig. 1). We review their interconnections and explore how systemic aging can affect the skin and to what extent skin can affect systemic biological aging. We discuss the need to integrate the concepts of skin aging and overall health to push the limits of therapeutic interventions. Lastly, we identify gaps in the field, particularly the need for development of biomarkers and human aging skin models.

Interplay of hallmarks of aging

Physiological decline associated with aging is driven by processes within cells, as well as intercellular communication, and is influenced by both intrinsic and extrinsic factors. Skin aging reflects a dynamic interplay of interconnected aging hallmarks, within skin itself, but also in the body as a whole. We provide descriptions and additional details on each separate hallmark in the Supplementary Information and focus here on their joint effects (Fig. 1).

The skin, a vital barrier that prevents water loss and acts as a key component of immune defense, is constantly exposed to environmental stressors such as pollution[3] and UVR, making it vulnerable to damage. UVR, for instance, creates harmful photoproducts within DNA, which, alongside endogenous DNA damage, accumulate with age[10] and contribute to genomic instability. Factors such as reactive oxygen species (ROS), telomere attrition and metabolic dysfunction can further promote DNA mutations in skin cells[11,12]. Damaged DNA affects gene expression, perturbs the fidelity of DNA replication and generates more mutations and chromosomal aberrations[13]. Persistent genomic instability compromises key cellular functions by activating cellular senescence pathways and apoptosis[10,14,15]. This triggers inflammation and increases the generation of ROS, partly through nuclear factor-κB-mediated cytokine signaling and immune cell recruitment[12], which ultimately promotes a variety of aging features[16]. The aging skin environment, characterized by increased cellular senescence and altered intercellular communication, may in turn perpetuate genomic instability[14,17].

The effects of DNA damage in skin vary across cell types. Upon UVA irradiation, melanocytes have been found to be more susceptible to oxidative lesions than keratinocytes[18]. Accumulation of DNA damage in melanocyte stem cells can trigger their premature differentiation, leading to the stem cell depletion and contributing to aging phenotypes such as hair graying[19]. On the other hand, bulge stem cells of the hair follicle, which are crucial for hair cycling, do not exhibit such rapid differentiation, suggesting that sensitivity of stem cells to DNA damage is tissue specific and that the inherent stem cell properties play a major role[20]. Furthermore, it has been shown that hair follicle stem cell activity carries mitotic rhythmicity, where hair growth is slower in the evening than in the morning, in turn making these stem cells sensitive to genotoxic stress and DNA damage in a time-of-day-dependent manner[21]. Additional studies revealed that human epidermal stem cells possess genes whose expression peaks at distinct temporal phases in a 24-h period, affording greater sensitivity to particular signals that modulate their proliferation and differentiation[22]. These cells undergo rhythmic transcriptome reprogramming based on metabolic cues and age-related traits, to cope with tissue-specific stress[23]. Tissue-specific reconstitution of the clock activity gene *Bmal1* elucidated communication between the central brain clock and a peripheral epidermal clock[24], demonstrating how the epidermal clock selectively integrates systemic signals to maintain skin homeostasis and align with daily physiological rhythms.

Hair follicle stem cells exhibit a marked reduction in activity during aging, and the aged skin microenvironment plays a dominant role in dictating the properties of these stem cells, further impairing their function[25,26]. The maintenance of hair follicle stem cells is also affected by the proteolysis of type XVII collagen (*COL17A1*) associated with hair follicle miniaturization and hair loss in aging[27], which was also shown to be reduced in the basement membrane of the dermal–epidermal junction, alongside collagen IV, laminin-332 and integrin β4 (ref. 28).

Adult stem cell exhaustion, as seen with $SOX2^+$ stem cells, can lead to cellular senescence and premature aging, as evidenced by increased kyphosis, hair graying and reduced fat mass in mouse models[29]. The reduction in stem cell activity or number is also a key feature of cellular senescence, which further has a profound effect on organismal aging, as evidenced in studies on hematopoietic stem cells, mesenchymal stromal stem cells, intestinal stem cells and muscle stem cells[30].

Work by Flores et al.[31] revealed that stem cell function is affected by telomere length. Mouse models with shortened telomeres exhibited decreased stem cell mobilization, proliferative capacity and hair growth, whereas mice with overexpression of the catalytic component telomerase reverse transcriptase (*Tert*) demonstrated an increase in these features. Reintroduction of the telomerase gene *Terc* in mice possessing shortened telomeres was sufficient to correct dysfunctional epidermal hair follicle stem cells, as well as to attenuate chromosomal instability in skin keratinocytes[32]. Telomere attrition in skin stem cells has been shown to correlate with the visible signs of aging, including changes in skin elasticity, thickness and overall architecture[33].

One of the mechanisms of interest for modeling stem cell-associated skin aging is epigenetic alterations, specifically DNA methylation in the hair follicle. Mice with epidermal deletion of DNA methyltransferase I exhibited decreased hair follicle stem cell activation and progressive alopecia[34].

Altered intercellular communication in signaling pathways that regulate skin stem cell activity is also observed during the aging process. For instance, the Wnt signaling pathway, which is crucial for maintaining stem cell self-renewal capacity, undergoes dysregulation with age. This dysregulation affects skin homeostasis and regeneration, leading to a decline in the regenerative potential of stem cells, in particular, hair follicle bulge stem cells and interfollicular epidermal stem cells. Similarly, the Notch signaling pathway, another key regulator of stem cell function, experiences changes that affect the balance between hair follicle stem cell self-renewal and differentiation[35].

Chronic inflammation that ensues with age, often referred to as 'inflammaging', leads to functional decline of the skin and other organs, promoting age-related diseases[36,37] and accelerating nearly every hallmark of aging[38]. Inflammatory mediators, such as cytokines and chemokines, influence the regenerative potential of epidermal stem cells and compromise their ability to maintain tissue homeostasis, as also evidenced in human skin fibroblasts[39].

Age-related inflammation contributes to the induction of ROS, which damages cellular DNA, proteins and lipids, impairing cellular functions and promoting tissue deterioration. Keratinocytes in the epidermis act as stress sensors, releasing pro-inflammatory lipid mediators such as PGE2, protein mediators such as cytokines and increasing ROS production[40,41]. This suggests that the skin contributes to systemic inflammation associated with aging[12]. Age-related alterations in skin structure and immune response, combined with alterations in the skin's antioxidant defense system, including reduced levels of antioxidants such as α-tocopherol, glutathione and ascorbic acid[42], amplify the effects of environmental stressors, exacerbating inflammation and accelerating skin aging[43,44] and thereby creating a feedback loop. ROS can cause damage to cellular components in the skin, including DNA, proteins and lipids. Melanocytes and dermal fibroblasts are particularly susceptible to oxidative stress, and the gradual accumulation of oxidative damage over time can contribute to their functional decline and premature aging[45].

Mitochondria play an important role in the maintenance of stem cell function both in the skin and other tissues. A tight connection has been identified between DNA repair deficiencies and mitochondrial dysfunction. As the repair of mitochondrial DNA relies on imported repair proteins, both nuclear and mitochondrial DNA are affected by the same repair defects[46].

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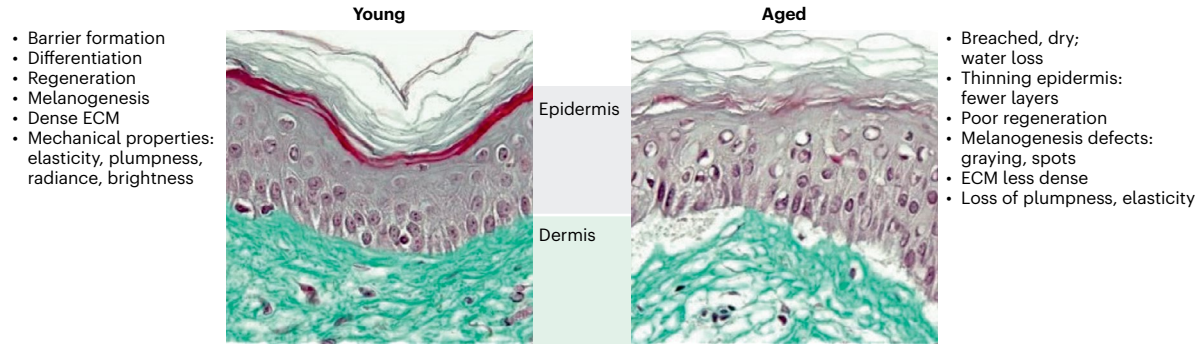

Loss of proteostasis
- Accumulation of oxidized and glycated protein with impaired function

Epigenomic alterations
- Dysregulation of key cellular processes
- Impaired transcriptional program
- Estimation of biological age and rejuvenation

Genomic instability
- Accumulation of DNA damage and impaired repair mechanism
- Major hallmark for premature aging syndromes
- Depletion of melanocytes

Telomeres
- Oxidative stress in skin impacts telomere length and maintenance
- Telomere deprotection in melanocytes contributes to age-associated decreased epidermal turnover
- Skin and hair defects strongly associated with telomere-related premature aging syndromes

Disabled macroautophagy
- Accumulation of cellular damage leading to inflammation and oxidative stress
- Increased levels of autophagosomes

Dysbiosis
- Destabilized ecosystem between skin and its flora
- Age-dependent alterations of skin (pH, sebum, immune functions, nutrients, sweat...) affects the skin microbiome
- Altered microbiota functions: immunity, antimicrobial defense, regulation of inflammatory response

Chronic inflammation
- Silent inflammation
- ROS-induced damage of cellular DNA, lipids and proteins
- ECM degradation

Altered intercellular communication
- Diminished cell-to-cell communication via gap junctions
- Deregulated cytokine signaling
- Altered comunication between skin cells and the ECM disrupts fiber production
- Altered immune cell regulation in aging syndromes

Stem cell exhaustion
- Loss of skin repair capital
- Thinness of the epidermis
- Loss of dermal plumpness
- Weakness of the dermal–epidermal junction

Mitochondrial dysfunction
- Decline in mitochondrial stress-response robustness
- Accumulation of nuclear damage and mitochondrial DNA mutations
- Accumulation of ROS
- Deregulated metabolism due to NAD^+ depletion
- Loss of ATP

Senescence
- Accumulation of senescent cells in all skin layers
- Pleiotropic phenotypes among different skin cells
- In vivo skin-specific-associated secretome (SASP)
- Juxtacrine secondary senescence inflammation

Dysregulated nutrient sensing
- Epidermis nutrition relies on the vascularized dermis
- Aging and lifestyle-dependent shortage of essential nutrients
- Sensing pathways altered: IGF-1 down/mTOR up
- Accumulation of AGEs with high glucose levels

Fig. 1 | Skin aging and the 'hallmarks of aging'. The progressive deterioration of skin architecture and function with age impacts systemic hallmarks of aging, as they also manifest in cutaneous biology. Histological panels compare young and aged human skin, highlighting thinning of the epidermis, reduction in dermal ECM density, and loss of elasticity and pigmentation in aged skin. Each of the aging hallmarks—including loss of proteostasis, epigenetic alterations, genomic instability, telomere attrition and mitochondrial dysfunction—is contextualized within skin-specific processes. For example, telomere erosion is linked to reduced melanocyte renewal, while mitochondrial dysfunction contributes to ROS accumulation and impaired ATP production. Chronic inflammation, altered intercellular communication and stem cell exhaustion are shown to affect epidermal integrity and dermal–epidermal junction stability. Dysbiosis, nutrient sensing dysregulation and macromolecular damage further compound aging effects, leading to visible and functional degeneration. The comprehensive map shows how systemic aging mechanisms converge in the skin, making it a key sentinel and therapeutic target for age-associated decline. AGEs, advanced glycation end products.

The amount of the oxidized form of cellular nicotinamide adenine dinucleotide (NAD^+) and its effect on mitochondrial activity acts as a switch to modulate neural and melanocyte stem cell senescence[47]. Epigenetic changes affect metabolic rewiring and mitochondrial activity, driving the degeneration of hair follicles[48], and triggering cell senescence, contributing to the decline in skin regenerative potential with advanced age[49].

The age-related decline in the robustness of the mitochondrial stress response (MSR) pathway is at the pinnacle of age-related physiological decline at the cellular, tissue (including skin) and organismal levels. Disruption of MSR resilience contributes to: (1) the accumulation of nuclear DNA damage[50] (also evidenced in chronically sun-exposed skin[51]) and mutations in mitochondrial DNA (often referred to as heteroplasmy) in somatic cells; (2) deregulated metabolism often driven by the depletion of the cellular NAD^+ pool[52], accumulation of bioactive lipids and ROS, and changes in tricarboxylic acid cycle intermediates that also have been described in the skin[53]; (3) epigenetic alterations tightly linked to (and to a large extent driven by) the above metabolic changes[54,55]; (4) proteotoxicity and accumulation of protein aggregates[56]; (4) decline in stem cell activity, including in melanocyte[47] and hair follicle stem cells[26]; (5) induction of senescence[16,57]; and (6) chronic inflammation, also termed meta-inflammation, fueled through the release of mitochondrial DNA, mitochondrial RNAs and/or metabolites[36,58].

Chronic inflammation is exacerbated by age-related accumulation of senescent cells[59]. They exhibit a local effect and propagation of cellular senescence to the surrounding microenvironment through paracrine (senescence-associated secretory phenotype (SASP)) and juxtacrine (direct cell-to-cell contact) mechanisms, a phenomenon called secondary senescence[60], but recent evidence also indicates that SASP factors can be found in extracellular vesicles secreted by senescent cells[61]. These extracellular vesicles have the potential to interact with distant cells and propagate the detrimental effects of skin senescent cells to other tissues. In vitro, senescent melanocytes have been found to affect the proliferation rate of co-cultured keratinocytes and, via their secretion of SASP, to activate a DNA damage response in dermal fibroblasts, providing proof-of-concept evidence that senescent melanocytes are intimately involved in human skin aging[62]. The

dysfunctional telomeres of aged melanocytes may also contribute to the reported upregulation of HLA-E expression in SASP-induced senescent dermal fibroblasts, a phenomenon that is likely to contribute to the persistence of senescent cells in the skin through the inhibition of immune response to clear tissue-resident senescent cells[63].

Increased autophagosome formation has been observed in both skin fibroblasts and keratinocytes upon cellular senescence[64,65]. However, the relationship between autophagy and senescence in skin is not entirely understood, as autophagy has been reported to have both anti-senescence and pro-senescence effects[66]. Dysregulation of autophagy in aged skin is similarly nuanced, as it appears that autophagy does not simply decline with age[65], but possibly suffers from impaired clearance mechanisms[67]. One of the drivers of disrupted autophagy is deregulated nutrient sensing. Under normal circumstances, nutrient depletion or stress leads to inhibition of the mechanistic target of rapamycin (mTOR) pathway and initiation of autophagy; however, aberrant mTOR complex 1 (mTORC1) signaling, commonly observed in aging, impairs activation of autophagic responses. Activated mTOR complex 2 (mTORC2) leads to chronic nuclear factor-κB activation with inflammatory consequences[68]. Dysregulated nutrient signaling and cellular senescence contribute to structural and functional changes in aging skin, including reduced cellular proliferation, impaired wound healing, chronic inflammation and a compromised oxidative stress response.

Signaling pathways that change with age include the endocrine, neuroendocrine and hormonal signaling pathways[69,70]. The skin not only is the target of neuroendocrine factors (or their dysregulation) but also acts as a source of neurotransmitters and hormones, as well as their coordinated responses to stressors that contribute to aging[71]. The effects of these altered signaling pathways are linked to increasing chronic inflammation and deterioration in immune function, resulting in a decline in immunosurveillance against premalignant cells and pathogens, as well as dysbiosis. Many of these signaling pathways directly affect the skin and the appearance of aging.

The mechanistic link between microbiome dysbiosis of the skin and host aging pathology is not entirely understood and is likely to be multifaceted. Two of these mechanisms involve the microbiome's regulation of host inflammation and metabolism[72]. Dysbiosis seems to be bidirectional in the context of aging, as it promotes low-grade, chronic inflammation in the host, leading to cellular dysfunction, tissue damage and the acceleration of organismal aging[72]. Moreover, microorganisms coexisting with the host can generate numerous metabolic products through their de novo metabolism or modify metabolic products derived from the host. Many of these metabolic products are known to benefit the host's metabolic and immune health and to promote host longevity[72,73]. Microbiome dysbiosis may impair the production of these beneficial metabolic products, contributing to metabolic disorders and inflammaging. It has been suggested that skin dysbiosis can exacerbate inflammatory skin conditions such as atopic dermatitis[74] and psoriasis[75], while a healthy skin microbiome promotes skin homeostasis, immune function and the production of antimicrobial peptides, contributing to skin health[76,77].

The role of the gut–skin axis in the inflammatory response during aging is also of interest. There are indications that gut dysbiosis can lead to increased intestinal permeability, the 'leaky gut syndrome', allowing microbial products and endotoxins to enter the bloodstream and potentially trigger cutaneous inflammation[75]. In mice, acute disruption of the epidermal permeability barrier increases not only cutaneous but also serum inflammatory cytokines in young mice[78]. It remains to be seen whether age-related barrier dysfunction could similarly contribute to the development of systemic inflammation in aged humans.

Environmental exposure, particularly at sites that are chronically exposed to the environment, such as the face, contributes to inflammation and skin aging. Direct photochemistry from UVR impacts the skin ECM proteins, contributing to reduced tissue function. Damaged proteins may be preferentially removed by tissue-resident matrix metalloproteinases in an attempt to restore tissue homeostasis[79]. However, with age, the gradual loss of proteostasis, with diminished ability to selectively remove damaged proteins, leads to protein damage accumulation, oxidative stress and inflammation[56,80]. The metabolic production of various free radicals and related oxygen-based and nitrogen-based oxidants, from mitochondria and other sources, may add to the array of damaging species that can affect skin proteins, both intracellularly and extracellularly[49,80]. Loss of proteostasis can affect various skin cell types, including skin fibroblasts and epidermal stem cells. Studies have shown that the proteome of skin fibroblasts changes with age, affecting key pathways such as autophagy, ROS scavenging and DNA repair[81]. This cumulative damage underscores the interplay between environmental and cellular factors that accelerates skin aging.

Skin aging and disease

Degradation of skin isn't just a reflection of aging; it plays an active role in the aging process itself (Fig. 2). Growing evidence indicates that skin aging has detrimental effects on the body, affecting systemic inflammation[12], bone loss[82] and potentially cognitive decline[83].

Environmental stressors combined with age-related deterioration are known to be implicated in skin conditions and carcinogenesis. For instance, UVR exposure has been shown to induce mutations in the *p53* tumor suppressor gene, which may subsequently lead to actinic keratoses and squamous cell carcinoma[84]. Genomic instability in skin cells gives rise to a phenomenon termed 'field change', wherein multiple cancers result from a clonal region of preneoplastic epithelium[85]. Inhibition of Notch signaling in progenitors possessing *p53* stabilizing mutations has demonstrated robust field changes in epithelium[85]. While these mutagenic events are primarily attributed to UVR irradiation, and not aging per se, they are more frequently observed in aged, sun-exposed skin. For example, a landmark study by Martincorena et al.[51] revealed a high frequency of Notch driver mutations for cutaneous squamous cell carcinomas in normal sun-exposed, aged epidermis.

While age-related DNA damage highlights the vulnerability of aging skin, changes in the skin microbiome may further exacerbate its susceptibility to pathogen invasion[86] and systemic effects[76]. The composition of the skin microbiome changes over the human lifespan[86] and has been used to predict chronological age[87]. Disruption of the skin microbiome has similarly been evidenced in atopic dermatitis, with increased colonization of the pathogenic strain *Staphylococcus aureus*, under normal conditions displaced by *Staphylococcus epidermidis*[88,89]. *S. aureus* overgrowth is associated with defects in stratum corneum integrity, decreased expression of structural epidermal barrier proteins and an altered lipid composition[90,91]. Inflammatory skin conditions such as psoriasis and atopic dermatitis impact the quality of life and pose important systemic health risks, and studies have linked these dermatoses with a higher risk of cardiovascular diseases, such as heart attacks and strokes[92], increased prevalence of type 2 diabetes[93], obesity, and more[94]. This warrants further research into whether age-related dysbiosis could share some of the same mechanisms to also play a role in diseases beyond the skin.

Age-associated systemic inflammation in older adults is evidenced by the detection of higher circulating levels of inflammatory cytokines and C-reactive protein[95]. Emerging evidence suggests that inflamed skin could also contribute to inflammatory bowel disease, as observed in studies investigating the relationship between skin inflammation and gut health[96]. This skin–gut axis was confirmed using a mouse model demonstrating that skin wounding disrupted homeostasis in intestinal host defense and altered the gut microbiome[97]. Studies on the human skin microbiome have revealed the association between its dysbiosis and skin disorders, as well as whole-body frailty and increased susceptibility to pathogens in older adults[98]. The skin microbiota was also found to serve as a primary reservoir for antimicrobial resistance, clinically recognized pathogens and nosocomial strains, potentially increasing disease risk and the spread of multidrug-resistant pathogens[98].

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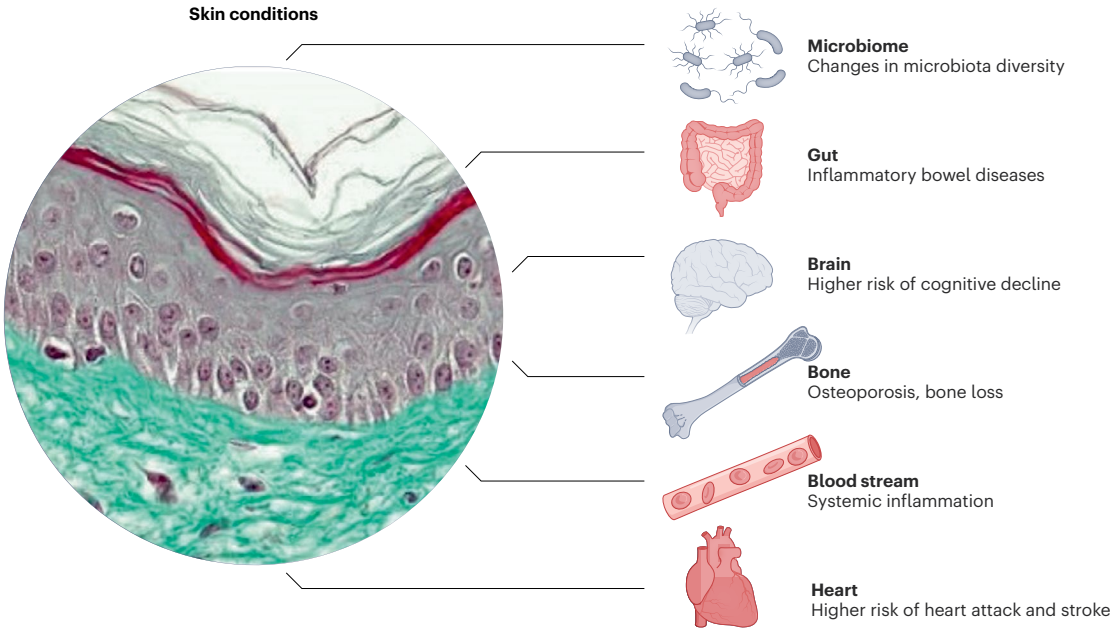

Fig. 2 | Skin conditions associated with major chronic diseases of aging. The interconnections between skin health and systemic physiological outcomes are shown. A histological image of the epidermis and dermis is depicted on the left, representing the structural and functional status of skin. To the right are six organ systems that are affected by skin-related pathophysiology, suggesting the skin's role as both a marker and mediator of systemic aging and inflammation. Alterations in the skin are linked with reduced microbiota diversity (microbiome), increased risk of inflammatory bowel diseases (gut), cognitive decline (brain), osteoporosis and bone loss (bone), systemic low-grade inflammation (bloodstream) and heightened cardiovascular risk including stroke and myocardial infarction (heart). This schematic emphasizes the skin as a window into organismal health and a potential noninvasive target for early detection and intervention in age-associated diseases.

Apart from detrimental systemic effects of dermatoses and microbiome disruptions, a correlation has been established between alterations of epidermal functions and coronary artery disease, which is very common in older adults. The rate of transepidermal water loss, used as a proxy to evaluate epidermal permeability, was 23% higher in individuals with coronary artery disease[99]. Furthermore, aged skin is known to have a reduced capacity to produce vitamin D_3, leading to systemic deficiencies, altered physiology and increased cancer incidence[100].

Recent research indicates a link between skin damage and bone loss, with findings suggesting that compromised skin function may affect the regulation of bone cells[82]. While an association between skin atrophy and bone loss during aging was clinically observed, this recent study characterized the underlying mechanism. With age, keratinocytes decreased their secretion of cystatin A, an important factor that mediates the proliferation of osteoblast and osteoclast progenitors[82].

Skin conditions could potentially have implications for brain health as well, as suggested by multiple studies. Atopic dermatitis and psoriasis have been shown to increase the risk of dementia and Alzheimer's disease[94] (Fig. 2). Research has suggested the involvement of inflammaging in the progression of these neurodegenerative conditions[83]. The skin–brain connection may also depend on the sensing of changes in sunlight exposure duration caused by the seasons. Low serum levels of melatonin, whose production is dependent on light exposure, are associated with relapse in multiple sclerosis[101].

Treatment implications

The interconnectedness of systemic and skin changes, as well as the complex interplay between hallmarks of aging, points to the need for a holistic approach to addressing aging. While skin aging serves as a visible indicator of biological aging, understanding and addressing hallmarks of aging in the skin can be a substantial contribution to systemic health, and not simply a cosmetic goal[31,102].

Implementing systemic strategies such as regular physical activity and proper sleep habits positively reflects on skin health. Exercise, a long-known intervention to combat aging, exerts antiaging effects on skin through the reduction of circulating inflammatory factors and an influence on hormones and metabolites[103]. Other methods to counteract inflammation, together with genomic instability, involve minimizing exposure to triggers of DNA damage, such as pollution and pesticides, various plasticizers and other immune system disruptors[104], as well as the use of sunscreen. Maintaining a balanced diet is also important, as evidence suggests that dietary micronutrients are bioavailable in the skin and contribute to enhanced protection against UVR exposure[105,106]. Beyond lifestyle modifications, the gut–skin axis plays a crucial role in skin health. Given the findings that gut dysbiosis can result in cutaneous inflammation[75], understanding the effects of dysbiosis on skin is vital for developing strategies to maintain a balanced skin microbiome and potentially harness its benefits for skin health. Current avenues for developing microbiome-based therapy include fecal microbiota transplantation, dietary prebiotics, enteral reconstitution of symbiotic bacteria, the introduction of engineered bacteria and supplementation of microbiome-derived bioactive compounds[107]. However, it is also true that inflamed skin can contribute to gut inflammation[97], and taking better care of skin can mitigate the harmful systemic effects of aging and improve overall health and potentially lifespan.

The skin's unique accessibility for topical applications, and efficient supplementation of nutrients, especially within the epidermis, offers promising avenues for interventions that extend beyond cosmetics. It is shown, for instance, that topical application of a drug that stimulates cystatin A production in the epidermis of mice alleviated osteoporosis[82]. Similarly, the use of topical antioxidants could counteract oxidative stress and target specific pathways involved in inflammation[43,108]. A relevant 3-year-long trial conducted on 200 individuals over 65 years old explored whether skin repair via topical emollient application could prevent cognitive decline. Notably, the treatment group showed significant differences in the quality of the skin and stable cognitive scores, unlike the control group[109]. While

these results are promising, researchers caution that more evidence is needed. Additionally, differences in skin types suggest that treatments may vary among individuals.

Oxidative stress, which appears as a latent variable in skin aging, affects and is affected by multiple hallmarks of aging. Reduction of oxidative stress and enhancement of DNA repair mechanisms are thus important points to consider in developing therapies. The tight connection between DNA repair deficiencies and other aging hallmarks, such as mitochondrial dysfunction, is another important feature to bear in mind when developing intervention strategies, as they need to be effective on both DNA repair and mitochondrial function. Understanding the heterogeneous effects of aging in different skin cell types may help deliver more effective treatments. For instance, given that melanocytes may be more susceptible to some forms of dysfunction than keratinocytes[18,110], protecting the telomeres of melanocytes against oxidative stress may provide important perspectives to delay skin aging and also prevent accelerated biological aging systemically. Research in telomerase-deficient mice suggests that telomerase activation could be harnessed therapeutically to address aging-associated skin changes without notably increasing the risk of carcinogenesis[32]. However, the potential to enhance malignancy in human skin, which is chronically exposed to UVR, unlike the skin of laboratory mice, cannot be fully ruled out.

Mitochondrial dysfunction is bidirectionally linked to oxidative stress and exemplified in the loss of resilience of the MSR network[36,58]. It is one of the contributing factors to age-related chronic inflammation. Many compounds targeting the mitochondria—dubbed mitochondrial medicines—are currently undergoing testing and clinical trials to delay age-related diseases and aging. Compounds that increase NAD^+ levels, so-called 'NAD boosters', and mitophagy inducers, such as urolithin A, have shown clinical benefits in both animal models and humans with various age-related disorders[52,111], although their mechanisms are not entirely understood[112]. Except for urolithin A[111,113], these mitochondrial medicines have not yet been tested in the context of skin aging. Should the outcome of such future trials be positive, several mitochondrial medicines may soon find a use as a topical or systemic interventions for skin aging.

Agents that induce autophagy or mitophagy to improve mitochondrial quality control are expected to be a promising strategy for combating aging[114]. For example, inhibition of the E1A-binding protein P300, a lysine acetyltransferase, using anacardic acid, curcumin, garcinol or spermidine has been proposed to induce autophagy and simultaneously inhibit mTORC1 (ref. 115).

Furthermore, understanding the molecular mechanisms involved in skin cellular senescence—another major contributor to chronic, sterile inflammation—may provide meaningful insights for developing effective therapeutics for many skin disorders and, more generally, for aging-related conditions[116]. Senescent cells are often considered primary targets for geroprotective interventions, through several complementary strategies: senolytic approaches aim at clearing senescent cells by inducing them into apoptosis, typically by downregulating components of the antiapoptotic pathways in these cells; senomorphic approaches attempt to turn off the SASP without clearing senescent cells. Both approaches have shown encouraging results. For example, rapamycin, which regulates protein synthesis and cell growth by targeting the mTOR pathways, inhibits the upregulation of IL-1α—a SASP factor—and the secretion of other SASP components in dermal fibroblasts and decreases the number of cells positive for the senescence marker SA-β-gal[117]. Hence, rapamycin's senomorphic effects might be responsible for the reduction in the aging effect of UVB irradiation on skin[117]. A clinical study showed that topical rapamycin treatment reduced markers of aging and senescence in the human skin, including p16INK4A and restoration of dermal collagen VII[118]. Different 'rapalogs' targeting different mTOR complexes, are now being tested for other age-related indications, such as immunological decline and accelerated cardiovascular aging[119,120]. Among other senolytic compounds that have been identified, dasatinib and quercetin administered together (D + Q) have shown particularly promising results in targeting senescent cells in the skin. Treatment with D + Q showed a reduction in the number of skin epidermal cells positive for p16INK4A and p21CIP1, two of the primary senescence-associated markers, as well as a reduction in the proportion of SASP proteins[121,122].

Cellular senescence is intricately involved with stem cell function, an important factor in skin rejuvenation. Numerous studies have explored potential strategies to preserve or restore the regenerative potential of skin stem cells. For example, the administration of certain growth factors was shown to enhance the proliferation and differentiation of both hair follicle and interfollicular epidermal stem cells, promoting tissue repair and regeneration[123,124]. Additionally, small molecules targeting specific signaling pathways have been investigated for their potential to modulate the activity of skin stem cells and mitigate the effects of aging[125]. One example to pharmacologically invigorate skin stem cell function is the supplementation with NAD boosters, such as nicotinamide riboside, which activate sirtuins and boost mitochondrial function. Nicotinamide riboside rescues the decline of melanocyte stem cells in hair follicles of aged mice, as reflected by increases in mast/stem cell growth factor receptor kit and short transient receptor potential channel 2, known mast/stem cell markers[47]. Interestingly, nicotinamide riboside treatment not only improved melanocyte stem cell function, but also beneficially affected muscle and neural stem cells, resulting in an increase in lifespan[47].

As circadian arrhythmia has a strong impact on stem cell function, the perturbation of this cyclical homeostasis is postulated to give rise to skin aging and carcinogenesis[22], and presents a suitable target to impact aging-associated skin disorders. Akin to dysfunctional hair cycling responsible for skin conditions such as alopecia, mouse models have demonstrated that the regenerative behavior of hair follicle stem cells declines with age, but that these cells can be reactivated, modulated by activating and inhibitory signaling in the dermis[126].

The most effective interventions will result from combining lifestyle modifications with systemic and skin-targeted treatments, while considering the complex interactions among aging hallmarks—both the known and those yet to be uncovered.

Outlook and current gaps

Research in skin aging is propelled by breakthroughs in related scientific fields and technological advancements, yet substantial gaps remain in our ability to treat skin aging and fully understand its impact on systemic health. Cutting-edge techniques, such as single-cell RNA sequencing and CRISPR–Cas9 gene editing, offer unprecedented insights into the molecular mechanisms underlying skin cell function and aging, enabling researchers to identify key regulatory pathways and potential therapeutic targets for mitigating the impact of aging in skin and beyond. Enhanced next-generation sequencing has also allowed a more granulated look into the diversity of the microbial populations, and future advances in microbiome therapy, especially those targeting niches beyond the gut, will provide potential interventions for promoting skin and overall health. Personalized medicine and targeted therapies tailored to an individual's genetic predisposition may open avenues for combating age-related skin disorders.

As connections between aging pathways in the skin and other organs become clearer, we anticipate more focus on the development of multi-target therapeutics and therapies that leverage skin treatments to support systemic health. Understanding progressive alterations in intercellular communication, which increase biological 'noise' and undermine homeostasis, will be essential for creating targeted interventions to preserve tissue integrity in later life.

Fully leveraging technological advancements in clinical and therapeutic settings will require the development of precise biomarkers to measure and model the effects of skin aging. The search for biomarkers

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Table 1 | Strengths and limitations of current and emerging models in skin aging research

Model type	Strengths	Weaknesses
Animal models		
Invertebrate	Captures some aspects of human aging Can test interventions Rapid experiments due to short lifespan; low maintenance cost	Lacks crucial organs and systems for modeling human complexity
Vertebrate	Some models resemble human organs and systems	Long lifespan, high cost (for example, primates) Low throughput Different than humans in disease susceptibility and treatment response Do not capture full human complexity Cannot model lifestyle effects Ethical considerations
Cell culture models		
2D cell cultures	Clear insights into cell-intrinsic factors Can examine different donor samples	Lacks tissue complexity, intercellular interactions
3D skin models	Mimics human skin structure and ECM; suitable for long-term studies Better for modeling tissue and organ states than 2D	Limitations in modeling drug responses, immune responses, interactions between organs and tissues
Organoids	Resembles structure and function of organs	May require reprogramming to embryonic-like state, erasing age-related hallmarks
Microfluidics-enhanced systems	Capture multi-organ interactions Improve tissue perfusion	Cannot fully replicate capillaries Added technical requirements and cost

has intensified in recent years despite a lack of consensus on which of these should be used to translate research into clinical trials[127]. For instance, the nonlinear, multivariable path leading to cellular senescence, calls for the use of multi-markers[59] to detect senescent cells, which is particularly challenging in human tissue samples. However, most studies performed on human skin used only one senescent marker. The well-known senescent marker $p16^{INK4A}$, an inhibitor of cyclin-dependent kinases, was initially described as a robust in vivo biomarker of cellular aging in human skin[128], and is still widely used. However, not all forms of senescence are dependent on p16 activity[129], and all individual senescent markers have similar limitations. Understanding the pleiotropic phenotypes of senescent cells, particularly in complex tissues with multiple cell types, will require the development of multi-parametric approaches and the identification of senescent markers that can be detected noninvasively. Raman microspectroscopy fingerprints were successful in distinguishing senescent from non-senescent cells in skin models and stand as a promising approach[130].

To identify treatments that slow down or partially reverse the aging of skin, it would be important to develop next-generation skin aging clocks. Relating the well-studied epigenetics modality of skin aging to other omics patterns, most notably transcriptomics, metabolomics and proteomics, as well as to cell-type composition, immunomics and imaging, may improve the robustness of quantifying skin aging and rejuvenation. Quantifying the levels of different inflammaging mediators in the interstitial space of the skin could also enable development of skin-specific inflammatory aging clocks, similar to the one that has been used to assess inflammaging in the circulatory system[131]. Furthermore, the appearance of skin—particularly of habitually photoexposed facial skin—may provide the basis for facial aging biomarkers.

The development of human models of skin aging is critical for testing interventions and gaining insight into the molecular mechanisms that drive aging. The aging field has gained much knowledge from highly valuable animal models that are able to recapitulate some aspects of human aging and test interventions[132]. However, some of these models are unable to reproduce the complexity of human aging, particularly the interconnection between organs. Invertebrate and some vertebrate model organisms lack important human organs and systems, while evolutionarily closer animals are long lived and, therefore, not suitable for fast experimentation[132]. In addition, a large part of human aging is impacted by individual lifestyle, which cannot be properly evaluated in animal models (Table 1).

In vitro two-dimensional (2D) human primary cell cultures from donors of different ages or from individuals with premature aging syndromes are also extremely informative, but they lack tissue complexity and do not recapitulate most of the important features of organismal aging. Notable progress has thus been made in building advanced integrated human three-dimensional (3D) skin models that better mimic human skin. Using various technologies, researchers can develop well-differentiated reconstituted epidermis, dermal equivalents with appropriate ECM and full-thickness skin models that closely resemble normal skin with all its layers. Bio-printing technologies have enhanced repeatability, allowed precise control over the addition of different skin cell types, and improved overall throughput[133].

Organoids, 3D models of organs and their features, derived from pluripotent, fetal or adult stem cells, have emerged as a valuable and high-throughput solution for studying aging. They range from 3D self-organized stratified epidermal equivalents derived from induced pluripotent stem (iPS) cells to nearly complete in vitro self-organized skin systems, providing advanced platforms that closely mimic human skin structure and function[134]. However, reprogramming old cells into iPS cells rejuvenates them by erasing age-related hallmarks. Strategies such as long-term culture, telomere shortening and genetic manipulation have been used to induce aging phenotypes in iPS cell-derived cells, but they may not fully replicate physiological aging conditions[135]. Furthermore, organoids, as well as other 3D models, have limitations in modeling tissue and organ interactions, immune responses and treatment responses[132]. Microfluidics systems emerged as a solution to overcome some of these challenges, paving the way toward connecting skin models with other 3D models of different human organs. These systems have been used to simulate blood vessels and enhance perfusion in skin organoids, contributing to improved barrier properties and phenotypic differentiation. However, fully replicating capillaries in organoids using microfluidic devices remains a challenge[134].

Advancing our understanding of skin aging requires comprehensive data collection from diverse populations across all ages, genders and ethnicities. Incorporating information about donors' global health status, lifestyle, environment and social factors in longitudinal studies will enrich this effort. Utilizing advanced skin models, combined with

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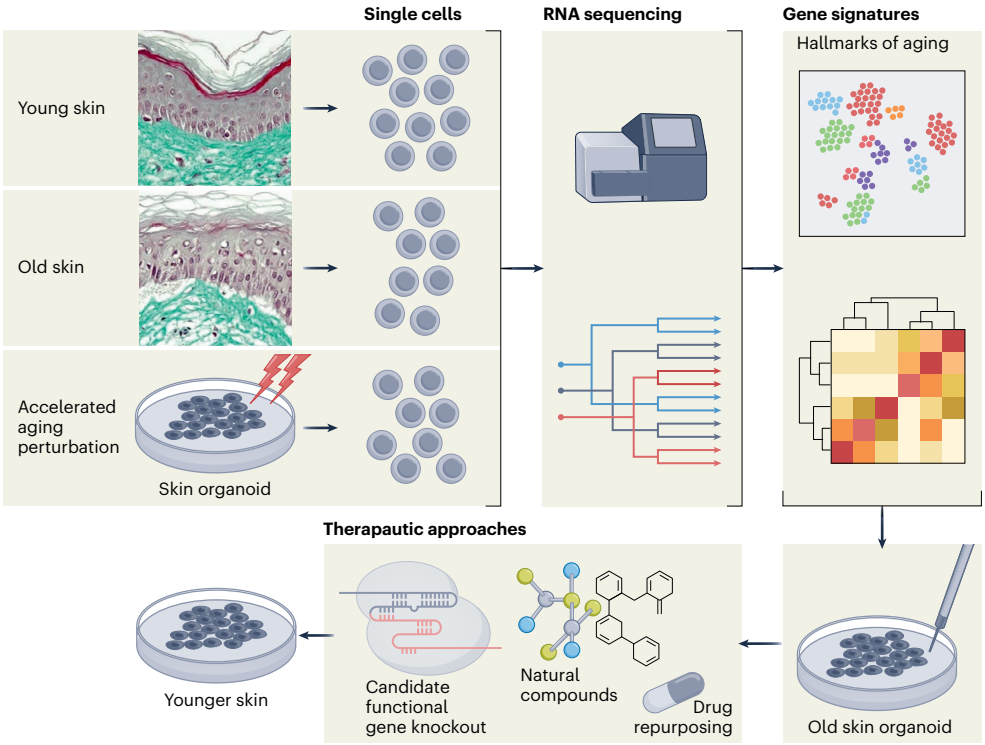

Fig. 3 | Methods to study skin aging and identify therapeutic interventions. A precision discovery pipeline to identify rejuvenation targets in aged skin using transcriptomic profiling and perturbation modeling is shown. Skin samples from young, old and experimentally aged (perturbed) skin organoids can be dissociated into single cells for RNA sequencing. High-resolution transcriptomic data can then be used to generate gene expression profiles and to identify aging-associated signatures mapped to known hallmarks of aging. Dimensionality reduction and clustering analyses reveal distinct aging-related molecular trajectories, while heat maps display the enrichment of hallmark pathways across conditions. These data enable systematic identification of candidate genes and pathways for functional intervention. Informed by this analysis, therapeutic strategies—including functional gene knockouts, drug repurposing and natural compound screening—can be tested for their ability to reverse aging signatures in old skin organoids, ultimately aiming to restore a youthful cellular phenotype. This integrated approach supports the development of targeted rejuvenation therapies grounded in single-cell systems biology.

approaches like single-cell RNA sequencing[136,137], researchers can more effectively study health and aging disparities. These models are refining our knowledge of skin aging biomarkers and hallmarks, paving the way for therapies that may prevent skin and potentially whole-body aging (Fig. 3).

Conclusion

Aging lies at a crossroads where numerous interlinked factors and physiological outcomes converge. In the context of skin aging, this complexity is magnified due to the skin's role as both a barrier and an active participant in systemic health. While valuable progress has been made in identifying the hallmarks of aging, translating this knowledge into effective interventions remains a formidable challenge. Developing precise biomarkers and advanced skin models will be essential to bridge the gap between understanding and intervention. Only a holistic and truly geroscientific approach to understand aging, not focused on its individual hallmarks, will allow this field to advance.

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Competing interests

The following authors are advisors to the Reverse Aging Science Board at Parfums Christian Dior: D.F., J.A., G.C., K.J.A.D., A.D., V.N.G., B.K. K., N.N., D.R., V.S., M.C.W. and K.W. The following authors are employees at Moët Hennessy Louis Vuitton LVMH or Parfums Christian Dior: A.-L.B., V.C., L.C., C.N. and K.P. The other authors declare no competing interests.

Additional information

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