Review

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The orchestrated network of skin photoaging: From intercellular crosstalk to molecular signaling

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SUMMARY: Photoaging is a distinct form of pathological skin aging driven primarily by chronic ultraviolet (UV) radiation, which clinically manifests as wrinkles, dyspigmentation, and loss of elasticity. Although core molecular events induced by UV—such as oxidative stress and DNA damage—are relatively well-understood, there is still a lack of a systematic and integrated understanding of how diverse cell types in the skin collectively drive photoaging through complex interactive networks. This review systematically elaborates the cellular and molecular mechanisms underlying skin photoaging. The key pathways involved are examined, including oxidative stress, apoptosis, dysregulated autophagy, activation of inflammatory cascades, and degradation of the extracellular matrix (ECM). This review further details the pivotal roles of and reciprocal crosstalk among fibroblasts, keratinocytes, melanocytes, and various immune cells. By providing an integrated perspective on these interactions, this review outlines the cellular and molecular mechanism of UV-associated senescence, which uniquely integrates the roles of the immune microenvironment and cellular crosstalk, providing a roadmap for next-generation anti-photoaging strategies.

Keywords: skin photoaging, senescence-associated secretory phenotype (SASP), inflammaging, extracellular matrix remodeling, therapeutic targets

1. Introduction

Photoaging results from chronic and repeated exposure to ultraviolet (UV) radiation—primarily UVA and UVB—along with other environmental factors such as infrared and visible light. Clinically, it is characterized by wrinkles, skin laxity, roughness, dyspigmentation, and telangiectasia. This condition represents a distinct, exogenous form of pathological skin aging. In contrast to intrinsic aging, photoaging is largely confined to areas exposed to the sun including the face, neck, the dorsum of the hands, and the extensors of the forearms. Oxidative stress constitutes the central molecular mechanism underlying its progression.

Chronic sun exposure is a major etiological factor in skin aging, with studies attributing up to 80% of facial skin aging to UV exposure (*1*). Solar UV radiation (UVR) consists of three wavelength ranges: UVA (320–400 nm), UVB (280–320 nm), and UVC (100–280 nm). Although UVC carries the highest energy, it is predominantly absorbed by the Earth's ozone layer and thus poses minimal risk to human health. The biologically relevant UVR that reaches the Earth's surface consists mainly of UVB and UVA. UVB, characterized by its short wavelength and high energy, penetrates the skin to a depth of approximately 160–180 μm and is largely absorbed by the epidermis. It induces DNA damage *via* oxidative stress, leading to sunburn, erythema, and skin carcinogenesis. In contrast, UVA constitutes 90–95% of solar UVR and is considered the primary driver of photoaging (*2*). Despite its lower energy, UVA's longer wavelength enables deeper penetration, penetrating as deep as 1,000 μm into the dermis. Rather than causing direct DNA damage, UVA promotes reactive oxygen species (ROS)-mediated skin aging and pigmentation (*3,4*).

This review discusses the cellular and molecular mechanisms underlying skin photoaging. Special emphasis is placed on the orchestrating roles of cells—fibroblasts, keratinocytes, melanocytes, and immune cells—as they interact with each other and jointly drive the development of the disease. This work contributes to the systematic understanding of the mechanisms underlying photoaging.

2. The pathogenesis of skin photoaging

2.1. Oxidative stress injury

Oxygen can be enzymatically or non-enzymatically converted into reactive intermediates, collectively termed ROS. Major ROS include the superoxide anion (O_2^-), the hydroxyl radical (·OH), and hydrogen peroxide (H_2O_2). The link between ROS and aging is well established and is historically rooted in two influential theories: the free radical theory of aging and the mitochondrial theory of aging (*5*). Chronic exposure to UV radiation promotes ROS accumulation in skin cells, resulting in oxidative damage, cellular dysfunction, and ultimately, skin photoaging (*6-8*). Multiple studies have demonstrated that UVR induces ROS and oxygen-derived free radicals in a dose-dependent manner (*9-12*). In skin keratinocytes and fibroblasts, UV exposure elevates lipid peroxidation, protein carbonylation, and DNA damage (*13-15*).

A primary defense against this oxidative stress is the Nrf2-Keap1 pathway, which plays a critical role in protecting skin cells from UV-induced damage during photoaging (Figure 1). Under basal conditions, Nrf2 is sequestered in the cytoplasm by its inhibitor Keap1. Oxidative stress triggers the dissociation of Nrf2 from Keap1, allowing Nrf2 to translocate to the nucleus, where it forms a heterodimer with a Maf protein (*16*). This Nrf2-Maf complex binds to antioxidant response elements (AREs) in the promoter regions of genes encoding antioxidant and detoxifying enzymes (*17*), thereby activating their transcription. The subsequent synthesis of these enzymes helps neutralize ROS and mitigate oxidative damage (*7,18*). In concurrence, molecular analyses have confirmed that UVA irradiation markedly upregulates oxidative stress-responsive genes such as heme oxygenase-1 (HO-1), NAD(P)H:quinone oxidoreductase 1 (NQO1), and the glutamate-cysteine ligase catalytic subunit (GCLC) (*19*). Beyond the Nrf2 system, peroxisomes also play an essential role in regulating cellular ROS levels, particularly under homeostatic conditions (*20*).

2.2. Apoptosis

Apoptosis is a genetically programmed, energy-dependent process of controlled cellular self-destruction and represents a key mechanism implicated in skin photoaging (*21*). UV-induced apoptosis proceeds through two temporally distinct pathways. In the early phase following exposure, UVA1 generates singlet oxygen, which depolarizes mitochondrial membranes and triggers immediate apoptosis. After 24 hours, ROS produced by both UVA and UVB subsequently induce oxidative DNA damage, leading to delayed apoptosis (*22,23*). The accumulation of DNA lesions activates the p53 pathway, which promotes the transcription of

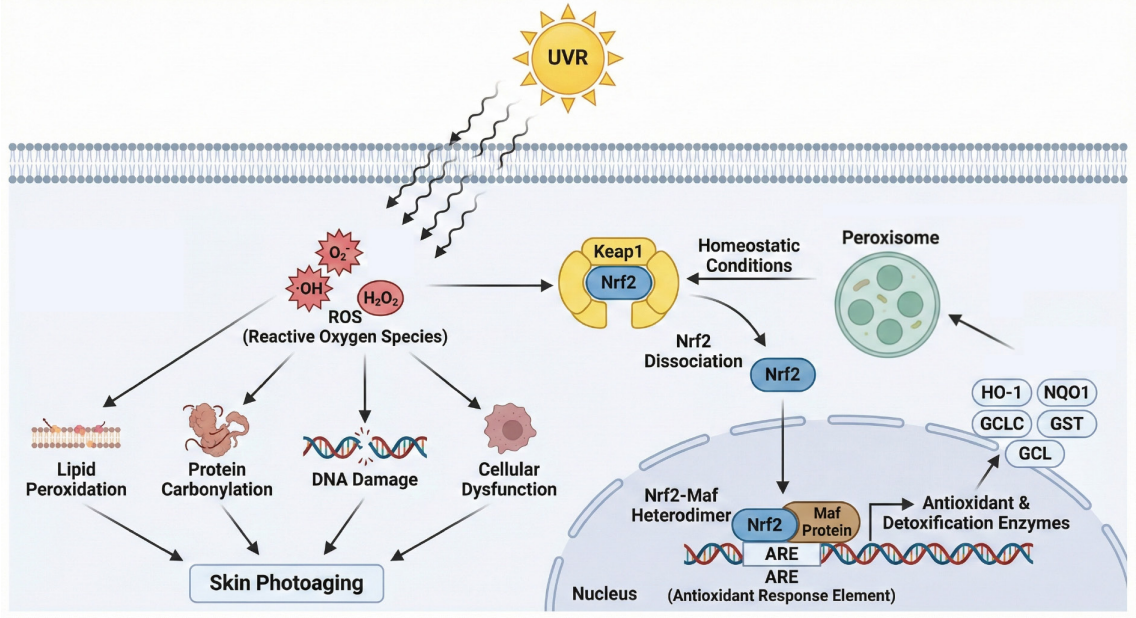

Figure 1. The mechanism of oxidative stress injury. Under ultraviolet (UV) radiation, oxygen is converted into reactive oxygen species (ROS), such as the superoxide anion (O_2^-), the hydroxyl radical (·OH), and hydrogen peroxide (H_2O_2). These ROS induce lipid peroxidation, protein carbonylation, DNA damage, and cellular dysfunction. The Nrf2-Keap1 pathway plays a critical role in protecting skin cells from UV-induced damage during photoaging. Under basal conditions, Nrf2 is sequestered in the cytoplasm by Keap1. Upon oxidative stress, Nrf2 dissociates from Keap1 and translocates into the nucleus, where it forms a heterodimer with a Maf protein. This complex binds to antioxidant response elements (AREs) in the promoters of genes encoding antioxidant and detoxifying enzymes, activating their transcription. The resulting enzymes help neutralize ROS and alleviate oxidative damage. Consistent with this mechanism, molecular analyses confirm that UVA irradiation markedly upregulates oxidative stress-responsive genes, including heme oxygenase-1 (HO-1), NAD(P)H:quinone oxidoreductase 1 (NQO1), and the glutamate-cysteine ligase catalytic subunit (GCLC).

autophagy-related genes such as AMP-activated protein kinase (AMPK), Sestrin 2 (SESN2), and Unc-51-like autophagy-activating kinase 1 (ULK1). Activated ULK1, in turn, phosphorylates Beclin-1 to initiate phagophore nucleation (*24*). The intrinsic (mitochondrial) apoptotic pathway is finely regulated by the balance between anti-apoptotic (*e.g.*, Bcl-2 and Bcl-xL) and pro-apoptotic (*e.g.*, Bax, Bak, and Bid) members of the Bcl-2 protein family, which ultimately determines cellular fate.

2.3. Autophagy

Autophagy is a highly regulated degradation process essential for maintaining cellular homeostasis through the clearance of damaged organelles, misfolded proteins, and other macromolecular debris (Figure 2). It is broadly categorized into macroautophagy, microautophagy, and selective autophagy (*25*). Based on the specific cellular components targeted for degradation, selective autophagy can be further classified into mitophagy (degrading damaged mitochondria), aggrephagy (degrading protein aggregates), and pexophagy (degrading peroxisomes) (*26,27*). In skin cells, mitochondria are a primary source of ROS. Sustained UVR induces mitochondrial DNA mutations and excessive ROS production. Mitophagy acts as a protective mechanism by removing dysfunctional mitochondria, thereby attenuating oxidative stress and genomic damage (*28*). Similarly, aggrephagy eliminates cytotoxic protein aggregates formed upon UV exposure, while pexophagy degrades impaired peroxisomes that would otherwise exacerbate oxidative stress and accelerate skin aging (*29,30*).

The autophagic process is orchestrated by a network of signaling pathways and effector molecules. In senescent human dermal fibroblasts, mitochondrial dysfunction is often associated with dysregulation of the PI3K/AKT/mTOR cascade (*31*). Conversely, AMPK signaling serves as a key positive regulator of autophagy (*32,33*). Both the inhibition of mTOR and activation of AMPK have protective roles in skin photoaging by promoting the clearance of damaged cellular components and reducing oxidative and DNA damage induced by UVR (*34-36*).

Central to autophagy are autophagy-related (ATG) proteins. ULK1, a key initiator kinase regulated upstream by mTOR and AMPK, phosphorylates downstream

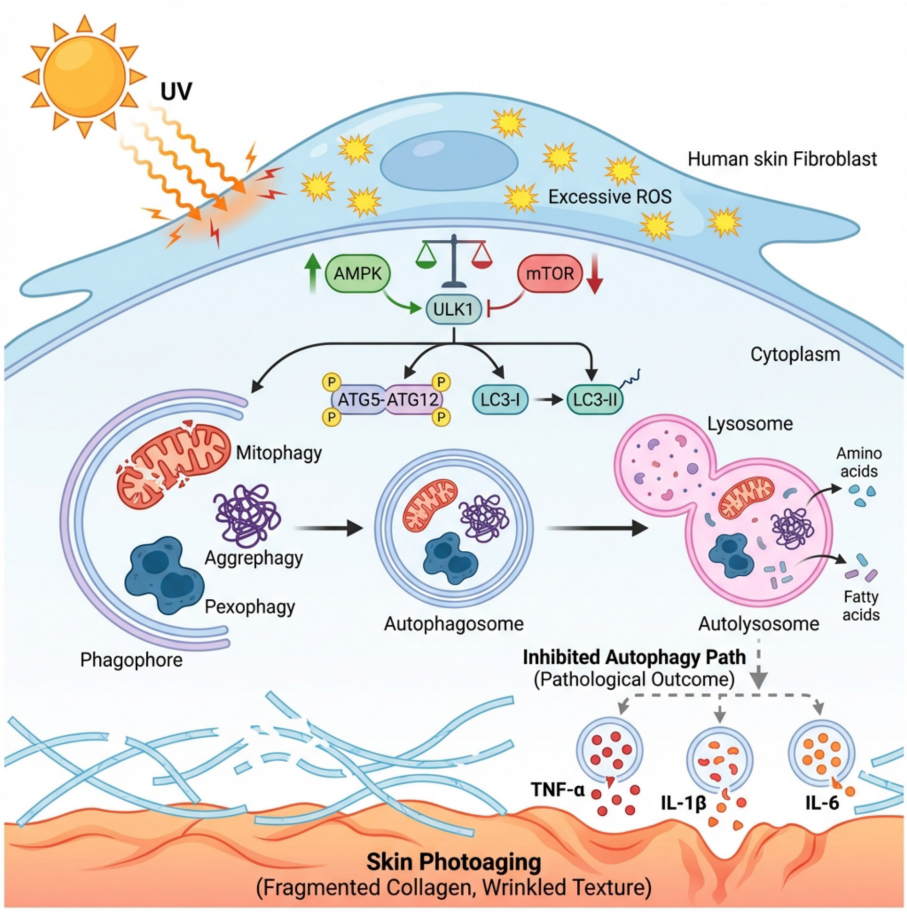

Figure 2. The mechanism of autophagy. Selective autophagy can be classified into mitophagy, aggrephagy, and pexophagy. In senescent human dermal fibroblasts, mitochondrial dysfunction is often accompanied by mTOR inhibition and AMPK activation, which subsequently activates the autophagy-related protein ULK1. ULK1 phosphorylates downstream ATG proteins, such as ATG5, ATG12, and LC3, thereby driving autophagosome formation. This process further promotes the expression of pro-inflammatory mediators, including TNF-α, IL-1β, and IL-6, collectively exacerbating skin photoaging.

ATG proteins such as ATG5, ATG12, and LC3 to drive autophagosome formation. Importantly, excessive UVR suppresses autophagic flux, leading to the subsequent activation of pro inflammatory mediators such as tumor necrosis factor-α (TNF α), interleukin 1β (IL-1β), and interleukin 6 (IL-6), which collectively exacerbate skin photoaging (*37*).

2.4. Inflammation-related pathways

The p38 MAPK and NF-κB signaling pathways are pivotal mediators of the inflammatory response triggered by UVR (*38*). UV exposure activates multiple members of the MAPK family, including extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK. While ERK primarily regulates cell proliferation and survival, its sustained activation upregulates the senescence-associated secretory phenotype (SASP), thereby driving cellular senescence (*39,40*). Concurrently, NF-κB is activated under UV stress and promotes the transcription of pro-inflammatory cytokines such as TNF-α, interleukin 1α (IL-1α), and IL-1β. These cytokines recruit immune cells—including monocytes, macrophages, and natural killer (NK) cells—to the site of damage (*41,42*). Subsequently, these infiltrating immune cells release additional inflammatory chemokines, such as CCL3, CXCL1, CXCL3, and CXCL5 (*43*). Moreover, MAPK signaling enhances cyclooxygenase-2 (COX-2) production, which exacerbates inflammation and tissue injury during photoaging (*44*). After the early vasodilatory phase, skin is infiltrated by neutrophils, monocytes, and T cells. These cells not only secrete pro-inflammatory mediators but also induce the release of anti-inflammatory cytokines, including IL-4, IL-10, and transforming growth factor β (TGF-β) (*45,46*). These regulatory cytokines facilitate the transition from acute inflammation to a prolonged, resolution-phase immunosuppression, a shift that accompanies tissue repair processes at the inflamed site.

2.5. Extracellular matrix (ECM) degradation-related pathways

The degradation of the ECM represents a central hallmark of skin photoaging. As previously outlined, excessive UVR elicits a robust inflammatory response. This process involves the upregulation of pro-inflammatory cytokines such as IL-1α and IL-1β, which in turn stimulate the expression of several matrix metalloproteinases (MMPs)—including MMP-1 (collagenase), MMP-3 (stromelysin), and MMP-9 (gelatinase). These enzymes collectively degrade collagen and other critical ECM components (*47,48*). Concurrently, UV-induced ERK activation promotes the expression of c-Fos, which forms the transcription factor AP-1 with c-Jun. AP-1 binds to promoter regions of MMP genes, further enhancing their transcription. The resultant overexpression of MMPs leads to extensive collagen breakdown and disruption of the three-dimensional elastin network, ultimately manifesting as skin wrinkling and loss of elasticity (*49,50*).

3. Roles of cells in skin photoaging

3.1. Fibroblasts

The pathogenesis of dermal fibroblast photoaging is predominantly initiated by chronic UVR, which induces a cascade of intracellular damage (*51*). Core mechanisms involve the excessive generation of ROS, accumulation of DNA damage, and mitochondrial dysfunction (*52,53*). Critically, prolonged UV exposure drives cellular senescence, marked by irreversible cell-cycle arrest and the acquisition of an SASP (*54*). Consequently, photoaged fibroblasts exhibit a profound decline in collagen and elastin production along with elevated expression of matrix-degrading enzymes such as MMPs, collectively leading to ECM disintegration (Table 1) (*55*).

3.2. Keratinocytes

As the outermost layer of the skin, the epidermis is directly and chronically exposed to solar UVR, rendering it highly susceptible to photoaging (*55*). In keratinocytes, UVR triggers photoaging through interconnected mechanisms, including oxidative stress with ROS generation, mitochondrial dysfunction, DNA damage, and activation of inflammatory pathways such

Table 1. Key regulators in skin photoaging

Cell type	Upregulated factors	Downregulated factors
Fibroblasts	ROS, SASP, MMPs	Collagen production, elastin production
Keratinocytes	ROS, SASP, MMP-1, MMP-9, IL-1β, IL-6	Antioxidant defenses
Melanocytes	Melanogenesis, β-catenin signaling	SDF1
Macrophages	MMP-1, MMP-3, MMP-9, Pro-inflammatory factors, M1/M2 ratio	Anti-inflammatory cytokines
Th17/Treg Cells	IL-17A, IL-8, IL-17F, IL-21, IL-22, IL-26, TNF-α, IL-10, TGF-β, SASPs	Immune surveillance
Mast Cells	Serine proteases (tryptase, chymase), Histamine, MMP-9	Not specified

Abbreviation: ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; MMPs, matrix metalloproteinases; SDF1, stromal cell-derived factor 1.

as NF-κB and MAPK signaling (*5657*). These negative factors collectively promote an SASP, characterized by elevated expression of MMPs (*e.g.*, MMP-1 and MMP-9), increased secretion of pro-inflammatory cytokines (*e.g.,* IL-1β, and IL-6), and a concomitant decline in antioxidant defenses (*58,59*).

3.3. Melanocytes

Melanocytes, situated primarily within the basal epidermal layer, are responsible for melanin production and proliferate at a low rate. Upon exposure to UVR, keratinocytes release paracrine factors including interleukin 17 (IL-17), endothelin 1 (ET 1), and stem cell factor (SCF) (*60*). These ligands bind to their respective receptors—MC1R, the endothelin B receptor (ETB), and c Kit—on melanocytes (Figure 3). ET 1 and SCF binding, in particular, activates the ERK1/2 MAPK pathway, thereby promoting melanogenesis (*61*). Newly synthesized melanin is subsequently transferred to adjacent keratinocytes, where it functions as a natural photoprotectant by absorbing UVR and mitigating DNA damage (*62*).

Beyond keratinocytes, senescent dermal fibroblasts also contribute significantly to skin hyperpigmentation (*63*). Senescent fibroblasts upregulate the secretion of pro-melanogenic growth factors such as hepatocyte growth factor (HGF), keratinocyte growth factor (KGF), and SCF, which directly stimulate melanocytic activity (*64-66*). Additionally, factors such as secreted frizzled related protein 2 (sFRP2) and growth differentiation factor 15 (GDF15) further enhance melanin synthesis by activating the β-catenin signaling pathway (*67*). Epigenetic alterations also play a regulatory role, including the downregulation of stromal cell-derived factor 1 (SDF1) and the upregulation of Wnt inhibitory factor 1 (WIF-1), collectively shaping the pigmentary response to chronic UV exposure (*68*).

3.4. Macrophages

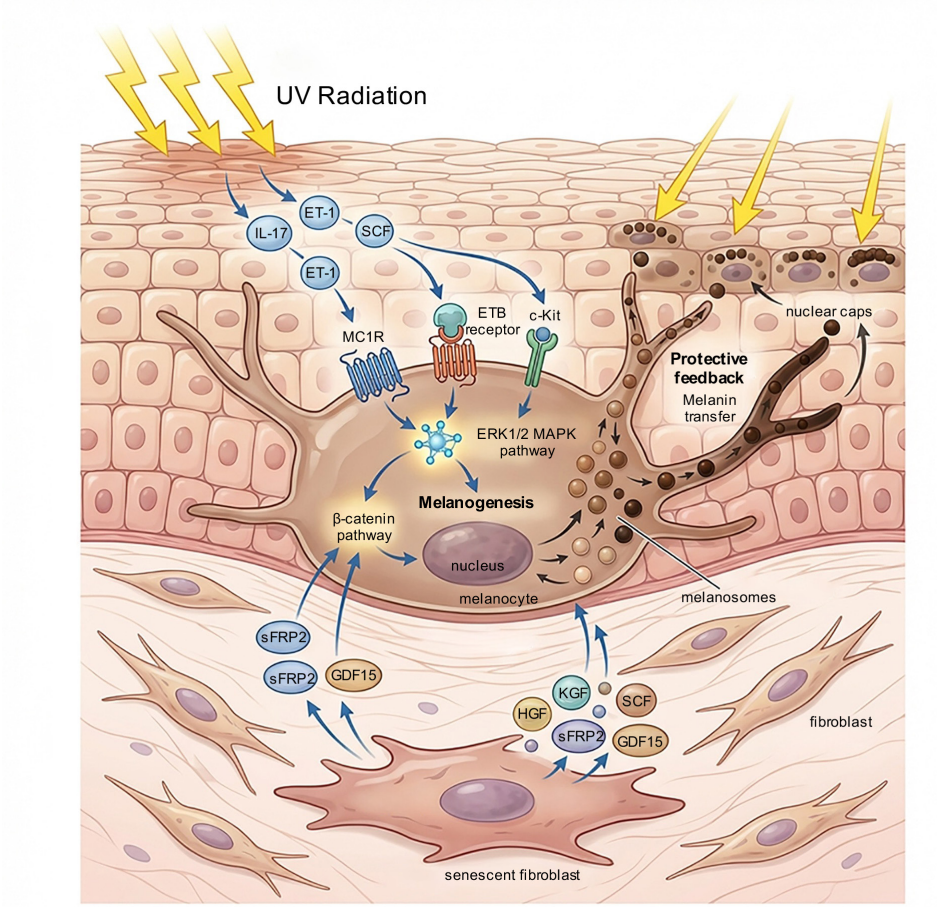

Figure 3. The alteration of melanocytes under UV exposure. Upon UVR, keratinocytes release paracrine factors such as interleukin-17 (IL-17), endothelin-1 (ET-1), and stem cell factor (SCF). These ligands bind to their respective receptors—MC1R, endothelin B receptor (ETB), and c-Kit—on melanocytes. The binding of ET-1 and SCF activates the ERK1/2 MAPK pathway, thereby promoting melanogenesis. In fibroblasts, UV-induced epigenetic alterations downregulate stromal cell-derived factor-1 (SDF1) and upregulate Wnt inhibitory factor-1 (WIF-1), which collectively enhance the secretion of pro-melanogenic factors including hepatocyte growth factor (HGF), keratinocyte growth factor (KGF), SCF, secreted frizzled-related protein 2 (sFRP2), and growth differentiation factor-15 (GDF15). These factors further stimulate melanin synthesis by activating the β-catenin signaling pathway. Newly synthesized melanin is transferred to adjacent keratinocytes, where it acts as a natural photoprotectant by absorbing UVR and reducing DNA damage.

As key components of the innate immune system, macrophages play an important role in maintaining skin homeostasis. In response to various stimuli, macrophages can polarize into two primary subsets: the pro-inflammatory M1 phenotype and the anti-inflammatory M2 phenotype. In response to UVR, M1 macrophages are recruited *via* activation of the p38 MAPK and NF-κB signaling pathways. They recognize damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) in photodamaged skin through Toll-like receptors (TLRs) and inflammasome signaling, thereby amplifying local inflammation (*69*). Moreover, they secrete MMPs, including MMP-1, MMP-3, and MMP-9, which are central to the degradation of type I collagen during photoaging (*70*). In contrast, M2 macrophages, which are polarized by cytokines such as IL-4 and IL-13 *via* the STAT6 pathway (M2a), or by immune complexes and IL-1 receptor antagonists (M2b), or *via* the JAK1/STAT3 pathway in response to IL-10 and TGF-β (M2c), are crucial to tissue repair and remodeling (*71*). M2 macrophages promote the activation of fibroblasts and ECM deposition by releasing growth factors (*e.g.*, PDGF, VEGF, TGF-β1, and IGF-1), while downregulating inflammatory markers and MMPs. In photoaged skin, the macrophage balance shifts toward an M1-dominant state, resulting in an elevated M1/M2 ratio (*72*). This imbalance is significantly correlated with reduced levels of type I, V, and VI collagen in the dermis (*73*). The sustained inflammatory environment may accelerate fibroblast senescence, which in turn exacerbates collagen dysregulation through the secretion of deleterious factors (*74*). Notably, the disruption particularly affects type V and VI collagen, which serve as critical bridging molecules that stabilize type I collagen fibrils. Consequently, the altered M1/M2 equilibrium contributes to chronic inflammation, impaired collagen homeostasis, and ultimately to the structural breakdown of the dermal matrix, manifesting as skin laxity and wrinkling (*75*).

3.5. Th17/Treg cells

T helper 17 (Th17) cells and regulatory T (Treg) cells, as key effector subsets derived from the differentiation of $CD4^+$ T cells, play functionally antagonistic roles in immune responses. Th17 cells are characterized by the production of interleukin (IL)-17A and also secrete pro-inflammatory cytokines such as IL-8, IL-17F, IL-21, IL-22, IL-26, and TNF-α, aggravating inflammation-induced skin photoaging (*76*). In contrast, Tregs, defined by the expression of the transcription factor FoxP3 and surface markers CD25 and CTLA-4, are central to maintaining immune tolerance and homeostasis, largely through the secretion of anti-inflammatory cytokines such as IL-10, IL-35, and TGF-β1. Beyond accelerating aging, UVR has also been implicated in skin immunosuppression, this phenomenon is predominantly governed by Tregs (*77*). Their activation in UV-exposed skin is initiated through two major pathways. Primarily, UVR triggers the migration of Langerhans cells (LC) to regional lymph nodes, where they present antigen and imprint Tregs with skin-homing specificity (*78,79*). Additionally, UVB acts as a direct photochemical trigger, converting tryptophan into the aryl hydrocarbon receptor (AhR) ligand 6-formylindolo[3,2-b] carbazole (FICZ) and activating the kynurenine pathway, the metabolites of which also serve as AhR agonists (*80,81*). UVR further stimulates the production of cis-urocanic acid, which results in an inflammatory environment and which promotes the synthesis of prostaglandin E2, collectively establishing a signaling cascade that expands and recruits Tregs to the skin (*82,83*).

Once localized, Tregs drive photoaging through two synergistic mechanisms that fuel a self-perpetuating cycle of damage. First, through the secretion of IL-10 and TGF-β, Tregs dampen the effector functions of $CD4^+$/$CD8^+$ T cells, NK cells, and dendritic cells (*84-86*). This suppression of immunosurveillance compromises the clearance of senescent cells, leading to their accumulation. The senescent cells release SASPs such as ROS, cytokines, and MMPs, exacerbating local inflammation and reinforcing the immunosuppressive microenvironment that sustains Treg activity (*87,88*). Second, Tregs directly promote tissue degradation. Treg-derived TGF-β inhibits keratinocyte proliferation, upregulates collagen-degrading MMPs, and can induce senescence in resident skin cells (*89-91*). While IL-10 typically has anti-inflammatory effects, under chronic photo-inflammatory conditions it disrupts proteostasis by suppressing autophagy and antigen presentation. Moreover, ROS released by recruited immune cells activate latent TGF-β, amplifying its tissue-destructive effects (*92,93*).

3.6. Mast cells

Mast cells are common innate immune cells, recognized as key effector cells in immunoglobulin E (IgE)-mediated allergic inflammation, and play important roles in various physiological and pathological processes (*94,95*). Mast cells contain a variety of bioactive substances. UV stimulation can promote their activation and degranulation, leading to the release of serine proteases and other mediators, such as tryptase, chymase, histamine, and TNF, which are involved in changes observed in photoaged skin, including solar elastosis, degradation of the ECM, disruption of the basement membrane, and hyperpigmentation (*96,97*). Tryptase is the most abundant serine protease in mast cells and also functions as a gelatinase. This enzyme is associated with degradation of the basement membrane and the formation of perivascular alterations induced by UVR. Tryptase participates in the degradation of the

dermal ECM by processing MMP precursors into active forms or directly damaging ECM proteins. Repeated UV exposure can also promote the production of mast cell tryptase (*98*). Mast cell tryptase activates MMP-9 and degrades type IV collagen, thereby promoting wrinkle formation. In summary, tryptase can contribute to ECM damage, disruption of the basement membrane, and solar elastosis in photoaged skin, thereby influencing the progression of photoaging (*99-101*). Thus, tryptase may serve as a promising therapeutic target for preventing skin photoaging (*102*).

Histamine is the only recognized amine stored in human mast cells. It can induce MMP-9 production in human primary keratinocytes, promote immune cell migration in the basal layer of the skin, and degrade type IV collagen. Malaviya *et al*. (*103*) found that under UVR, upregulated histamine release from dermal mast cells in human skin may enhance collagen degradation and promote wrinkle formation. Kim *et al*. (*104*) treated mice chronically exposed to UV with the antihistamine ketotifen, and they found that ketotifen significantly reduced UV-induced wrinkles and effectively inhibited and delayed skin aging. Besides promoting wrinkle formation in photoaged skin, histamine is also associated with the development of hyperpigmentation. Yoshida *et al*. (*105*) found that treating human melanocytes with histamine induced morphological changes and increased tyrosinase activity, and they confirmed that histamine activates protein kinase A *via* the H_2 receptor, stimulating melanogenesis in cultured human melanocytes. Topical application of famotidine (an H_2 antagonist) to UVB-irradiated mouse skin significantly reduced skin pigmentation and the increase in Dopa-positive melanocytes (*105*).

4. SASP-mediated intercellular crosstalk

In the pathophysiology of skin photoaging, the SASP serves as a central mechanistic hub orchestrating complex intercellular crosstalk among fibroblasts, keratinocytes, melanocytes, and infiltrating immune cells (Figure 4). Chronic UVR initially leads to fibroblast and keratinocyte senescence and SASP accumulation, including MMPs, pro-inflammatory cytokines (*e.g.,* IL-1β, and IL-6), and growth factors, that not only degrade the ECM but that also have paracrine effects on neighboring cells. Specifically, senescent fibroblast-derived SASP factors such as IGF-1 induce keratinocyte senescence *via* p53/p21 activation, while HGF, KGF, and SCF promote melanogenesis and contribute to hyperpigmentation (Figure 4) (*54,106,107*). This secretome further recruits and polarizes macrophages toward a pro-inflammatory M1 phenotype, elevating the M1/M2 ratio and perpetuating MMP-mediated collagenolysis. Concurrently, UV-induced Tregs suppress immune surveillance *via* IL-10 and TGF-β, impairing senescent cell clearance and fostering a self-sustaining niche of SASP-producing cells. Mast cells, activated by

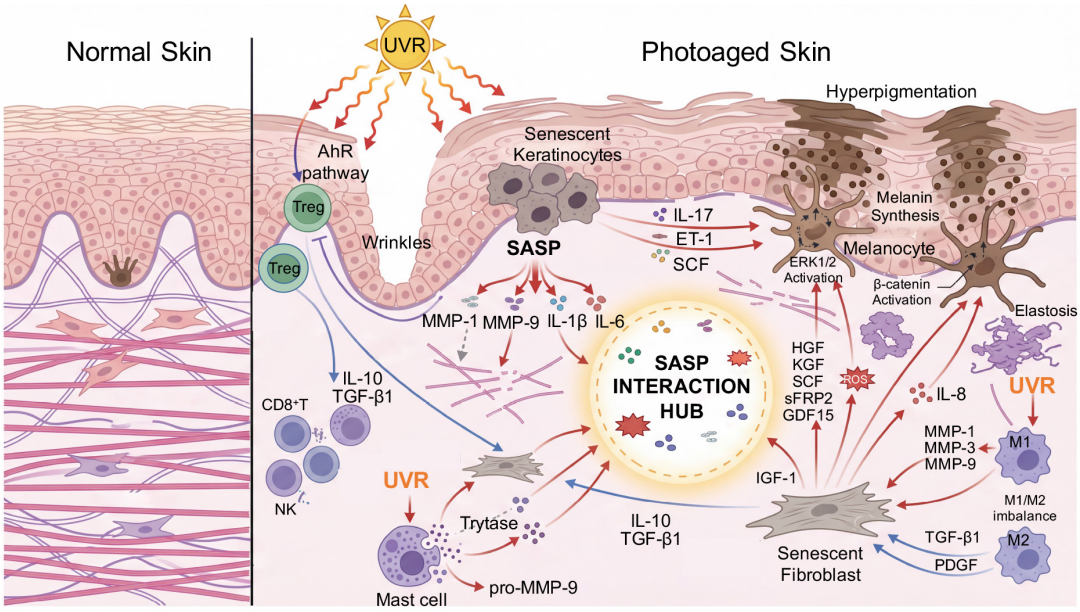

Figure 4. The multicellular SASP network driving skin photoaging. In skin photoaging, the senescence-associated secretory phenotype (SASP) acts as a central hub for intercellular communication. Chronic UV exposure induces senescence in fibroblasts and keratinocytes, leading them to secrete SASP factors (*e.g.*, MMPs, IL-1β, and IL-6). This secretome degrades the extracellular matrix (ECM) and drives paracrine effects: SASP from fibroblasts promotes senescence in keratinocytes (via IGF-1), stimulates melanogenesis (via HGF/KGF/SCF), and recruits pro-inflammatory M1 macrophages, which amplify MMP-driven collagen breakdown. Concurrently, UV-induced regulatory T cells (Tregs) suppress immune clearance of senescent cells *via* IL-10/TGF-β, while mast cells release proteases that further degrade the ECM. These interactions form a vicious cycle—immune and epidermal signals exacerbate fibroblast senescence, the SASP of which in turn reinforces inflammation and matrix destruction—leading to the hallmark deterioration of photoaged skin.

UV, release tryptase and histamine, which amplify MMP activity and ECM degradation. The resultant chronic inflammatory microenvironment establishes reciprocal feedback loops—wherein inflammatory signals from immune and epidermal cells exacerbate fibroblast senescence, while SASP from fibroblasts reinforces immune dysregulation and matrix disintegration—collectively driving the progressive structural and functional deterioration characteristic of photoaged skin (*51,63*).

5. Emerging therapeutic strategies

Current therapeutic strategies targeting skin photoaging focus on antioxidants, ECM metabolism modulators, and senescence-directed interventions (Table 2). In keratinocytes, several natural compounds such as hesperetin and chrysanthemum attenuate senescence by suppressing the MAPK/AP-1 and NF-κB signaling axes, thereby reducing MMP expression (*108,109*). Nicotinamide (NAM) promotes DNA repair and enhances cellular energy metabolism to delay senescence (*110*), while mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) deliver tissue inhibitor of metalloproteinase 1 (TIMP1) to inhibit Notch1 signaling, concurrently alleviating inflammation and cellular aging (*111*). Additional keratinocyte-targeted strategies include pharmacological inhibition of protease-activated receptor 2 (PAR2), enhancement of δ-catenin-mediated DNA repair, and activation of CISD2—a mitochondrial protein that reduces ROS production, suppresses MMP-1 expression, and restores mitochondrial function (*112*). In parallel, fibroblast-oriented interventions are categorized into antioxidants, ECM metabolism modulators, and senescence-directed therapies. Numerous phytochemicals, such as resveratrol, salvianolic acid B, galangin, and urolithin A, have antioxidant effects *via* activation of stress-responsive NRF2 and SIRT1 pathways, leading to upregulated antioxidant enzymes (HO-1 and SOD), ROS scavenging, and mitophagy-mediated mitochondrial rejuvenation (*113-116*). Other agents, including protocatechuic aldehyde, gallic acid, and Scutellaria barbata extracts, primarily remodel ECM homeostasis by inhibiting MMP expression through an AP-1/NF-κB blockade and concurrently enhancing collagen synthesis *via* TGF-β/IGF-1 pathway activation (*117,118*). As senescence-targeting approaches, chlorogenic acid attenuates fibroblast senescence by inhibiting the glycolytic enzyme ENO1 and suppressing the SASP (*119*), whereas metformin modulates the PI3K/AKT/mTOR axis and alleviates excessive mitophagy (*31*). Physical and cell-based approaches, such as low-dose aminolevulinic acid photodynamic therapy (*120*), microneedling (*121*), and MSC-based therapies (*122,123*), represent complementary avenues for restoring dermal homeostasis. Beyond these preclinical and translational efforts, several intervention paradigms have advanced to clinical-stage investigation. For example, 0.5% retinol serums and topical rapamycin provide significant clinical benefits against photoaging, including improved uniformity of skin color, enhanced overall skin tone, increased elasticity, and optimized moisture retention (*124,125*). Moreover, topical and systemic modulation of the cutaneous microbiome has emerged as a novel strategy to reinforce epidermal barrier function and mitigate low-grade inflammatory drift associated with photoaging (*126,127*). These evolving

Table 2. Therapeutic strategies for skin photoaging

Therapeutic mechanism	Target/Pathway	Candidate drug/Intervention	*Ref.*
Antioxidant/Anti-inflammatory	MAPK/AP-1, NF-κB signaling	Hesperetin, chrysanthemum	(*108,109*)
Antioxidant/Mitochondrial rejuvenation	NRF2, SIRT1 pathways	Resveratrol, salvianolic acid B, galangin, urolithin A	(*113-116*)
DNA repair	DNA repair	Nicotinamide	(*110*)
ECM metabolism modulation	AP-1/NF-κB, TGF-β/IGF-1, TIMP1/Notch1	Protocatechuic aldehyde, gallic acid, Scutellaria barbata extracts	(*117,118*)
Anti-SASP	ENO1, PAR2, PI3K/AKT/mTOR	Chlorogenic acid, metformin	(*31,119*)
Physical therapy	Photodynamic effect, mechanical stimulation	Aminolevulinic acid photodynamic therapy, microneedling	(*120,121*)
MSC-based therapy	Skin regeneration	Adipose-derived MSC, MSC-EVs	(*122,123*)
Clinical stage	Retinoic acid receptor	0.5% retinol serums	(*124,125*)
Clinical stage	mTOR inhibition	Topical rapamycin	(*124,125*)
Clinical stage	Cutaneous microbiome modulation	Topical and systemic modulation	(*126,127*)

therapeutic strategies collectively define a precision-oriented landscape for the clinical management of skin photoaging.

6. Perspective

In the investigation of pathogenesis, single-cell sequencing technologies have provided a revolutionary perspective for understanding the complex mechanisms underlying photoaging. Compared to bulk analysis, this technology has enabled the construction of a high-resolution transcriptomic atlas of human skin aging, revealing distinct changes in cellular composition that differentiate photoaging from chronological aging (*128,129*). Moreover, single-cell analysis has precisely identified key regulators in photoaging, such as HES1 and KLF6 (*130*). Furthermore, by integrating analyses of intercellular communication networks, this approach has elucidated the underlying mechanism (*129*). Epigenetics is another approach that has further revealed the pathogenesis of photoaging. DNA methylation and histone alterations alter the three-dimensional conformation of DNA and subsequent gene expression without altering the underlying genetic sequence, thereby mediating cutaneous photoaging. Given the enduring and heritable nature of these epigenetic modifications, their cumulative effects are considered a key mechanism driving chronic photodamage and the aging process (*131*).

Over the past few years, rapid progress has been made in artificial intelligence-assisted diagnosis of dermatological conditions. Studies have shown that AI-assisted analysis of reflectance confocal microscopy (RCM) images, which evaluates the morphology (degree of flattening) of the dermal-epidermal junction (DEJ) and classifies dermal collagen fiber types, can intelligently identify photoaging (*132*).

Therapeutically, exosomes afford a promising strategy to treat photoaging. Derived from stem cells and plants, exosomes have been proven to have regenerative effects on photo-damaged skin. Moreover, as natural extracellular vesicles, exosomes show considerable potential as drug delivery vehicles. Future research could focus on the bioengineering of exosomes—including modification with targeting peptides, cargo optimization (*e.g.*, with specific circRNAs or miRNAs), and the development of novel delivery systems—to achieve efficient and precise delivery (*133*). Concurrently, investigations into the skin microbiome have revealed that certain probiotic derivatives, such as the supernatant from Pediococcus acidophilus LS, have photoprotective and anti-melanogenic effects by inhibiting both the PKA/CREB and MAPK signaling pathways. This offers early evidence for a "microbe-skin axis" in photoaging regulation, although the mechanisms underlying the interaction between microbial metabolites and the host epigenome remain largely unexplored (*134*).

7. Conclusion

Photoaging is a distinct form of skin aging primarily caused by chronic exposure to UVR (UVA and UVB), clinically manifesting as wrinkles, pigmentation disorders, and loss of elasticity. Its core molecular mechanisms involve oxidative stress, apoptosis, dysregulated autophagy, activation of inflammatory pathways, and degradation of the ECM. Multiple types of skin cells—including fibroblasts, keratinocytes, melanocytes, and immune cells—interact through complex signaling networks to collectively drive disease progression. Recent advances in photoaging research, encompassing the elucidation of pathogenic mechanisms, AI-assisted diagnosis, and therapeutic development, have not only increased our understanding of this process but also expanded the potential for clinical translation. These breakthroughs have laid a robust theoretical foundation for the further development of targeted interventions and precision treatment strategies, holding promise for developing anti-photoaging therapies for more personalized and precision-based approaches.

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References

1. Guan LL, Lim HW, Mohammad TF. Sunscreens and photoaging: A review of current literature. Am J Clin Dermatol. 2021; 22:819-828.
2. Ronsch H, Bauer A. The preventive value of sun protection. Curr Probl Dermatol. 2021; 55:316-328.
3. Gromkowska-Kepka KJ, Puscion-Jakubik A, Markiewicz-Zukowska R, Socha K. The impact of ultraviolet radiation on skin photoaging - Review of *in vitro* studies. J Cosmet Dermatol. 2021; 20:3427-3431.
4. Pourang A, Tisack A, Ezekwe N, Torres AE, Kohli I, Hamzavi IH, Lim HW. Effects of visible light on mechanisms of skin photoaging. Photodermatol Photoimmunol Photomed. 2022; 38:191-196.
5. Schneider JL, Rowe JH, Garcia-de-Alba C, Kim CF, Sharpe AH, Haigis MC. The aging lung: Physiology, disease, and immunity. Cell. 2021; 184:1990-2019.
6. Tada T, Sakamoto R, Wajima T. Effects of metformin on high glucose- and UVA-induced oxidative stress and cellular senescence in Rat Keratinocytes. Biol Pharm Bull. 2025; 48:1732-1740.
7. Hajialiasgary Najafabadi A, Soheilifar MH, Masoudi-Khoram N. Exosomes in skin photoaging: Biological functions and therapeutic opportunity. Cell Commun Signal. 2024; 22:32.
8. Wang L, Lee W, Oh JY, Cui YR, Ryu B, Jeon YJ. Protective effect of sulfated polysaccharides from

celluclast-assisted extract of Hizikia fusiforme against ultraviolet B-induced skin damage by regulating NF-κB, AP-1, and MAPKs signaling pathways *in vitro* in human dermal fibroblasts. Mar Drugs. 2018; 16:239.
9. Jang J, Ye BR, Heo SJ, Oh C, Kang DH, Kim JH, Affan A, Yoon KT, Choi YU, Park SC, Han S, Qian ZJ, Jung WK, Choi IW. Photo-oxidative stress by ultraviolet-B radiation and antioxidative defense of eckstolonol in human keratinocytes. Environ Toxicol Pharmacol. 2012; 34:926-934.
10. Budluang P, Kim JE, Park ES, *et al*. N-benzyl-N-methyldecane-1-amine derived from garlic ameliorates UVB-induced photoaging in HaCaT cells and SKH-1 hairless mice. Sci Rep. 2025; 15:6979.
11. Jo WS, Yang KM, Park HS, Kim GY, Nam BH, Jeong MH, Choi YJ. Effect of microalgal extracts of Tetraselmis suecica against UVB-induced photoaging in human skin fibroblasts. Toxicol Res. 2012; 28:241-248.
12. Ung TPL, Lim S, Solinas X, Mahou P, Chessel A, Marionnet C, Bornschlogl T, Beaurepaire E, Bernerd F, Pena AM, Stringari C. Simultaneous NAD(P)H and FAD fluorescence lifetime microscopy of long UVA-induced metabolic stress in reconstructed human skin. Sci Rep. 2021; 11:22171.
13. Duan X, Wu T, Liu T, Yang H, Ding X, Chen Y, Mu Y. Vicenin-2 ameliorates oxidative damage and photoaging *via* modulation of MAPKs and MMPs signaling in UVB radiation exposed human skin cells. J Photochem Photobiol B. 2019; 190:76-85.
14. Rodrigues RB, de Oliveira MM, Garcia FP, Ueda-Nakamura T, de Oliveira Silva S, Nakamura CV. Dithiothreitol reduces oxidative stress and necrosis caused by ultraviolet A radiation in L929 fibroblasts. Photochem Photobiol Sci. 2024; 23:271-284.
15. Wang L, Jayawardena TU, Hyun J, Wang K, Fu X, Xu J, Gao X, Park Y, Jeon YJ. Antioxidant and anti-photoaging effects of a fucoidan isolated from Turbinaria ornata. Int J Biol Macromol. 2023; 225:1021-1027.
16. Niture SK, Khatri R, Jaiswal AK. Regulation of Nrf2-An update. Free Radic Biol Med. 2014; 66:36-44.
17. Bellezza I, Giambanco I, Minelli A, Donato R. Nrf2-Keap1 signaling in oxidative and reductive stress. Biochim Biophys Acta Mol Cell Res. 2018; 1865:721-733.
18. Lee JJ, Ng SC, Hsu JY, Liu H, Chen CJ, Huang CY, Kuo WW. Galangin reverses H_2O_2-induced dermal fibroblast senescence *via* SIRT1-PGC-1alpha/Nrf2 signaling. Int J Mol Sci. 2022; 23:1387.
19. Vikram A, Patel SK, Pathania D, Srivastava N, Rai AK, Ratnasekhar CH, Singh S, Ray RS, Dwivedi A. Ferulic acid photoconversion maintains Nrf2-mediated antioxidant defense against UVA damage. Phytomedicine. 2026; 150:157616.
20. Bellezza I, Mierla AL, Minelli A. Nrf2 and NF-kappaB and their concerted modulation in cancer pathogenesis and progression. Cancers (Basel). 2010; 2:483-497.
21. Bernerd F, Passeron T, Castiel I, Marionnet C. The damaging effects of long UVA (UVA1) rays: A major challenge to preserve skin health and integrity. Int J Mol Sci. 2022; 23:8243.
22. Breuckmann F, von Kobyletzki G, Avermaete A, Radenhausen M, Hoxtermann S, Pieck C, Schoneborn P, Gambichler T, Freitag M, Hoffmann K, Altmeyer P. Mechanisms of apoptosis: UVA1-induced immediate and UVB-induced delayed apoptosis in human T cells *in vitro*. J Eur Acad Dermatol Venereol. 2003; 17:418-429.
23. Godar DE. UVA1 radiation triggers two different final apoptotic pathways. J Invest Dermatol. 1999; 112:3-12.
24. Sample A, He YY. Autophagy in UV damage response. Photochem Photobiol. 2017; 93:943-955.
25. Zhang Z, Tan R, Xiong Z, Feng Y, Chen L. Dysregulation of autophagy during photoaging reduce oxidative stress and inflammatory damage caused by UV. Front Pharmacol. 2025; 16:1562845.
26. Bajdzienko J, Bremm A. Mammalian pexophagy at a glance. J Cell Sci. 2024; 137:jcs259775.
27. Rubio-Tomas T, Sotiriou A, Tavernarakis N. The interplay between selective types of (macro)autophagy: Mitophagy and xenophagy. Int Rev Cell Mol Biol. 2023; 374:129-157.
28. Picca A, Faitg J, Auwerx J, Ferrucci L, D'Amico D. Mitophagy in human health, ageing and disease. Nat Metab. 2023; 5:2047-2061.
29. Gallagher ER, Holzbaur ELF. SQSTM1/P62 promotes lysophagy *via* formation of liquid-like condensates maintained by HSP27. Autophagy. 2023; 19:3029-3030.
30. Li L, Hongying C, Heng G. Autophagy-related LncRNA PRDM10-DT responds to UVB radiation in keratinocytes. Biochem Biophys Res Commun. 2023; 677:105-112.
31. Chen Q, Zhang H, Yang Y, Zhang S, Wang J, Zhang D, Yu H. Metformin attenuates UVA-induced skin photoaging by suppressing mitophagy and the PI3K/AKT/mTOR pathway. Int J Mol Sci. 2022; 23:6960.
32. Chu J, Xiang Y, Lin X, He M, Wang Y, Ma Q, Duan J, Sun S. Handelin protects human skin keratinocytes against ultraviolet B-induced photodamage *via* autophagy activation by regulating the AMPK-mTOR signaling pathway. Arch Biochem Biophys. 2023; 743:109646.
33. Lin X, Chu J, Xiang Y, He M, Ma Q, Duan J, Wang Y, Sun S. Kangfuxin liquid reduces the ultraviolet B-induced photodamage of HaCaT cells by regulating autophagy. Biosci Biotechnol Biochem. 2023; 87:1485-1494.
34. Vikram A, Patel SK, Singh A, Pathania D, Ray RS, Upadhyay AK, Dwivedi A. Natural autophagy activators: A promising strategy for combating photoaging. Phytomedicine. 2024; 132:155508.
35. Tang QQ, Wang ZD, An XH, Zhou XY, Zhang RZ, Zhan X, Zhang W, Zhou J. Apigenin ameliorates H_2O_2-induced oxidative damage in melanocytes through nuclear factor-E2-related factor 2 (Nrf2) and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathways and reducing the generation of reactive oxygen species (ROS) in zebrafish. Pharmaceuticals (Basel). 2024; 17:1302.
36. Gu Y, Han J, Jiang C, Zhang Y. Biomarkers, oxidative stress and autophagy in skin aging. Ageing Res Rev. 2020; 59:101036.
37. Rubinsztein DC, Marino G, Kroemer G. Autophagy and aging. Cell. 2011; 146:682-695.
38. Ciazynska M, Olejniczak-Staruch I, Sobolewska-Sztychny D, Narbutt J, Skibinska M, Lesiak A. Ultraviolet radiation and chronic inflammation-molecules and mechanisms involved in skin carcinogenesis: A narrative review. Life (Basel). 2021; 11:326.
39. Bhui K, Prasad S, George J, Shukla Y. Bromelain inhibits COX-2 expression by blocking the activation of MAPK regulated NF-kappa B against skin tumor-initiation triggering mitochondrial death pathway. Cancer Lett. 2009; 282:167-176.
40. Kim KM, Im AR, Park SK, Shin HS, Chae SW. Protective effects of timosaponin AIII against UVB-radiation induced

inflammation and DNA injury in human epidermal keratinocytes. Biol Pharm Bull. 2019; 42:1524-1531.
41. Hasegawa T, Nakashima M, Suzuki Y. Nuclear DNA damage-triggered NLRP3 inflammasome activation promotes UVB-induced inflammatory responses in human keratinocytes. Biochem Biophys Res Commun. 2016; 477:329-335.
42. Korhonen E, Bisevac J, Hyttinen JMT, Piippo N, Hytti M, Kaarniranta K, Petrovski G, Kauppinen A. UV-B-induced inflammasome activation can be prevented by cis-urocanic acid in human corneal epithelial cells. Invest Ophthalmol Vis Sci. 2020; 61:7.
43. Dawes JM, Antunes-Martins A, Perkins JR, Paterson KJ, Sisignano M, Schmid R, Rust W, Hildebrandt T, Geisslinger G, Orengo C, Bennett DL, McMahon SB. Genome-wide transcriptional profiling of skin and dorsal root ganglia after ultraviolet-B-induced inflammation. PLoS One. 2014; 9:e93338.
44. Surowiak P, Gansukh T, Donizy P, Halon A, Rybak Z. Increase in cyclooxygenase-2 (COX-2) expression in keratinocytes and dermal fibroblasts in photoaged skin. J Cosmet Dermatol. 2014; 13:195-201.
45. Salminen A, Kaarniranta K, Kauppinen A. Photoaging: UV radiation-induced inflammation and immunosuppression accelerate the aging process in the skin. Inflamm Res. 2022; 71:817-831.
46. Enk CD, Sredni D, Blauvelt A, Katz SI. Induction of IL-10 gene expression in human keratinocytes by UVB exposure *in vivo* and *in vitro*. J Immunol. 1995; 154:4851-4856.
47. Lee TH, Chen JL, Tsai MM, Wu YH, Tseng HC, Cheng LC, Shanmugam V, Hsieh HL. Protective effects of sophoraflavanone G by inhibiting TNF-alpha-iduced MMP-9-mediated events in brain microvascular endothelial cells. Int J Mol Sci. 2023; 25:283.
48. Feng C, Chen X, Yin X, Jiang Y, Zhao C. Matrix metalloproteinases on skin photoaging. J Cosmet Dermatol. 2024; 23:3847-3862.
49. Imokawa G, Ishida K. Biological mechanisms underlying the ultraviolet radiation-induced formation of skin wrinkling and sagging I: Reduced skin elasticity, highly associated with enhanced dermal elastase activity, triggers wrinkling and sagging. Int J Mol Sci. 2015; 16:7753-7775.
50. Nakajima H, Ezaki Y, Nagai T, Yoshioka R, Imokawa G. Epithelial-mesenchymal interaction during UVB-induced up-regulation of neutral endopeptidase. Biochem J. 2012; 443:297-305.
51. Shin JW, Kwon SH, Choi JY, Na JI, Huh CH, Choi HR, Park KC. Molecular mechanisms of dermal aging and antiaging approaches. Int J Mol Sci. 2019; 20:2126.
52. Haser WG, Saito H, Koyama T, Tonegawa S. Cloning and sequencing of murine T3 gamma cDNA from a subtractive cDNA library. J Exp Med. 1987; 166:1186-1191.
53. Hooda R, Madke B, Choudhary A. Photoaging: Reversal of the oxidative stress through dietary changes and plant-based products. Cureus. 2023; 15:e37321.
54. Zheng Y, Lei J, Zhang A, Cao C, Xu A, Zhou M, Lin F. Regulatory mechanisms of transforming growth factor-beta in senescence of fibroblast associated with refractory skin diseases. Exp Gerontol. 2025; 211:112900.
55. Ke Y, Wang XJ. TGFbeta signaling in photoaging and UV-induced skin cancer. J Invest Dermatol. 2021; 141:1104-1110.
56. Ge Y, Li M, Bai S, Chen C, Zhang S, Cheng J, Wang X. Doxercalciferol alleviates UVB-induced HaCaT cell senescence and skin photoaging. Int Immunopharmacol. 2024; 127:111357.
57. Belzer A, Parker ER. Climate change, skin health, and dermatologic disease: A guide for the dermatologist. Am J Clin Dermatol. 2023; 24:577-593.
58. Pal S, Bandyopadhyay S. Thermal unfolding of barstar and the properties of interfacial water around the unfolded forms. J Chem Phys. 2013; 139:235101.
59. Bang E, Kim DH, Chung HY. Protease-activated receptor 2 induces ROS-mediated inflammation through Akt-mediated NF-kappaB and FoxO6 modulation during skin photoaging. Redox Biol. 2021; 44:102022.
60. Swope VB, Abdel-Malek ZA. Significance of the melanocortin 1 and endothelin B receptors in melanocyte homeostasis and prevention of sun-induced genotoxicity. Front Genet. 2016; 7:146.
61. Yang G, Li Y, Nishimura EK, Xin H, Zhou A, Guo Y, Dong L, Denning MF, Nickoloff BJ, Cui R. Inhibition of PAX3 by TGF-beta modulates melanocyte viability. Mol Cell. 2008; 32:554-563.
62. Lin P, Hwang E, Ngo HTT, Seo SA, Yi TH. Sambucus nigra L. ameliorates UVB-induced photoaging and inflammatory response in human skin keratinocytes. Cytotechnology. 2019; 71:1003-1017.
63. Kim JC, Park TJ, Kang HY. Skin-aging pigmentation: Who is the real enemy? Cells. 2022; 11:2541.
64. Kovacs D, Cardinali G, Aspite N, Cota C, Luzi F, Bellei B, Briganti S, Amantea A, Torrisi MR, Picardo M. Role of fibroblast-derived growth factors in regulating hyperpigmentation of solar lentigo. Br J Dermatol. 2010; 163:1020-1027.
65. Hasegawa K, Fujiwara R, Sato K, Shin J, Kim SJ, Kim M, Kang HY. Possible involvement of keratinocyte growth factor in the persistence of hyperpigmentation in both human facial solar lentigines and melasma. Ann Dermatol. 2015; 27:626-629.
66. Kim M, Kim SM, Kwon S, Park TJ, Kang HY. Senescent fibroblasts in melasma pathophysiology. Exp Dermatol. 2019; 28:719-722.
67. Kim Y, Kang B, Kim JC, Park TJ, Kang HY. Senescent fibroblast-derived GDF15 induces skin pigmentation. J Invest Dermatol. 2020; 140:2478-2486.e4.
68. Yoon JE, Kim Y, Kwon S, Kim M, Kim YH, Kim JH, Park TJ, Kang HY. Senescent fibroblasts drive ageing pigmentation: A potential therapeutic target for senile lentigo. Theranostics. 2018; 8:4620-4632.
69. Battie C, Jitsukawa S, Bernerd F, Del Bino S, Marionnet C, Verschoore M. New insights in photoaging, UVA induced damage and skin types. Exp Dermatol. 2014; 23 Suppl 1:7-12.
70. Fligiel SE, Varani J, Datta SC, Kang S, Fisher GJ, Voorhees JJ. Collagen degradation in aged/photodamaged skin *in vivo* and after exposure to matrix metalloproteinase-1 *in vitro*. J Invest Dermatol. 2003; 120:842-848.
71. Wynn TA, Vannella KM. Macrophages in tissue repair, regeneration, and fibrosis. Immunity. 2016; 44:450-462.
72. Horiba S, Kami R, Tsutsui T, Hosoi J. IL-34 Downregulation–associated M1/M2 macrophage imbalance is related to inflammaging in sun-exposed human skin. JID Innov. 2022; 2:100112.
73. Horiba S, Kawamoto M, Tobita R, Kami R, Ogura Y, Hosoi J. M1/M2 macrophage skewing is related to reduction in types I, V, and VI collagens with aging in sun-exposed human skin. JID Innov. 2023; 3:100222.

74. Kim H, Jang J, Song MJ, Park CH, Lee DH, Lee SH, Chung JH. Inhibition of matrix metalloproteinase expression by selective clearing of senescent dermal fibroblasts attenuates ultraviolet-induced photoaging. Biomed Pharmacother. 2022; 150:113034.
75. Fisher GJ, Sachs DL, Voorhees JJ. Ageing: Collagenase-mediated collagen fragmentation as a rejuvenation target. Br J Dermatol. 2014; 171:446-449.
76. Kroemer G, Maier AB, Cuervo AM, Gladyshev VN, Ferrucci L, Gorbunova V, Kennedy BK, Rando TA, Seluanov A, Sierra F, Verdin E, Lopez-Otin C. From geroscience to precision geromedicine: Understanding and managing aging. Cell. 2025; 188:2043-2062.
77. Schwarz T. 25 years of UV-induced immunosuppression mediated by T cells-From disregarded T suppressor cells to highly respected regulatory T cells. Photochem Photobiol. 2008; 84:10-18.
78. Schwarz A, Maeda A, Schwarz T. Alteration of the migratory behavior of UV-induced regulatory T cells by tissue-specific dendritic cells. J Immunol. 2007; 178:877-886.
79. Yamazaki S, Odanaka M, Nishioka A, Kasuya S, Shime H, Hemmi H, Imai M, Riethmacher D, Kaisho T, Ohkura N, Sakaguchi S, Morita A. Ultraviolet B-induced maturation of CD11b-type langerin(-) dendritic cells controls the expansion of Foxp3(+) regulatory T cells in the skin. J Immunol. 2018; 200:119-129.
80. Rannug A, Rannug U. The tryptophan derivative 6-formylindolo[3,2-b]carbazole, FICZ, a dynamic mediator of endogenous aryl hydrocarbon receptor signaling, balances cell growth and differentiation. Crit Rev Toxicol. 2018; 48:555-574.
81. Vogeley C, Esser C, Tuting T, Krutmann J, Haarmann-Stemmann T. Role of the aryl hydrocarbon receptor in environmentally induced skin aging and skin carcinogenesis. Int J Mol Sci. 2019; 20:6005.
82. Walterscheid JP, Nghiem DX, Kazimi N, Nutt LK, McConkey DJ, Norval M, Ullrich SE. Cis-urocanic acid, a sunlight-induced immunosuppressive factor, activates immune suppression *via* the 5-HT2A receptor. Proc Natl Acad Sci U S A. 2006; 103:17420-17425.
83. Newson J, Motwani MP, Kendall AC, Nicolaou A, Muccioli GG, Alhouayek M, Bennett M, Van De Merwe R, James S, De Maeyer RPH, Gilroy DW. Inflammatory resolution triggers a prolonged phase of immune suppression through COX-1/mPGES-1-derived prostaglandin E2. Cell Rep. 2017; 20:3162-3175.
84. Ghiringhelli F, Menard C, Terme M, *et al*. CD4+CD25+ regulatory T cells inhibit natural killer cell functions in a transforming growth factor-beta-dependent manner. J Exp Med. 2005; 202:1075-1085.
85. Salminen A. Activation of immunosuppressive network in the aging process. Ageing Res Rev. 2020; 57:100998.
86. Nasti TH, Yusuf N, Sherwani MA, Athar M, Timares L, Elmets CA. Regulatory T cells play an important role in the prevention of murine melanocytic nevi and melanomas. Cancer Prev Res (Phila). 2021; 14:165-174.
87. Xie Y, Yang A, Li N, Zheng H, Zhong Y, Jin Y, Li J, Ye R, Du L, Hu F. Lapagyl mitigates UV-induced inflammation and immunosuppression *via* Foxp3+ Tregs and CCL pathway: A single-cell transcriptomics study. Phytomedicine. 2024; 129:155679.
88. Nelson G, Wordsworth J, Wang C, Jurk D, Lawless C, Martin-Ruiz C, von Zglinicki T. A senescent cell bystander effect: Senescence-induced senescence. Aging Cell. 2012; 11:345-349.
89. Toyama S, Moniaga CS, Nakae S, Kurosawa M, Ogawa H, Tominaga M, Takamori K. Regulatory T cells exhibit interleukin-33-dependent migratory behavior during skin barrier disruption. Int J Mol Sci. 2021; 22:7443.
90. Gao W, Yuan LM, Zhang Y, Huang FZ, Gao F, Li J, Xu F, Wang H, Wang YS. miR-1246-overexpressing exosomes suppress UVB-induced photoaging *via* regulation of TGF-beta/Smad and attenuation of MAPK/AP-1 pathway. Photochem Photobiol Sci. 2023; 22:135-146.
91. Liu Z, Li Y, Song H, He J, Li G, Zheng Y, Li B. Collagen peptides promote photoaging skin cell repair by activating the TGF-beta/Smad pathway and depressing collagen degradation. Food Funct. 2019; 10:6121-6134.
92. Harris J. Autophagy and cytokines. Cytokine. 2011; 56:140-144.
93. Wu TT, Li WM, Yao YM. Interactions between autophagy and inhibitory cytokines. Int J Biol Sci. 2016; 12:884-897.
94. Iddamalgoda A, Le QT, Ito K, Tanaka K, Kojima H, Kido H. Mast cell tryptase and photoaging: possible involvement in the degradation of extra cellular matrix and basement membrane proteins. Arch Dermatol Res. 2008; 300 Suppl 1:S69-S76.
95. Korhonen J, Siiskonen H, Haimakainen S, Harvima RJ, Harvima IT. Expression of mast cell tryptase and immunoglobulin E is increased in cutaneous photodamage: Implications for carcinogenesis. J Dermatolog Treat. 2024; 35:2307488.
96. Hernandez-Barrera R, Torres-Alvarez B, Castanedo-Cazares JP, Oros-Ovalle C, Moncada B. Solar elastosis and presence of mast cells as key features in the pathogenesis of melasma. Clin Exp Dermatol. 2008; 33:305-308.
97. Lestarevic S, Savic S, Dejanovic M, Mijovic M, Mandic P, Marjanovic D, Filipovic M, Rancic IB, Jorgacevic T. The effect of aging on mast cell density in human skin: A comparative analysis of photoexposed and photoprotected regions. Folia Morphol (Warsz). 2024. doi: 10.5603/fm.102163.
98. Fajardo I, Pejler G. Human mast cell beta-tryptase is a gelatinase. J Immunol. 2003; 171:1493-1499.
99. Bosset S, Bonnet-Duquennoy M, Barre P, Chalon A, Kurfurst R, Bonte F, Schnebert S, Le Varlet B, Nicolas JF. Photoageing shows histological features of chronic skin inflammation without clinical and molecular abnormalities. Br J Dermatol. 2003; 149:826-835.
100. Lee H, Hong Y, Kim M. Structural and functional changes and possible molecular mechanisms in aged skin. Int J Mol Sci. 2021; 22:12489.
101. Helfrich YR, Maier LE, Cui Y, Fisher GJ, Chubb H, Fligiel S, Sachs D, Varani J, Voorhees J. Clinical, histologic, and molecular analysis of differences between erythematotelangiectatic rosacea and telangiectatic photoaging. JAMA Dermatol. 2015; 151:825-836.
102. Ishitsuka Y, Maniwa F, Koide C, Kato Y, Nakamura Y, Osawa T, Tanioka M, Miyachi Y. Increased halogenated tyrosine levels are useful markers of human skin ageing, reflecting proteins denatured by past skin inflammation. Clin Exp Dermatol. 2012; 37:252-258.
103. Malaviya R, Morrison AR, Pentland AP. Histamine in human epidermal cells is induced by ultraviolet light injury. J Invest Dermatol. 1996; 106:785-789.
104. Kim MS, Lee DH, Lee CW, Kim YK, Lee MJ, Shin CY, Cho KH, Chung JH. Mast cell stabilizer, ketotifen, prevents UV-induced wrinkle formation. J Invest

Dermatol. 2013; 133:1104-1107.
105. Yoshida M, Hirotsu S, Nakahara M, Uchiwa H, Tomita Y. Histamine is involved in ultraviolet B-induced pigmentation of guinea pig skin. J Invest Dermatol. 2002; 118:255-260.
106. Bohm M, Stegemann A, Paus R, Kleszczynski K, Maity P, Wlaschek M, Scharffetter-Kochanek K. Endocrine controls of skin aging. Endocr Rev. 2025; 46:349-375.
107. Wlaschek M, Maity P, Makrantonaki E, Scharffetter-Kochanek K. Connective tissue and fibroblast senescence in skin aging. J Invest Dermatol. 2021; 141:985-992.
108. Shen ZQ, Chang CY, Yeh CH, Lu CK, Hung HC, Wang TW, Wu KS, Tung CY, Tsai TF. Hesperetin activates CISD2 to attenuate senescence in human keratinocytes from an older person and rejuvenates naturally aged skin in mice. J Biomed Sci. 2024; 31:15.
109. Xu S, Sun X, Zhu Z, Xin Y, Chen C, Luo J. The extract of buds of Chrysanthemum morifolium ramat alleviated UVB-induced skin photoaging by regulating MAPK and Nrf2/ARE pathways. J Ethnopharmacol. 2024; 332:118352.
110. Tan CYR, Tan CL, Chin T, Morenc M, Ho CY, Rovito HA, Quek LS, Soon AL, Lim JSY, Dreesen O, Oblong JE, Bellanger S. Nicotinamide prevents UVB- and oxidative stress–induced photoaging in human primary keratinocytes. J Invest Dermatol. 2022; 142:1670-1681 e1612.
111. Zhang H, Xiao X, Wang L, Shi X, Fu N, Wang S, Zhao RC. Human adipose and umbilical cord mesenchymal stem cell-derived extracellular vesicles mitigate photoaging *via* TIMP1/Notch1. Signal Transduct Target Ther. 2024; 9:294.
112. Shen Y, Kim K, Zhu Z, Zhang S, Jiang M, Liu Z, Zheng Y, Li X, Jin L, Cong W. delta-catenin requirement in keratinocyte proliferation and DNA repair identifies a therapeutic target for photoaging. J Invest Dermatol. 2023; 143:26-36 e28.
113. Liu W, Yan F, Xu Z, Chen Q, Ren J, Wang Q, Chen L, Ying J, Liu Z, Zhao J, Qiu J, Zhang C, Jiang M, Xiang L. Urolithin A protects human dermal fibroblasts from UVA-induced photoaging through NRF2 activation and mitophagy. J Photochem Photobiol B. 2022; 232:112462.
114. Xia Y, Zhang H, Wu X, Xu Y, Tan Q. Resveratrol activates autophagy and protects from UVA-induced photoaging in human skin fibroblasts and the skin of male mice by regulating the AMPK pathway. Biogerontology. 2024; 25:649-664.
115. Sun JM, Liu YX, Liu YD, Ho CK, Tsai YT, Wen DS, Huang L, Zheng DN, Gao Y, Zhang YF, Yu L. Salvianolic acid B protects against UVB-induced skin aging *via* activation of NRF2. Phytomedicine. 2024; 130:155676.
116. Wen SY, Ng SC, Chiu YT, Tai PY, Chen TJ, Chen CJ, Huang CY, Kuo WW. Enhanced SIRT1 activity by galangin mitigates UVB-induced senescence in dermal fibroblasts *via* p53 acetylation regulation and activation. J Agric Food Chem. 2024; 72:23286-23294.
117. Hwang E, Park SY, Lee HJ, Lee TY, Sun ZW, Yi TH. Gallic acid regulates skin photoaging in UVB-exposed fibroblast and hairless mice. Phytother Res. 2014; 28:1778-1788.
118. Jung JM, Choi JK, Kwon OY, Lee SH. Anti-photoaging activity of Scutellaria barbata D. Don (Family Lamiaceae) on ultraviolet B-irradiated NIH-3T3 skin fibroblast and SKH-1 hairless mouse. Molecules. 2022; 27:3803.
119. He X, Wang C, Zhang Q, Yang T, Guo Q, Wang Y, Guo J, Wang P, Zhang J, Tang H, Zhu Y, Wang J. Identifying ENO1 as a protein target of chlorogenic acid to inhibit cellular senescence and prevent skin photoaging in mice. Aging Cell. 2025; 24:e14433.
120. Chen J, Luo J, Tan Y, Wang M, Liu Z, Yang T, Lei X. Effects of low-dose ALA-PDT on fibroblast photoaging induced by UVA irradiation and the underlying mechanisms. Photodiagnosis Photodyn Ther. 2019; 27:79-84.
121. Tang Z, Liu Z, Zhang Y, Luo S, Xu Y, Ren L. Functional hyaluronic acid microneedles for skin photoaging based on collagen induction and oxidative stress regulation strategies. Int J Biol Macromol. 2024; 277:134080.
122. Gentile P, Garcovich S. Adipose-derived mesenchymal stem cells (AD-MSCs) against ultraviolet (UV) radiation effects and the skin photoaging. Biomedicines. 2021; 9:532.
123. Yan T, Huang L, Yan Y, Zhong Y, Xie H, Wang X. Bone marrow mesenchymal stem cell-derived exosome miR-29b-3p alleviates UV irradiation-induced photoaging in skin fibroblast. Photodermatol Photoimmunol Photomed. 2023; 39:235-245.
124. Zasada M, Budzisz E, Erkiert-Polguj A. A clinical anti-ageing comparative study of 0.3 and 0.5% retinol serums: A clinically controlled trial. Skin Pharmacol Physiol. 2020; 33:102-116.
125. Chung CL, Lawrence I, Hoffman M, Elgindi D, Nadhan K, Potnis M, Jin A, Sershon C, Binnebose R, Lorenzini A, Sell C. Topical rapamycin reduces markers of senescence and aging in human skin: An exploratory, prospective, randomized trial. Geroscience. 2019; 41:861-869.
126. Seo E, Song HH, Kim H, Kim BY, Park S, Suh HJ, Ahn Y. Oral administration of mixed probiotics improves photoaging by modulating the cecal microbiome and MAPK pathway in UVB-irradiated hairless mice. Mol Nutr Food Res. 2023; 67:e2200841.
127. Qu L, Ma X, Wang F. The roles of gut microbiome and metabolites associated with skin photoaging in mice by intestinal flora sequencing and metabolomics. Life Sci. 2024; 341:122487.
128. Yu GT, Ganier C, Allison DB, Tchkonia T, Khosla S, Kirkland JL, Lynch MD, Wyles SP. Mapping epidermal and dermal cellular senescence in human skin aging. Aging Cell. 2025; 24:e14358.
129. Hu X, Du S, Chen M, Yang H, He J, Zhang L, Tan B, Wu T, Duan X. Single-cell sequencing combined with transcriptome sequencing to explore the molecular mechanisms related to skin photoaging. J Inflamm Res. 2024; 17:11137-11160.
130. Zou Z, Long X, Zhao Q, *et al*. A single-cell transcriptomic atlas of human skin aging. Dev Cell. 2021; 56:383-397 e388.
131. Barnes BM, Shyne A, Gunn DA, Griffiths CEM, Watson REB. Epigenetics and ultraviolet radiation: Implications for skin ageing and carcinogenesis. Skin Health Dis. 2024; 4:e410.
132. Mehrabi JN, Baugh EG, Fast A, Lentsch G, Balu M, Lee BA, Kelly KM. A clinical perspective on the automated analysis of reflectance confocal microscopy in dermatology. Lasers Surg Med. 2021; 53:1011-1019.
133. Tang H, Wang F, Yang R, Zhao Z, Zhang Y, Yang L, Li B. Baricitinib-loaded EVs promote alopecia areata mouse hair regrowth by reducing JAK-STAT-mediated inflammation and promoting hair follicle regeneration. Drug Discov Ther. 2025; 18:368-374.

134. Sinha S, Lin G, Ferenczi K. The skin microbiome and the gut-skin axis. Clin Dermatol. 2021; 39:829-839.

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