Ageing Research Reviews 118 (2026) 103109

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review article

Modeling aging in a culture dish: towards the development of more sophisticated in vitro models of human skin aging

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ARTICLE INFO

Keywords:
Aging
Human skin
In vitro models
Organotypic
Senescence
Skin equivalent

ABSTRACT

With age, human skin undergoes a progressive decline in essential functions, including barrier protection, immunity, and wound healing capacity, which underlie many age-related skin diseases. Skin aging is not only driven by chronological aging, but also strongly influenced by extrinsic stressors, notably ultraviolet radiation, pollutants, and diet. Thus, understanding the complex interplay between these intrinsic and extrinsic factors is essential for developing strategies to preserve skin health across the lifespan. Given the growing appreciation for the physiologic differences between humans and animal models, more advanced *in vitro* and *ex vivo* models are needed to dissect the human-specific mechanisms of skin aging and test emerging therapies. In this review, we summarize the major hallmarks of human skin aging and provide an overview of current *in vitro* modeling approaches that capture both intrinsic and environmental aging mechanisms. We highlight recent advances in complex 3D *in vitro* systems — including full-thickness human skin equivalents, organoids, and microphysiological platforms — and discuss how these emerging models can be leveraged to interrogate aging biology and support translational research. Together, these developments pave the way for more predictive and mechanistically informed tools to study skin aging and to accelerate the development of next-generation therapeutic and preventive strategies.

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https://doi.org/10.1016/j.arr.2026.103109
Received 22 December 2025; Received in revised form 14 March 2026; Accepted 21 March 2026
Available online 22 March 2026

1. Introduction

As a major interface with the external environment, human skin is essential for protecting the body, maintaining immunity, and regulating metabolism. With age, the skin undergoes a progressive and irreversible decline in tissue functions, leading to increased skin fragility and the risk of conditions like chronic wounds, infections, and cancer. Skin aging is heavily influenced by environmental (extrinsic) factors such as ultraviolet radiation (UVR), diet, and pollution, as well as by intrinsic chronological aging, which results from disruptions in signaling pathways and the normal deterioration of genetic, biochemical, and cellular processes (Tobin, 2017; Wong and Chew, 2021).

Greater insight into the underlying mechanisms of skin aging has the potential to improve skin health, functionality, and disease resiliency as we age, thereby contributing to increased healthspan. However, a major challenge is the development and implementation of appropriate experimental models that capture the complex and multifactorial processes involved in human skin aging. There is increasing appreciation that animal models do not accurately replicate key features of human skin (Ansell et al., 2012; Gerber et al., 2014; Pasparakis et al., 2014), and traditional two-dimensional (2D) monocultures do not reflect the multi-cellular and structural features of the skin. These factors have motivated significant efforts to develop more complex and three-dimensional (3D) *in vitro* models of human skin that enable mechanistic and translational studies of aging. Such models are needed for discovery research to dissect the underlying mechanisms of skin aging and identify potential therapeutic targets, as well as to enable predictive safety and efficacy testing of drugs, cell therapies, medical devices, and consumer health products. In this review, we explore recent advances in the development of tools to model intrinsic and extrinsic drivers of skin aging, outline how these can be applied to basic and translational skin research, and provide future directions for developing more sophisticated aging skin models.

2. Hallmarks of skin aging

Research over the last several decades has led to a well-developed understanding of the key hallmarks of aging skin and the associated changes in tissue function and susceptibility to disease. These hallmarks include structural, cellular, and biochemical alterations within the skin and represent the essential design criteria for building and validating *in vitro* models of human skin aging (Fig. 1).

Skin aging is a highly complex process that is driven by an interplay between intrinsic chronological aging and exogenous factors such as air pollution, nutrition, and UVR. In addition, ethnicity, sex, and co-morbidities may influence the impacts of these factors. The functional hallmarks of aged skin include a loss of elasticity, increased fragility, compromised barrier function, impaired immunity, hair loss and graying, reduced sweating capacity, impaired wound healing, and increased skin cancer risk (Farage et al., 2008; Makrantonaki and Zouboulis, 2007; Persa et al., 2021; Rittié and Fisher, 2015). Indeed, UVR and aging are the major risk factors for all types of skin cancer, including melanoma, basal cell carcinoma (BCC), and squamous cell carcinoma (SCC).

2.1. Age-dependent changes in epidermal structure

The epidermis, connected to the dermis by the basement membrane (BM)—a thin extracellular matrix (ECM) layer rich in laminin 332, type IV collagen, and nidogens—forms a protective barrier and continually regenerates through a balance between keratinocyte proliferation and coordinated terminal differentiation (Fuchs, 2016; Watt, 2014). Epidermal homeostasis is sustained by stem and progenitor cell

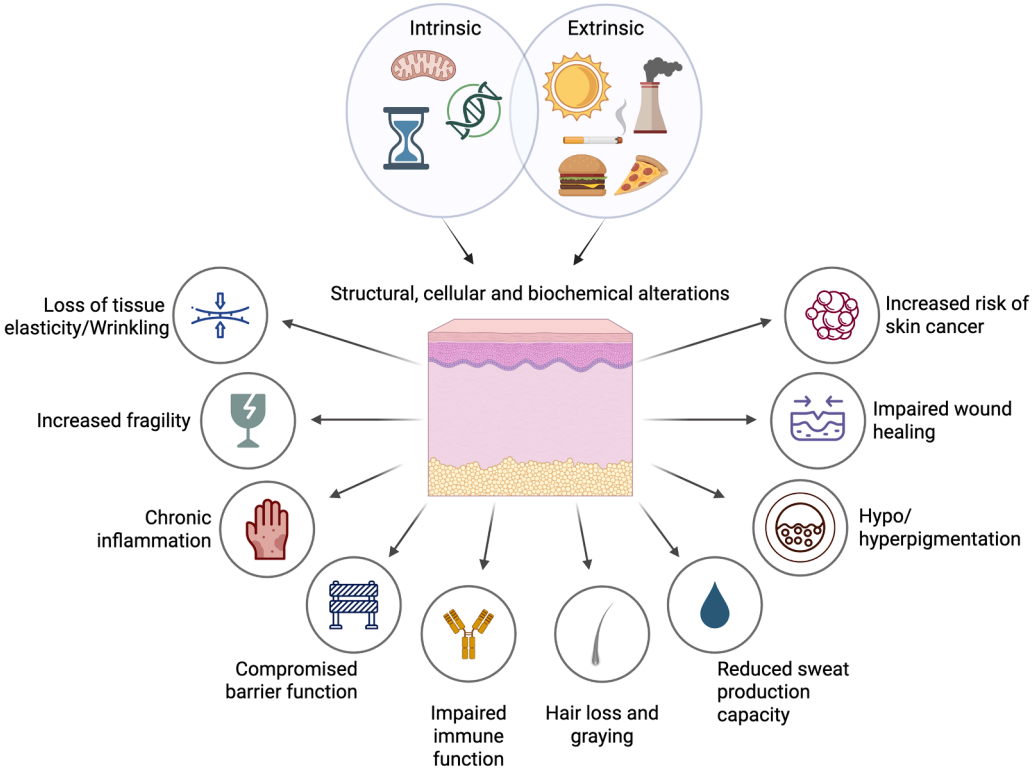

Fig. 1. Hallmarks of skin aging. Schematic overview of the major drivers and consequences of skin aging. Intrinsic factors (chronological aging, cellular senescence, mitochondrial dysfunction) and extrinsic factors (UV radiation, pollution, diet) converge to produce structural, cellular, and biochemical alterations in the skin. These changes manifest as various functional impairments, including loss of tissue elasticity/wrinkling, increased fragility, chronic inflammation, compromised barrier function, impaired immunity, hair loss and graying, reduced sweat production, hypo- and hyperpigmentation, impaired wound healing, and increased risk of skin cancer.

populations, including hair follicle stem cells that activate following injury (Ito et al., 2005).

Intrinsic aging generally results in a thinner epidermis, whereas photoaging promotes initial hyperthickening of the epidermis followed by atrophy. Basal keratinocytes in aged skin display greater heterogeneity in size and nuclear shape, a phenotype that is more severe in photoaged skin (Rittié and Fisher, 2015). In contrast to the overall thinning of the epidermis, the stratum corneum is thickened in aged skin, and the corneocytes are larger, flatter, and more cohesive (Biniek et al., 2015; Choe et al., 2018). These cellular changes also correlate with functional increases in stiffness of the cornified layer. Conversely, UVR decreases corneocyte integrity, further impairing barrier function in photoaged skin (Biniek et al., 2015). Another key structural change to the aging epidermis is the flattening of the dermal-epidermal junction alongside thickening and stiffening of the BM (Kazanci et al., 2017; Rittié and Fisher, 2015) and a reduction in specialized BM proteins, such laminin 332, type IV collagen, and type XVII collagen, suggesting that precise expression and assembly of BM components declines with age (Roig-Rosello and Rousselle, 2020). The mechanical properties of the BM are also critical for maintaining the regenerative potential of the hair follicle stem cell niche (Koester et al., 2021). Thus, aging of the epidermis is defined by major structural and cellular changes, which contribute to the functional decline in the barrier.

These features highlight the need for *in vitro* models that recapitulate age-related changes in epidermal stratification, BM architecture, and keratinocyte differentiation, as these elements are essential for assessing tissue function and evaluating aging-targeted interventions. Such requirements are increasingly met by innovative *in vitro* models that will be further discussed throughout this article.

2.2. Structural and mechanical effects of aging on the dermis

Aging significantly impacts dermal structure and function. The dermis—composed of a rich ECM of collagens, elastic fibers, and proteoglycans—becomes progressively thinner with age (Marcos-Garcés et al., 2014), due to reduced collagen, proteoglycan, and water content (Ahmed et al., 2017), and these changes occur alongside an increase in collagen fiber fragmentation (Fisher et al., 2009) and cross-linking (Yamauchi et al., 1988). The hypodermis and white adipose content are likewise reduced in aged skin (Kotani et al., 1994).

These ECM alterations lead to complex changes in tissue mechanics. Many *in vivo* and *ex vivo* mechanical analyses report increased stiffness and decreased recoil in aged skin (Agache et al., 1980; Boyer et al., 2009; Escoffier et al., 1989; Grahame, 1970; Jansen and Rottier, 1958; Lynch et al., 2017), although some studies show reduced stiffness depending on measurement scale and anatomical location (Blair et al., 2020; Boyer et al., 2012; Park, 2022; Sanders, 1973). Nanoscale analyses indicate intrinsically stiffer collagen fibers and greater stiffening of the reticular versus papillary dermis in aged skin (Achterberg et al., 2014; He et al., 2023). Age-associated biomechanical changes arise from both an intrinsic decline in ECM biosynthesis and remodeling and extrinsic factors such as UVR-induced oxidative damage, matrix metalloproteinase (MMP) activation, and collagen cross-linking (He et al., 2023; Shao et al., 2019). Differences in sun exposure, sex, and ancestry further influence aged skin mechanics (Grahame, 1970; Langton et al., 2017; Wilkinson and Hardman, 2021).

While it is clear that the skin experiences significant biomechanical changes with age, the functional impact of altered biomechanics on cell behavior and tissue function is not fully understood, and tractable experimental models are needed to directly dissect these relationships. Approaches such as cross-linked collagen matrices and mechanically tunable hydrogels (**see Section 4.3**) provide *in vitro* platforms for investigating the mechanobiology of skin aging.

2.3. Hair follicle and appendage aging

The pilosebaceous unit, including the hair follicle and its associated sebaceous gland, exhibits widely recognizable age-associated changes. During puberty, there is striking transformation of fine and nearly invisible hairs (produced by low sebum-secreting vellus hair follicles) to coarse, terminal hairs on certain body sites (e.g., the male chin) produced by high sebum-secreting pigmented hair follicles (Randall, 2008). By contrast, miniaturization of scalp hair fibers occurs during age-related male pattern alopecia (common baldness) (Randall, 2008). This age-associated change does not significantly alter the absolute number of pilosebaceous units on the scalp until very late in life ('senescent alopecia') (Deng et al., 2023). Sebaceous glands by contrast, become hyperplastic in balding skin but with reduced sebum production contributing to xerosis (dryness) of aged skin (Hou et al., 2022). Sebum secretion is also significantly reduced in postmenopausal women, suggesting these glands are estrogen sensitive (Thornton, 2013).

Hair graying results from specific depletion of melanocytes from anagen hair bulbs, less so from the outer root sheath and sebaceous gland (Paus et al., 2024). This change is likely due to increasing instability of bulbar melanocytes and reduced survival of melanocyte stem cells due in part to oxidative stress (Kauser et al., 2011; Paus et al., 2024). Graying is also associated with a concomitant change in hair fiber structure, with evidence that gray and white hair fibers exhibit different mechanical properties (Bechthold et al., 2018). Pigment-free hairs are not only coarser but can be wavier with a more prominent medulla than pigmented hairs, and the average diameter of white hair fibers may be significantly greater than in pigmented hairs. Surprisingly, they may grow faster than pigmented hair (Paus et al., 2024).

Finally, aged skin also has fewer eccrine sweat glands, and both eccrine and apocrine glands become smaller (Rittié and Fisher, 2015). The reduction in sweating capacity can therefore contribute to impaired thermoregulation in older people. Effective modeling of appendage aging *in vitro* requires preservation of epithelial–mesenchymal interactions and melanocyte stem cell dynamics. Advanced hair follicle organoids and *ex vivo* follicle cultures (see **Section 4.4**) now offer powerful systems for dissecting mechanisms underlying alopecia, pigmentation decline, and sebaceous gland dysfunction, and for testing targeted interventions.

2.4. Cellular senescence

Cellular senescence is a key contributor to tissue aging and characterized by a stable cell-cycle arrest together with active metabolic and secretory functions that influence the surrounding microenvironment. Although senescent cells lose the ability to divide, they remain viable and metabolically active. Senescent cells acquire a number of distinct phenotypic features that contribute to tissue dysfunction and organismal aging (Baker et al., 2011; Herranz and Gil, 2018). Cellular senescence induces progressive changes in cellular morphology involving increased cell volume, flattened shape with numerous extensions and increased granularity (Zhang et al., 2020). Additionally, cell cycle inhibitors, such as p21 and p16, are upregulated while gene expression profiles, chromatin organization, and protein metabolism are progressively dysregulated (Shelton et al., 1999; Trougakos et al., 2006; Zhang et al., 2007). Senescent cells have a characteristic secretory phenotype called the SASP (senescence-associated secretory phenotype) (Coppé et al., 2008) that is induced by the DNA damage response (DDR) (Rodier et al., 2009) following telomere shortening or exposure to DNA damaging agents (IJpma and Greider, 2003). Consequently, increased expression of pro-inflammatory cytokines and chemokines, growth factors and MMPs can lead to changes in the structure and function of the surrounding tissue.

Aging skin displays a classical accumulation of senescent cells, notably fibroblasts within the dermis (Ressler et al., 2006; Zhang et al., 2024). While the continued turnover of the epidermis facilitates removal

of senescent keratinocytes under normal homeostatic conditions, senescent keratinocytes have been observed in pre-cancerous actinic keratoses (Azazmeh et al., 2020; Hodges and Smoller, 2002; Wang et al., 2022) and following direct exposure to UVR, suggesting that keratinocyte senescence might contribute to aging of photo-damaged skin (Wang et al., 2017). Recent studies also indicate that senescent melanocytes accumulate in the aging epidermis and can hinder keratinocyte proliferation through paracrine effects (Victorelli et al., 2019). Moreover, melanocytic naevi are comprised of oncogene-induced senescent melanocytes (Michaloglou et al., 2005). Nevertheless, the functional impact of different senescence triggers and cell types on tissue-level aging is not fully understood. Because senescent cells accumulate in specific niches and exert profound paracrine effects on neighboring cells, accurately modeling their spatial distribution and SASP dynamics is essential. Incorporating senescent cell heterogeneity, stability of growth arrest, and SASP dynamics into 3D human skin equivalents and microfluidic platforms is expected to improve the prediction of tissue-level aging dysfunction and therapeutic responses (see **Sections 4.1 and 6.2**).

2.5. Accumulation of DNA damage

Senescence in skin cells occurs due to a complex interplay of extrinsic and intrinsic factors, with DNA damage playing a crucial role (Ho and Dreesen, 2021). Increased DNA damage is a hallmark and mediator of cellular senescence, with persistent DNA damage in telomeric and non-telomeric regions being a main driver (Rodier et al., 2009). DNA damage impacts skin aging both directly and indirectly. Accumulation of DNA mutations over time leads to genomic instability and cellular senescence, evidenced by increased dysfunctional telomeres in aged skin cells such as fibroblasts and melanocytes[54,56]. Studies on premature aging syndromes reveal that increased reactive oxygen species (ROS) and oxidative stress lead to DNA damage and mitochondrial dysfunction, linking DNA damage with disrupted redox balance and cellular bioenergetics (Pallardó et al., 2010). This link is particularly well-documented in skin aging (Kammeyer and Luiten, 2015), with manifestations like hair graying resulting from cumulative oxidative and DNA damage, mitochondrial dysfunction, and DNA mutations in cutaneous epithelial and hair follicle dermal papilla cells (Dai et al., 2023; Natarelli et al., 2024). Additional exposome factors (particulate matter, PM; polyaromatic hydrocarbons, PAHs; tobacco smoke; heavy metals; microplastics) can also inflict direct and indirect damage to skin cell DNA and trigger senescence (Panich et al., 2016; Samra et al., 2024; Schuch et al., 2017).

DNA damage also affects stem cell function, leading to cell exhaustion, reduced self-renewal capacity, and impaired tissue repair and regeneration (Panich et al., 2016; Peng et al., 2015). Cells that evade senescence may proliferate despite DNA damage, contributing to cellular transformation and malignancies, as seen in UV-irradiated cells (Lewis et al., 2008). Recent evidence shows that senescent melanocytes induce paracrine telomere damage during skin aging, potentially driving the propagation of senescent cells (Victorelli and Passos, 2020). Conditioned medium from senescent melanocytes can induce telomere dysfunction and reduce dermal fibroblast proliferation, with similar effects observed in keratinocytes, suggesting that SASP components secreted by senescent melanocytes mediate these adverse paracrine effects (Victorelli and Passos, 2020). Together, these findings indicate that DNA damage is both a hallmark and an active driver of cellular senescence, amplifying autocrine and paracrine aging processes within skin.

These mechanisms highlight the need for models that can induce and sustain chronic UVR or oxidative stress to mimic cumulative photodamage and stem cell decline. Human skin equivalents and skin explants (see **Section 5.1**) are particularly suited for studying mutational load, repair capacity, and early carcinogenic events linked to aged skin phenotypes.

2.6. Age-related changes in metabolism

Aging disrupts cellular metabolism and proteostasis in skin, leading to the accumulation of damaged proteins and organelles. Proteasomal activity and autophagic flux are reduced in aged keratinocytes and fibroblasts, undermining key quality-control pathways (Chapman et al., 2019; Chondrogianni et al., 2015, 2008; Soroka et al., 2008). Mitochondrial dysfunction further increases ROS production and decreases metabolic efficiency, linking impaired oxidative phosphorylation with elevated oxidative stress (Bakula and Scheibye-Knudsen, 2020; Cavinato et al., 2024; Chapman et al., 2019). These processes reinforce each other, driving a cycle of damage accumulation and maladaptive stress responses. Evidence also suggests that altered lysosomal and autophagic substrate clearance plays a direct role in dermal and epidermal aging (Cavinato et al., 2017; Guerrero-Navarro et al., 2024a; Ma et al., 2022). Additionally, the activity of key stress response regulators, including AMPK and SIRT1, declines with age, further diminishing metabolic flexibility (Cao et al., 2009).

Because metabolic dysfunction manifests differently across cutaneous cell types, *in vitro* aging models benefit from controlled manipulation of mitochondrial activity and proteostasis pathways to capture these diverse phenotypes. Incorporating metabolic readouts—such as oxygen consumption, redox status, and autophagic flux—into 3D human skin equivalents and co-culture systems (see **Sections 4.1 and 5.2**) offers a more precise framework for assessing metabolic roles in senescence, impaired ECM remodeling, and delayed wound healing. These platforms are ideal for testing interventions that target cellular metabolism in aged skin.

2.7. Lipid markers of skin aging and photoaging

A prominent feature of skin aging is xerosis, characterized by a compromised skin barrier and reduced hydration (Görög et al., 2022). This phenotype reflects alterations in lipid composition, which is essential for maintaining skin integrity (Feingold and Elias, 2014), and thus, lipid damage is central to both intrinsic and extrinsic skin aging (Gruber et al., 2020b).

Skin surface lipids (SSLs), composed of epidermal and sebaceous lipids, form the first-line protective barrier against external stressors like UVR (Valacchi et al., 2010; Zouboulis et al., 2008). While SSLs absorb and protect against UVA and UVB, squalene photooxidation products can also mediate metabolic and inflammatory responses of keratinocytes to UVR exposure (Kostyuk et al., 2012). Squalene hydroperoxide, for example, is associated with chronic sun damage and photoaging (Gabe et al., 2021; Kostyuk et al., 2012). Likewise, phospholipids, free fatty acids, and cholesterol are all targets of UVR-induced oxidative stress, generating bioactive mediators like eicosanoids (Wölfle et al., 2014), and these bioactive lipids can provide signals for activating inflammation, senescence, and autophagy in photodamaged skin (Gresham et al., 1996; Gruber et al., 2020a; Ma et al., 2022; Narzt et al., 2021; Rockenfeller et al., 2016).

Together, the senescence-associated lipid profile, characterized by lipid accumulation, oxidative modifications, and adduct formation between reactive carbonyl species (RCS) and amino acids in proteins, is a major feature of skin aging (Chin et al., 2023; Gruber et al., 2020a; Negre-Salvayre and Salvayre, 2022). Aldehydes from lipid peroxidation, like 4-hydroxynonenal (4-HNE), acrolein, and malondialdehyde, are some of the most notable RCS and accumulate in photoaged skin (Guéraud et al., 2010; Jørgensen et al., 2014; Negre-Salvayre and Salvayre, 2022; Rabbani and Thornalley, 2015; Zhang and Forman, 2017). While it is clear that aging has widespread and complex effects on skin lipids, the functional relationships between specific age-associated changes in lipid composition and skin health are not well defined.

In vitro models of aging skin benefit from incorporating physiologically relevant lipid compositions and controlled oxidative stress to reproduce barrier impairment. Experimental approaches that induce

pollutant- or UV-driven lipid peroxidation (see **Section 5.2**) are particularly useful for studying barrier decline and for evaluating lipid-restoring or antioxidant interventions.

2.8. Advanced glycation end products (AGEs)

AGEs are a heterogeneous group of molecular modifications formed through glycation, i.e. non-enzymatic reactions between reducing sugars and proteins, lipids, or nucleic acids, leading to the formation of stable adducts (Maillard reaction) (Waseem et al., 2023). Excessive AGE formation and accumulation occurs in diabetes and chronic inflammatory conditions, across a range of adult human tissues, including the skin (Prasad et al., 2019; Vlassara and Uribarri, 2014). Consequently, the accumulation of AGEs in the skin increases linearly with age (Kellow et al., 2018; Verzijl et al., 2000), contributing to tissue stiffening and loss of elasticity (Huijberts et al., 2008; Lee et al., 2016; Pageon et al., 2014; Yoshinaga et al., 2012). Moreover, AGEs are involved in the pathogenesis of various skin complications in chronic metabolic diseases, such as diabetic skin ulcers, infections, and non-healing wounds (de Macedo et al., 2016; Ohshima et al., 2009). Because the glycation process is slow due to the absence of enzymes, proteins with a slow turnover rate, such as ECM proteins, are primary targets of glycation in the skin (Havas et al., 2022). The toxicity of AGEs arises not only from the altered physicochemical properties of the glycated proteins, but also in their interaction with the multi-ligand receptors for AGEs (RAGE). RAGE, a member of the immunoglobulin superfamily, is expressed on the surface of various epidermal and dermal cells, especially in sun-exposed areas of the skin (Lohwasser et al., 2006). Activation of RAGE by various AGEs triggers signaling cascades that reduce cellular proliferation and migration, promote cellular senescence and apoptosis, decrease ECM synthesis, increase collagen cross-linking, and increase formation of reactive species and pro-inflammatory mediators (Bierhaus et al., 2005).

Because AGE-driven changes integrate mechanical, metabolic, and inflammatory aspects of aging, *in vitro* models benefit from ECM systems that mimic collagen crosslinking and altered matrix architecture. Tunable biomaterials and preglycated collagen matrices (see **Section 4.3**) offer suitable platforms for studying how AGEs influence fibroblast behavior, matrix remodeling, and inflammation, and for testing interventions aimed at preventing or reversing glycation-associated dysfunction.

2.9. Inflammaging and age-related changes in immunity

Skin inflammaging, a term coined to describe the age-related chronic, low-grade inflammation in the skin (Pilkington et al., 2021), manifests through a myriad of clinical phenotypes that negatively impact skin function. Dysregulation of the innate immune system is suggested to play a pivotal role in driving skin inflammaging (Zhuang and Lyga, 2014). Age-related changes in the expression and activity of pattern recognition receptors, such as toll-like receptors (TLRs) (Iram et al., 2012) or NLR family pyrin domain containing 3 (NLRP3), lead to heightened immune activation and cytokine production in response to endogenous and exogenous stimuli (Salminen et al., 2025). Moreover, cellular senescence and the SASP amplify the inflammatory milieu within the skin microenvironment (Rodier et al., 2009).

The upregulation of pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α) further disrupts barrier function, perpetuating a cycle of inflammation and barrier impairment (Junghans et al., 1998; Macleod et al., 2021). UVR and ROS activate nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), triggering inflammatory cascades(Yaar and Gilchrest, 2007). This chronic low-grade inflammation accelerates the degradation of ECM components such as collagen and elastin, contributing to the loss of skin elasticity and resilience (O'Brien et al., 2019). In addition, exposure of the skin to pollution can further exacerbate the inflammatory state (Valacchi et al., 2012).

The emergence of senile purpura underscores the vascular component of skin inflammaging (Rayner et al., 2019). Fragile blood vessels and impaired hemostasis render the skin prone to spontaneous bruising and petechiae formation. Endothelial dysfunction, characterized by decreased nitric oxide bioavailability and increased vascular permeability, contributes to vascular fragility. Additionally, age-related alterations in the microcirculation, including capillary rarefaction and vascular basement membrane thickening, exacerbate tissue hypoxia and compromise nutrient delivery to the skin (Camargo and Gemperli, 2018).

Immunosenescence, which is the gradual decline of the immune system that occurs with aging, reduces the skin's capacity to defend against infections, inflammation and skin cancer (Pająk et al., 2023; Sunderkötter et al., 1997). One of the key mechanisms of immunosenescence is the reduced function of skin-resident antigen presenting cells, particularly Langerhans cells and dermal dendritic cells, which play crucial roles in recognizing and responding to pathogens (Chambers and Vukmanovic-Stejic, 2020). Additionally, the gradual involution of the thymus and, consequently, diminished thymopoiesis leads to shrinking of the naïve T cell pool and the ability to respond to novel antigens (Nacka-Aleksić et al., 2019; Pido-Lopez et al., 2001). The decline of T cell function in aged individuals (Zhang et al., 2021), characterized by the exhaustion and functional suppression of effector T cells through programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) signaling (Chambers and Vukmanovic-Stejic, 2020; Papa et al., 2023), leads to diminished capacity to mount effective T cell responses in the skin, contributing to an increased susceptibility to skin infections and malignancies such as melanoma and other skin cancers (Ahmadzadeh et al., 2008; Clark et al., 2008). This is further facilitated by the accumulation of peripheral $Foxp3^+$ T regulatory (Treg) cells in the skin, which might skew the immune microenvironment and attenuate adaptive immune responses (Lages et al., 2008).

Together, inflammaging and immunosenescence, in conjunction with impaired barrier function, create a permissive environment for chronic inflammation, impaired defense, and tumor development. *In vitro* models that incorporate resident immune cells or permit controlled immune cell trafficking (see **Sections 4.1 and 6.2**) provide new opportunities to study these age-related immune alterations and to evaluate interventions that target chronic inflammation or immune decline.

2.10. The aging microbiome

The surface of the skin is colonized by a complex population of commensal microbiota that play an essential role in the prevention of pathogen colonization, the education of immune system, and the breakdown of natural products, which are beneficial for skin health (Byrd et al., 2018). These populations interact heavily among themselves, resulting in a dynamic and continuous crosstalk with the skin (Sfriso et al., 2020). As skin ages, the protective barrier capacity is diminished providing a gateway for the potential colonization of opportunistic and pathogenic bacteria (Blume-Peytavi et al., 2016; Choi et al., 2007). Thus, skin aging is a process that entails the alteration of the dominant bacteria of skin (Shibagaki et al., 2017). However, the directionality and functional consequences of microbiome shifts during intrinsic aging remain poorly understood. Thus, determining direct causality of altered microbiomes in aging will be an important question in future studies. Incorporating microbiome components into reconstructed human skin equivalents (see **Section 6.3**) will support the study of barrier decline and direct mechanistic testing of microbe–host interactions skin aging.

3. Two-dimensional (2D) models of skin aging and limitations

In vitro human cell culture is essential for studying skin aging mechanisms. Simple 2D models, where isolated cells grow on plastic in

optimized media, are accessible, affordable, and flexible. They allow research on primary keratinocytes, fibroblasts, or melanocytes from human skin to investigate cellular and molecular aging processes. These models use stimuli like oxidative stress, DNA damage, mitochondrial dysfunction, replicative senescence (RS), and ECM manipulation to induce aging-associated phenotypes *in vitro*. Induction of cellular senescence can be achieved through simple and cost-effective triggers, such as serial passaging, oncogene activation, radiation exposure, or treatment with DNA-damaging and ROS-producing agents.

One of the key advantages of 2D models is their flexibility in experimental design. Genetic engineering technologies, such as RNA interference or CRISPR/Cas9, can be easily employed to study the roles of specific genes or pathways in aging processes (Colville et al., 2023; Tyler et al., 2021). Simple co-culture systems allow researchers to examine cell-cell interactions, such as the crosstalk between keratinocytes and fibroblasts, or the impact of melanocytes on keratinocyte pigmentation and aging. Tunable 2D models also easily facilitate the exploration of how external factors, such as UV radiation or pollutants, influence cellular responses within a controlled experimental environment. Moreover, 2D models are highly scalable and advantageous for genetic or compound screening (Chen et al., 2025).

Many 2D models used to study skin aging rely on primary skin cells obtained directly from human biopsies. Fibroblasts, keratinocytes, and melanocytes retain donor-specific aging signatures and allow investigation of intrinsic cellular aging, including changes in morphology, proliferation, senescence marker profiles, and stress responses (Nedachi et al., 2023; Rorteau et al., 2022). Although 2D models do not replicate the multicellular and structural complexity of skin, they remain a fundamental tool for understanding the mechanisms of age-related phenotypes.

3.1. Methods for inducing aging phenotypes in 2D cultures

3.1.1. Oxidative stress

Oxidative stress can easily be induced *in vitro* with addition of oxidizing agents, such as H_2O_2, to the culture medium, but the response can vary depending on factors such as cell type, exposure duration, and the intensity of the applied stress (Kamat et al., 2025; Wallis et al., 2022). Similarly, treatment with tert-butyl hyperoxide (tBHP) generates ROS and represents another inducer of cellular senescence (Kim et al., 2008). Additional agents such as paraquat, 2,2′-azobis(2-amidinopropane) dihydrochloride (AAPH), or D-galactose elevate intracellular ROS, linking redox imbalance to mitochondrial dysfunction (Chinta et al., 2018; Gu et al., 2022; Nacka-Aleksić et al., 2025). Similarly, the mitochondrial complex I inhibitor rotenone was used in skin fibroblasts to activate expression of cellular senescence markers (Waaijer et al., 2018).

3.1.2. UV Radiation

Both UVA and UVB irradiation are used to trigger senescence in keratinocytes and fibroblasts *in vitro* (Cao et al., 2009; Hur et al., 2022; Liu et al., 2018). The sensitivity to both types of UVR varies between cell types and with donor age, whereby cells from older donors demonstrate greater resistance to oxidative stress compared to cells from younger donors (Matsuo et al., 2004). UVR induced senescence can be variable or unstable, single PUVA (8-methoxy psoralen plus UVA) treatment has also been explored for establishing long-lasting growth arrest with morphological changes and gene expression indicative of cellular senescence (Herrmann et al., 1998).

3.1.3. Replicative senescence (RS)

RS induced by telomere erosion and associated DNA damage responses can also be induced *in vitro* by long term culture and serial passaging of cells. This approach has been used to model intrinsic aging of fibroblasts (Kamat et al., 2025; Noren Hooten and Evans, 2017; Wallis et al., 2022). RS is also a critical phenomenon in understanding the aging process of melanocytes, which like other cells, undergo RS in culture after a certain number of divisions, leading to decreased proliferation and altered functionality (Victorelli et al., 2019). RS can also be induced in keratinocytes *in vitro*, but the physiological relevance of keratinocyte RS is a matter of debate, as most keratinocytes *in vivo* will undergo terminal differentiation before approaching critical telomere shortening (Victorelli et al., 2019). By contrast, UVR-induced senescence may be more relevant for keratinocytes, particularly in the context of photo-aging and precancerous lesions (Hodges and Smoller, 2002; Wang et al., 2022).

3.2. Critical challenges in 2D aging models

Inter-donor variability poses a significant challenge for modeling aging *in vitro*, as cells isolated from different donors often require optimization of senescence-inducing conditions to achieve stable yet non-toxic growth arrest. Other key factors influencing cellular stress sensitivity include seeding density, donor age and body site, the clonal makeup of expanded cells, and the number of passages post-isolation. It also remains unclear whether the dosage of certain senescence triggers, such as ROS, and levels of DNA damage are physiologically relevant, despite effectively inducing a stable senescent state *in vitro*. It is also crucial to choose appropriate controls. In many studies, senescent cells are only compared with proliferating cells, even though human skin cells do not continually divide *in vivo*. Therefore, quiescent yet growth-capable cells provide a more physiologically relevant comparison and can be induced by contact inhibition or growth factor withdrawal. Lastly, because senescence is heterogeneous and no single marker is fully specific, confirming that the culture contains a high proportion of senescent cells at the time of analysis requires a multi-marker panel that includes cell-cycle arrest, DDR activation, morphological changes, and SASP-related features (González-Gualda et al., 2021). In addition, senescence is a dynamic, multistep process. After the initial stimulus, cells require several days to undergo chromatin remodeling and to establish a mature SASP profile, progressing into “full” or “deep” senescence (Herranz and Gil, 2018). These temporary dynamics must be accounted for when designing experiments, selecting endpoints and comparing studies across platforms.

In conclusion, 2D *in vitro* skin models offer significant advantages, including simplicity, cost-effectiveness, reproducibility, and ease of manipulation, making them well-suited for high-throughput screening and mechanistic studies. However, their two-dimensional configuration limits their physiological relevance, as they lack complex tissue architectures such as the stratified epidermis, epidermal-dermal junctions, appendages, and native ECM organization. Standard cell culture conditions - rigid tissue culture plastics, supra-physiological oxygen levels, and growth-promoting, serum-supplemented media – differ from the *in vivo* skin microenvironment and can alter cellular behavior. These models also fail to capture interactions with the vasculature, immune system, and the microbiome—elements that are crucial in skin aging processes. Consequently, 2D systems have lower predictive power for clinical outcomes than 3D models or *in vivo* studies (Quílez et al., 2024). Despite these limitations, 2D models remain valuable for preliminary screening; however, integrating them with 3D models, organoids, or organ-on-a-chip systems could substantially improve their predictive capabilities (Fig. 2).

4. 3D models of intrinsic skin aging

As outlined above, skin aging is a highly complex process and involves crosstalk between many different cell types, the external environment, and the immune system, which are challenging to capture in simple 2D cultures. Accordingly, numerous recent efforts have focused on developing more physiologically relevant *in vitro* skin models using 3D culture systems that better recapitulate tissue architecture, mechanical properties, and microenvironmental cues that shape aging phenotypes. In this section, we describe how 3D skin models can be

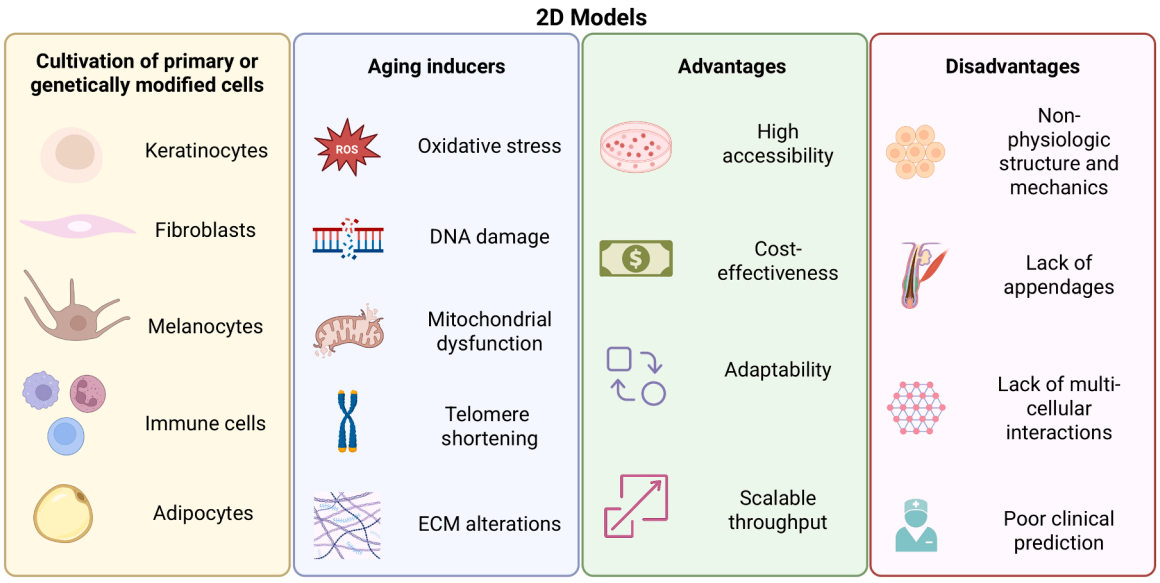

Fig. 2. Overview of 2D models for studying skin aging. Summary of 2D *in vitro* approaches to model skin aging. Primary cells (keratinocytes, fibroblasts, melanocytes) and supportive cell types (immune cells, adipocytes) can be cultured and exposed to various aging inducers, including oxidative stress (ROS), DNA damage, mitochondrial dysfunction, telomere shortening, and ECM alterations. These models offer significant advantages, including high accessibility, cost-effectiveness, adaptability, and scalable throughput for screening studies. However, limitations include non-physiological structures and mechanics, lack of skin appendages, absence of multicellular interactions, and poorer clinical prediction than in more complex 3D models.

constructed and applied to investigating mechanisms of intrinsic skin aging (Fig. 3).

4.1. *3D models of intrinsic skin aging: effects of donor age and senescence*

4.1.1. *Effects of donor cell age*

To date, several *in vitro* models have been developed from primary human skin cells to better characterize the aging process. The reconstructed 3D human skin equivalent (HSE) is one of the most well-

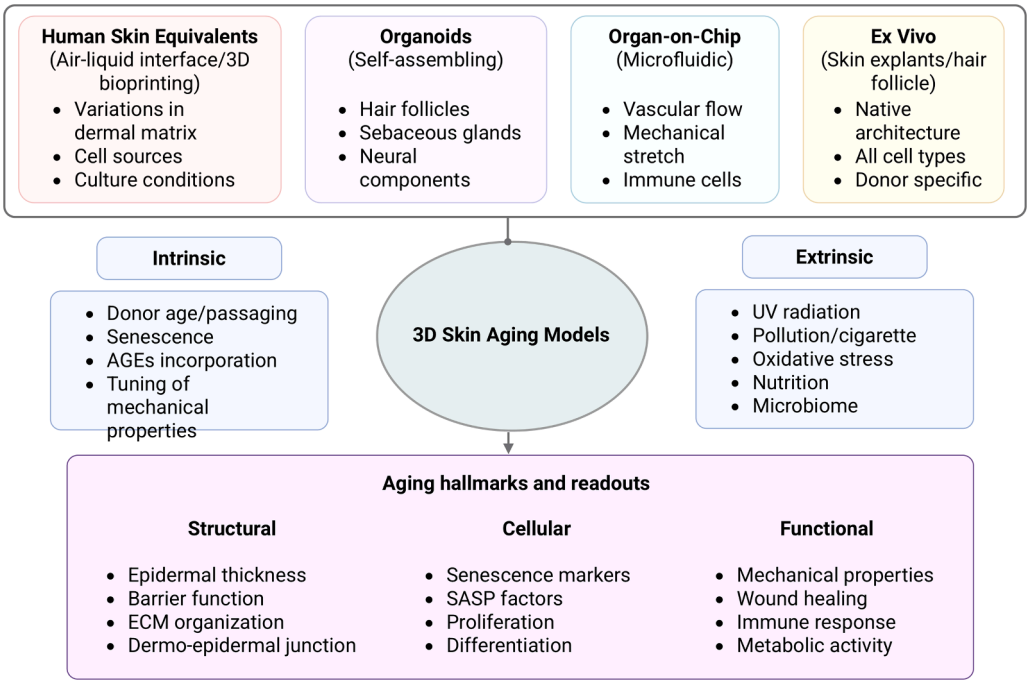

Fig. 3. 3D models of skin aging. Comprehensive framework for 3D *in vitro* skin aging models. Four main model types are shown: Human Skin Equivalents (HSE) with customizable dermal matrices and culture conditions; self-assembling organoids containing hair follicles, sebaceous glands, and neural components; microfluidic organ-on-chip platforms enabling vascular flow, mechanical stretch, and immune cell integration; and *ex vivo* skin explants and hair follicle organ cultures preserving native architecture with all endogenous cell types. These models can incorporate both intrinsic aging factors (donor age/passaging, cellular senescence, AGEs, tunable mechanics) and extrinsic stressors (UV radiation, pollution, oxidative stress, nutrition, microbiome). The models enable assessment of multiple aging hallmarks and readouts across structural (epidermal thickness, barrier function, ECM organization, dermo-epidermal junction), cellular (senescence markers, SASP factors, proliferation, differentiation), and functional (mechanical properties, wound healing, immune response, metabolic activity) parameters.

established and utilized 3D models for investigating both intrinsic and extrinsic drivers of skin aging. Briefly, dermal equivalents are first created by culturing fibroblasts within a 3D ECM matrix, typically collagen-based. Keratinocytes are subsequently seeded onto the dermal equivalents and cultured at the air-liquid interface for 10 or more days (Duplan-Perrat et al., 2000). A number of variations in the dermal matrix, cell sources, and culture conditions have been employed for HSEs, and have recently been reviewed elsewhere (Quílez et al., 2024).

Using the HSE model, it has been shown that fibroblasts isolated from an older donor (49 years old) induced a thinner and disorganized epidermis, along with an impairment of fibroblast collagen and fibrillin gene expression, when compared to HSEs generated from a younger donor (19 years old) (Lacroix et al., 2007). Similar studies investigating the impact of donor age on the phenotype of HSEs demonstrated that HSEs created with keratinocytes from older donors displayed a disorganized basal cell layer with reduced Ki67 expression, reduced spinous and granular layers, and impaired differentiation, evidenced by decreased filaggrin immunostaining (Adamus et al., 2014). In addition, over very long-term culture periods (120 days), HSEs prepared with young donor cells acquired a similar pattern of human aged skin, including decreased expression of keratinocyte differentiation markers, reduction of hyaluronan, and an increase of senescent markers such as p16 (Dos Santos et al., 2015). Overall, the use of skin cells from donors of different ages generally replicates some key hallmarks of aging skin, but variation between different donors presents challenges for precisely dissecting causative relationships and underlying mechanisms. This variability reflects true biological heterogeneity yet underscores the need for careful donor selection, standardized culture conditions, and appropriate controls to accurately interpret intrinsic aging mechanisms.

4.1.2. Senescence-driven aging in HSEs

As previously discussed, cellular senescence can be activated by distinct triggers in cultured skin cells and therefore provides a controllable strategy to mimic aging within HSE models. For example, overexpression of p16 in young keratinocytes can be used to increase the number of epidermal senescent cells in HSEs (Adamus et al., 2014). Another model of transgenic HSEs mimicking aged skin was obtained by over-expression of the age-induced miR-30a in primary keratinocytes (Muther et al., 2017). The model displayed several features of aged epidermis, including impairment of epidermal barrier, increased cell death, and defects in the mitophagy pathway (Chevalier et al., 2022).

Likewise, inclusion of senescent fibroblasts in the dermal matrix of HSEs replicates key aspects of aging skin. The addition of ROS-induced senescent fibroblasts (H_2O_2 treatment) reduced epidermal thickness and barrier function of HSEs; however, no dermal impairment was observed (Weinmüllner et al., 2020). This dissociation suggests that epidermal effects dominate in models with senescent fibroblasts, likely via SASP factors rather than via direct contact or structural changes.

Similarly, HSEs prepared with serially passaged fibroblasts showed dermal changes akin to aged skin (Janson et al., 2013), while fibroblasts with premature senescence induced by GDF15 depletion promoted decreased epidermal thickness, mirroring intrinsic skin aging (Wedel et al., 2023). Others have also demonstrated that HSEs with premature senescent fibroblasts induced by depletion of a calcium-activated chloride channel accessory protein showed impaired epidermal differentiation and reduced thickness (Guerrero-Navarro et al., 2024b). These studies underscore the significance of intercellular communication, particularly through the SASP, in skin function and aging. In addition, they highlight the experimental advantages of using donor-matched proliferative and senescent cells to study direct mechanisms of skin aging and the importance of maintaining spatial organization and temporal dynamics of senescent cells within 3D models, as the magnitude and composition of SASP vary with cell type, senescence trigger, and culture duration. Future HSE studies incorporating donor-matched comparisons of senescent and proliferating cells, multiparameter SASP profiling, and analysis of senescent cell heterogeneity will enhance mechanistic understanding and validate targets for senotherapy.

4.2. Incorporation of AGEs in models of skin aging

As AGEs are another key hallmark of aged skin (Kellow et al., 2018; Pageon et al., 2014), incorporating AGEs into *in vitro* skin models enables investigation of their role in promoting cellular senescence, oxidative stress, collagen degradation and remodeling, cellular signaling pathways and gene expression, but also development of novel therapeutic strategies to inhibit AGE formation or remove their adducts from the skin. AGE-modified biomolecules represent a distinct aging driver that can act synergistically with cellular senescence and oxidative stress, making their incorporation into 3D models particularly valuable for understanding multifactorial mechanisms of skin aging.

Common AGEs used for *in vitro* skin research include glycolaldehyde- or glucose-modified (Masaki et al., 1999), bovine serum albumin (Xu et al., 2018) (BSA-AGE), D-glucose-glycated bovine type I collagen (AGE-collagen), or collagen treated with sodium cyanoborohydride and sodium glyoxylate acid (Alikhani et al., 2007). Such AGEs can be incorporated into culture medium with photoaged human dermal fibroblasts (Alikhani et al., 2007; Masaki et al., 1999) or full-thickness HSEs (Lee et al., 2016). In other studies, reconstructed skin models with a modified dermal compartment prepared with preglycated collagen were developed (Pageon et al., 2014; Pageon and Asselineau, 2005; Pennacchi et al., 2015). Also, glycation can be induced *in situ* within HSEs by exposing the reconstructed epidermis to glycating agents (e.g., glyoxal) in the culture medium, more closely mimicking the slow, endogenous accumulation of AGEs *in vivo* (Yokota and Tokudome, 2016).

Introducing AGEs to skin models results in a range of phenotypic changes, which contribute to the visible signs of aging and increased vulnerability to skin damage. One of the primary effects of AGEs on skin models is the disruption of the ECM (Pageon et al., 2014; Pageon and Asselineau, 2005). AGEs non-enzymatically bind to collagen and elastin fibers and form cross-links that decrease their flexibility and increase their stiffness, while at the same time stimulating MMP activity (Pageon et al., 2014). The accumulation of AGEs and prolonged stimulation of RAGEs within HSE models could also be used to investigate altered inflammatory responses in aged skin. Finally, AGEs can interfere with skin barrier integrity. The glycation process can damage lipid structures, leading to a compromised barrier that is more prone to dehydration and environmental damage. This weakened barrier increases the risk of infections and reduces the skin's ability to retain moisture (Lee et al., 2017; Park et al., 2011; Yokota and Tokudome, 2016).

4.3. Modeling age-associated changes in skin mechanics

There are also several approaches to modelling the biomechanics of aged skin and investigating the impacts on cell and tissue function (Bajpai et al., 2021). As detailed in Section 2.2, aged skin exhibits complex biomechanical changes, including increased stiffness, altered collagen organization, and reduced viscoelasticity. The ability of cells to sense and respond to their mechanical environment is well established across nearly all tissues and organs, including the skin (Biggs et al., 2020; Vining and Mooney, 2017). For example, tissue stiffening can stimulate keratinocyte proliferation (Kenny et al., 2018) and promote myofibroblast differentiation and fibrotic phenotypes in dermal fibroblasts (Younesi et al., 2024), while reduced ECM stiffness can trigger keratinocyte terminal differentiation (Trappmann et al., 2011). To understand the causative relationships between mechanical cues and cellular responses, *in vitro* models with tunable mechanical properties have become essential tools in the field of mechanobiology. These models can include simple 2D hydrogel or elastomer coatings, in which the elastic moduli can be precisely controlled by the polymer cross-linking or weight percentage (Kenny et al., 2018; Laly et al., 2021; Pelham and Wang, 1997). Recent studies have also expanded the use of

mechanically tunable materials to the dermal support matrices in 3D skin equivalent models. For example, increasing the collagen cross-linking (Meng and Shen, 2018) or weight percentage of fibrin hydrogels (Montero et al., 2021) has been used to increase the rigidity of the dermal component and limit contraction. Tensional homeostasis within 3D models has been shown to play a critical role in fibroblast behavior and ECM remodeling (Kimura et al., 2020).

However, only a few studies have directly investigated the impact of tissue mechanics on the skin aging phenotype. This represents a significant knowledge gap, as mechanical cues could profoundly influence senescence, the SASP, and regenerative capacity. On 2D hydrogel substrates, reduced ECM stiffness reversibly downregulates expression of senescence markers, such as p21, in senescent cells (Starich et al., 2024). Senescent fibroblasts have also been shown to possess intrinsic changes in their cytoskeleton and mechanotransduction machinery, which impacts their force-sensing ability (Rebehn et al., 2023). While these studies highlight the importance of the interplay between tissue biomechanics and cellular senescence, future research should examine a wider range of age-associated cellular phenotypes, determine the underlying molecular mechanisms, and explore these relationships in more physiologic 3D environments. The use of 3D *in vitro* models with tunable mechanics (Meng and Shen, 2018; Montero et al., 2021), age-associated non-enzymatic cross-linking (Mason et al., 2013), and purified matrices from young and old tissues may provide new opportunities to manipulate and study different aspects of aging skin mechanics (Choi et al., 2011). In addition to modeling the effects of skin elasticity, viscoelastic responses are a key consideration in aging skin and require further investigation. Here, the use of hydrogels with independently adjustable elastic and viscous behaviors could be valuable tools, and recent studies have shown that mesenchymal stem cells display distinct cellular responses to elastic and viscous cues (Chaudhuri et al., 2016).

4.4. Aging hair follicle models

The human hair follicle is a highly complex and dynamic structure. It consists of an intricate 3D arrangement of multiple cell types, and it undergoes a cycle of growth, regression, and resting phases. Critical for hair growth is the interplay between the epithelia and the dermal papilla (DP), specialized mesenchymal cells that orchestrate hair morphogenesis and cycling (Morgan, 2014). *In vitro* modeling of human hair follicles has therefore been a long-standing challenge, but recent advances in biofabrication and skin organoid technologies have facilitated the development of highly sophisticated *in vitro* models of the hair follicle. For many years, the gold standard involved the *ex vivo* culture of isolated human hair follicles under the appropriate conditions to support hair growth and cycling (Philpott et al., 1990). Recognizing the importance of DP in hair follicle morphogenesis, key studies established 3D spheroid culture models, which were essential for maintaining DP gene signatures and hair inducibility compared to 2D culture (Higgins et al., 2013, 2010). The subsequent combination of DP spheroids with human keratinocytes within a micromolded scaffold mimicked the native hair follicle structure and led to the first *de novo* construction of growing human hair follicles *in vitro* (Abaci et al., 2018). More recently, the cultivation of human pluripotent cells within 3D aggregates and conditions mimicking epithelial and neural crest development has led to the development of skin organoids containing pigmented and innervated pilosebaceous units (Lee et al., 2020).

Although *in vitro* modeling of human hair follicles is still in its early stages, several studies have begun applying these tools to aging research. For example, cultivation of DP from balding and non-balding follicles demonstrated that balding DP were more sensitive to oxidative stress and suggested that DP senescence may contribute to androgenic alopecia in aged scalp (Upton et al., 2015). Similarly, *ex vivo* culture of human hair follicles has implicated Nrf2 as a key mediator of oxidative stress (Haslam et al., 2017), and treatment of DP spheroids with dihydrotestosterone has been used to mimic androgenic alopecia and investigate the role of Wnt/PI3K signaling (Lee et al., 2024; Xiao et al., 2025). A couple of recent studies have also begun to employ skin organoids to investigate DP-vasculature crosstalk in aging (Zhou et al., 2025) and to mimic hair greying through knockdown of pigmentation genes (Tu et al., 2025). These models, therefore, have the potential to provide important fundamental insights into hair follicle aging and become essential tools in the development and testing of therapeutics for the pilosebaceous unit. However, notable challenges include the long cultivation time (4–5 months) and inverted structure of skin organoids, and further technological developments may therefore be required to implement organoids into translational pipelines.

5. Extrinsic models of aging

Human skin is exposed daily to various environmental factors such as air pollutants, cigarette smoke and UVR, which synergistically exacerbate cellular damage and promote skin aging. Air pollution, consisting of gases and urban particulate matter (UPM), and other harmful substances, such as heavy metals (e.g., lead) and PAHs, pose significant risks to skin health, promoting aging, inflammation, and the onset of skin disorders like wrinkles and pigmentation issues through ROS-induced cellular stress. Additionally, exposure to UVR, including UVA and UVB, causes cumulative damage, leading to premature signs of skin aging and increased risk of skin cancer. While the effects of these environmental stressors can be studied in simple 2D cultures, their effects on skin health often involve dynamic crosstalk between multiple different cells and the ECM. Therefore, advanced 3D models are needed to replicate and investigate these intricate mechanisms (Fig. 3).

5.1. UV radiation models

The study of UVB-induced senescence and skin aging has advanced significantly through the development of various *in vitro* and *in vivo* models with controlled UV exposure. 3D skin models exhibit several phenotypic changes upon UVB irradiation that closely resemble those observed in natural skin aging. These changes include the formation of sunburn cells (keratinocytes undergoing apoptosis) (Cavinato et al., 2017), increased expression of MMPs (Lee et al., 2020), which degrade collagen and other ECM proteins, and alterations in skin barrier function (Kim et al., 2023). Additionally, 3D models exposed to UVB display increased oxidative stress (Gao et al., 2021), DNA damage, and activation of inflammatory pathways (Lelièvre et al., 2024).

Skin explants cultivated *ex vivo* provide another valuable tool for studying UVB-induced skin aging. These explants preserve the complex architecture and cell-cell interactions of native skin, making them an excellent model for studying the direct effects of UVB radiation. Phenotypic changes in skin explants upon UVB exposure include similar markers of damage and aging seen in 3D *in vitro* models, such as DNA damage, oxidative stress, and MMP expression, as well as alterations in skin structure and function (Alkawar et al., 2020; Martins et al., 2022). Interestingly, pre-exposure to certain wavelengths of visible light (e.g., green) may protect against later UVR exposure, as indicated by cyclobutane pyrimidine dimer formation (Moreiras et al., 2021). While much work has focused on UVR, recent findings also indicate that visible light, notable blue light, can elicit both positive and negative effects on skin cells (Bacqueville et al., 2021), highlighting the need to explore the tissue-level impacts of visible light in HSEs in the future.

5.2. Models of pollution and cigarette smoke

Given the powerful impacts of environmental stressors, such as pollution and cigarette smoke on skin aging, several studies have begun to build these factors into *in vitro* models. For example, a tBHP-induced stress model has been used to successfully replicate the effects of air pollutants, particularly cigarette smoke, in 3D full-thickness HSEs and *ex vivo* skin models. Systemic treatment with tBHP reduced epidermal

thickness and induced collagen degradation in these models (Wedel et al., 2020). Similarly, the combined exposure to cigarette smoke extract and UVR in skin organoids reduced epidermal thickness and collagen synthesis by inhibiting the TGF-β/Smad signaling pathway and increasing MMP-1 activity, providing a model to study the synergistic effects of the exposome on skin aging (Grenier et al., 2023).

Along the same lines, a recent study found that combined treatment of human dermal fibroblasts with UVA, UVB, and UPM impairs autophagy and mitochondrial function, shifting cells from senescence to apoptosis. In contrast, UPM alone did not significantly affect cell fate, while UVA plus UVB primarily induced senescence (Guerrero-Navarro et al., 2024a). Additionally, the combination of pollutants, such as particulate matter and ozone, has been shown to induce extrinsic skin aging in full-thickness HSEs. This is characterized by decreased collagen gene and protein expression, increased expression and activity of MMPs, disrupted lipid homeostasis, and heightened inflammation (Reynolds et al., 2023). These studies together underscore the importance of studying the synergistic effects of exposome components in extrinsic skin aging.

5.3. Models to investigate the effect of nutrients on skin aging

Diet and nutrient signaling play pivotal roles in modulating pathways involved in skin aging. These pathways impact the skin's structural integrity and appearance through regulation of cellular metabolism, oxidative stress, and inflammation (Cao et al., 2020), and they can be modulated *in vitro* through the composition of cell culture medium and exposure of models to defined nutrients and regulatory factors. For example, using a photo-aging model induced by repeated UVA exposure, metformin showed the ability to alleviate aging cell markers by mechanisms related to the PI3K/AKT/mTOR signaling pathway and mitochondrial autophagy (Chen et al., 2022). Inhibition of 3-phosphoinositide-dependent protein kinase 1 (PDK1) also rescued senescence hallmarks and reversed cellular senescence in human fibroblasts by suppressing both NFκB and mTOR signaling, and PDK1 inhibition restored skin regeneration capacity in 2D culture and a 3D HSE model (An et al., 2020). Furthermore, protective effects of specific nutrients such as polyphenols, vitamins C and E, and omega-3 polyunsaturated fatty acids (n-3 PUFA) can be systematically investigated within controlled 3D *in vitro* models (Simard et al., 2021).

In contrast to the beneficial effects of certain dietary and nutritional factors, poor diet and lifestyle are major contributors to the prevalence of type II diabetes (T2D) in the Western world, and diabetes can have major impacts on age-associated skin disorders, most notably chronic, non-healing wounds (Lima et al., 2017). A number of approaches have been explored to model diabetic skin in the laboratory and investigate the pathogenic mechanisms of diabetes-associated skin disorders For example, *ex vivo* culture of skin explants from healthy and T2D patients has been employed to replicate impaired wound healing in diabetic skin (Wilkinson et al., 2021). Moreover, several key diabetic pathologies, including insulin resistance, impaired wound healing, and vascular dysfunction, could all be replicated in 3D bioprinted skin models with the inclusion of fibroblasts and pre-adipocytes from diabetic patients (Kim et al., 2021; Maione et al., 2015). In addition to the use of patient-derived cells, other strategies to mimic the diabetic microenvironment have used high glucose medium (Ueck et al., 2017) or manipulation of AGEs (see Section 4.2).

6. Outlook and future directions

The landscape of skin aging research is rapidly developing, driven by advances in stem cell biology, computational modeling, immunocompetent tissue engineering, and mechanistic insights into senescence and external stressors. Traditional 2D cultures and animal models have provided foundational knowledge, but they fall short in recapitulating the complex, multicellular, and dynamic nature of human skin aging. In this context, 3D skin models offer an unprecedented opportunity to bridge basic science and translational applications, enabling the study of aging at cellular, molecular, and systemic levels in physiologically relevant environments. This section highlights the emerging directions that are shaping the future of the field—including integration of organoid and organ-on-chip technologies, immune cells, microbiota, predictive *in silico* approaches, and senotherapeutics, — highlighting the multifaceted efforts aimed at unraveling and ultimately mitigating the mechanisms of skin aging (Fig. 3).

6.1. Organoids and organ-on-chip platforms

While 3D and full thickness *in vitro* skin models have been used for decades and replicate the basic structure of human skin, they lack more complex cellular compositions and interactions that are often essential for skin function. However, recent advances in organoid and organ-on-chip technologies have opened up new opportunities to model intricate skin structures and processes, such as appendages, nerves, vasculature and immune responses. Skin organoids are self-assembling 3D cultures that are derived from pluripotent stem cells and mimic key developmental processes, to produce innervated and pigmented pilosebaceous units (Lee et al., 2020). As noted above, these models have become powerful tools for modeling human hair follicles, and the recent addition of macrophages to these models has enhanced vascular development within the system, thereby adding new levels of complexity (Gopee et al., 2024).

Organ-on-chip technologies have likewise facilitated significant advances in skin modeling. These platforms consist of microfluidic devices that support the essential 3D architecture and physical cues, such as mechanical stretch and fluid flow, to better replicate the *in vivo* microenvironment (Huh et al., 2010; Ingber, 2022). A wide range of skin-on-chip systems have been developed to date (Cho et al., 2024; Ismayilzada et al., 2024), and these have been applied to modeling normal tissue homeostasis, as well as pathologies such as infection (Hindle et al., 2025; Sun et al., 2022), inflammatory diseases (Kim et al., 2022), and skin cancer (Barros et al., 2025). Still, there has been little work modeling skin aging using organoid or skin-on-chip approaches, and in the future, these tools have the potential to provide new mechanistic insight into complex age-associated pathologies that involve appendages, neuro-vascular components, or immune responses (discussed further below) and controllably model environmental drivers of skin aging.

6.2. Immuno-competent skin models

Increased inflammation and a decline in immunity are hallmarks of skin aging. However, capturing these complex age-related immunological changes within existing human *in vitro* models remains a significant challenge due to the diverse repertoire of immune cells present within the skin and the dynamic nature of immune cell trafficking between the skin, circulatory system, and secondary lymphoid organs. Several recent studies have begun to make inroads into replicating essential immune responses *in vitro* through the development of immuno-competent human skin models. For example, tissue-resident immune cells, including macrophages, T cells, and Langerhans cells, have been introduced into 3D HSEs, where they have been shown to mimic key processes in inflammatory skin diseases and drug sensitivity (Bechetoille et al., 2011; Kuenzel et al., 2024; Michielon et al., 2024; van den Bogaard et al., 2014). In addition, several platforms have integrated perfusable vasculature into 3D HSEs and skin-on-chip models to support delivery and trafficking of circulating immune cells (Hindle et al., 2025; Michielon et al., 2024; Sun et al., 2022). These systems have been used to model the response of neutrophils to viral infection (Sun et al., 2022) and monocyte trafficking and differentiation following skin inflammation triggered by bacterial products (Hindle et al., 2025). Moreover, skin-on-chip models have been linked to other tissue models within

multi-organ chips to study systemic immune and toxicity responses (Koning et al., 2022; Ronaldson-Bouchard et al., 2022). In the future, these systems could be extended to modelling age-related immune dysfunction through the introduction of aged/senescent skin cells or mimicking the aging skin microenvironment or key stressors, such as UVR. For example, in one recent study, the introduction of senescent fibroblasts into a microfluidic HSE accurately replicated the heightened inflammatory response and monocyte recruitment observed in older people (Hindle et al., 2025). This work highlights the potential for immuno-competent *in vitro* models to provide new insights into processes such as inflammaging and immunosenescence.

6.3. Modeling the microbiome in aging skin

The complex interplay of skin cells and the microbiome has yet to be fully integrated into skin aging models, but there is increasing recognition that the microbiome plays an important role in skin health as we age and should be considered in aging skin models. For example, in acne vulgaris, which displays 11% prevalence in the elderly, there is chronic and recurrent inflammation, with colonization and uncontrolled proliferation of *Cutibacterium acnes* (White, 1998). Similarly, in seborrheic dermatitis, more prevalent in older patients, *Malassezia* yeasts produce lipase to break down lipids and activate inflammatory reactions (Adalsteinsson et al., 2020; Sowell et al., 2022). External factors, such as lifestyle habits, UVR, or drug treatments, can also contribute to shifts from commensal to pathogenic microorganisms during aging (Yang et al., 2022). Thus, the development of aging models that accurately reflect these tissue microenvironments would permit the investigation of specific microbiome compositions, thereby allowing the study of the mechanisms underlying these pathologies.

Recent advances in integrating microbiota into 3D skin models have opened up new opportunities to interrogate these relationships in human skin. One method for modeling the microbiota involves using microbial communities directly isolated from clinical samples and applying them to 3D *in vitro* or *ex vivo* human skin models (Loomis et al., 2021; Wilkinson et al., 2024). Alternatively, microbiota modeling can be achieved by incorporating commercially obtained pure bacterial strains into *in vitro* models alone or in defined combinations (Loomis et al., 2021; Rademacher et al., 2018; Rikken et al., 2023). Regardless of the modeling approach used, microbiota integration would allow the mechanistic study of age-related changes in the skin microbiome and impact of dysbiosis on skin aging. However, key challenges will include accurate modeling of microbiome composition and dynamics, accounting for inter- and intrapersonal variation in the microbiome, and capturing key immunological responses and regulators of the microbiome.

6.4. Computational modeling

In silico models of skin aging represent a cutting-edge approach in dermatological research, utilizing computer algorithms, mathematical equations and biological data to simulate the effects of aging on skin structure, function, and physiology (Limbert, 2017; Tanaka and Ono, 2013). By integrating biochemical pathways, genetic factors, environmental influences, and cellular dynamics, *in silico* models aim to provide insights into the underlying mechanisms of aging, explore hypothetical scenarios and predict the efficacy of potential anti-aging interventions (Menendez et al., 2019) in a more cost-effective and efficient alternative to traditional experimental methods. For instance, these models can simulate the accumulation of oxidative stress, DNA damage, collagen degradation, and other molecular changes that contribute to skin aging (Markiewicz and Idowu, 2022). *In silico* models are currently being developed to predict the formation of wrinkles using finite element modeling (FEM). These models simulate the multilayered structure of the skin and apply mechanical principles to replicate how age-related changes—such as collagen degradation or loss of elasticity—lead to wrinkling over time (Flynn and McCormack, 2010). In addition, numerous studies have exploited computational modeling, either alone or with complementary *in vitro* studies, to assess the efficacy and putative mechanistic pathways of various anti-aging formulations (Feng et al., 2024; Gok et al., 2024; Jariwala et al., 2024; Nutho and Tungmunnithum, 2024).

However, despite their potential, *in silico* models also face challenges and limitations. Accurate modeling requires comprehensive and validated data inputs, which may be lacking or incomplete for certain aspects of skin aging. Additionally, the complexity of biological systems and the interactions between different cellular and molecular components pose challenges in accurately predicting real-world outcomes. Despite these limitations, *in silico* models of skin aging represent a powerful tool for advancing our understanding of aging mechanisms and developing innovative strategies for anti-aging interventions. As computational techniques and biological data continue to advance, these models hold promise for facilitating the discovery of effective treatments that can enhance skin health and mitigate the effects of aging. It is likely that these computational models will also be employed in conjunction with advanced *in vitro* models, which can be used both as data sources for model development and platforms for validating model predictions.

6.5. Applications in geroprotection and senolytic research

As our mechanistic understanding of skin aging deepens, there is growing interest in identifying therapeutic approaches that prevent age-related functional decline instead of just addressing late-stage disease. In this context, geroprotectors and senotherapeutics have emerged as promising classes of compounds targeting fundamental aging mechanisms and senescent cells, respectively.

Geroprotectors act on conserved pathways involved in nutrient sensing, mitochondrial function, inflammation, and oxidative stress, which play critical roles in tissue homeostasis. Representative examples include phytochemicals and dietary supplements such as quercetin, genistein, curcumin, resveratrol, naringenin, kaempferol, and rutin (Nichols and Katiyar, 2010; Proshkina et al., 2024). These compounds can modulate antioxidant defenses, mitochondrial activity, and pro-inflammatory signaling in cutaneous cells (Nichols and Katiyar, 2010). However, their long-term safety, bioavailability, and efficacy in humans are still uncertain (Luo et al., 2021). Some of these agents can also have context-dependent or paradoxical effects, such as potentiating UV-induced DNA damage under specific conditions (Proshkina et al., 2024; Seve et al., 2005). These complexities highlight the need for physiologically relevant systems to dissect dose-response relationships and mechanisms of action before clinical translation.

Senotherapeutics, by contrast, are designed to specifically target senescent cells and their deleterious secretome (Park and Shin, 2022). Senotherapeutics are classified as: i) senolytics, agents that selectively eliminate senescent cells or ii) senomorphics, compounds that suppress senescence-related pathways without inducing apoptosis or hindering induction of senescence (Calabrò et al., 2024). Senolytic compounds can act through multiple mechanisms (Robbins and Niedernhofer, 2017). For example, fisetin, quercetin, and HSP90 aim to disrupt pro-survival pathways to induce apoptosis in senescent cells (Fuhrmann-Stroissnigg et al., 2017; Zhu et al., 2017), while procyanidin C1 and 25-hydroxycholesterol induce senolysis by activating oxidative or proteotoxic stress responses in senescent cells (Limbad et al., 2022; Xu et al., 2021). Senomorphic agents, including rapamycin, metformin, and aspirin, may ameliorate senescence-associated phenotypes in skin by modulating mTOR, metabolic signaling, or inflammatory cascades (Bode-Böger et al., 2005; Chung et al., 2019; Kulkarni et al., 2020).

As the field of geroprotectors and senolytics advances, testing these compounds into well-validated *in vitro* skin aging models will be essential for establishing the safety, efficacy, and mechanisms of action of emerging therapeutics. Ultimately, integrating mechanistically

informed senotherapeutic strategies with advanced human skin models could speed up the development of targeted treatments that enhance skin health span.

7. Conclusion

Collectively, these advancements underscore a future in which skin aging can be understood and addressed through highly integrative, multimodal approaches. The convergence of 3D tissue engineering, immune and microbiome modeling, computational simulations, and targeted therapeutics such as stem cell-based interventions and senolytics promises not only deeper mechanistic insight but also more precise and effective interventions. However, the field must navigate critical challenges, including model standardization, scalability, long-term validation, and ethical and regulatory considerations. A continued emphasis on interdisciplinary collaboration, combining insights from dermatology, systems biology, materials science, and computational modeling, will be essential. As these technologies mature, 3D skin models stand poised to become the central platform for decoding the complexities of human skin aging and accelerating the development of next-generation anti-aging therapies.

CRediT authorship contribution statement

All authors contributed to conceptualization, writing – original draft, and writing – review and editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This article is based on work from COST Action European Network for Skin Engineering and Modelling (NETSKINMODELS) EU COST Action (CA21108, 2022–2026), supported by COST (European Cooperation in Science and Technology) (www.cost.eu).

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