REVIEW

Involvement of the nuclear structural proteins in aging-related responses of human skin to the environmental stress

Ewa Markiewicz
Olusola Clement Idowu

Hexis Lab, Science Central, The Core, Newcastle upon Tyne, UK

Abstract: Human skin is a stratified endocrine organ with primary roles in protection against detrimental biochemical and biophysical factors in the environment. Environmental stress causes gradual accumulation of the macromolecular damage and clinical manifestations consistent with chronic inflammatory conditions and premature aging of the skin. Structural proteins of cell nucleus, the nuclear lamins and lamina-associated proteins, play an important role in the regulation of a number of signal transduction pathways associated with stress. The nuclear lamina proteins have been implicated in a number of degenerative disorders with frequent clinical manifestations of the skin conditions related to premature aging. Analysis of the molecular signatures in response of the skin to a range of damaging factors not only points at the likely involvement of the nuclear lamina in transmission of the signals between the environment and cell nucleus but also defines skin's sensitivity to stress, and therefore the capacities to counteract external damage in aging.

Keywords: genotoxic, nuclear lamina, progeroid syndrome, fibroblast

Introduction

Human skin constitutes the largest outermost layer of the body, with a primary function of protection of the underlying tissues from environmental factors such as infection, and chemical and biophysical stress.[1,2] Skin is a stratified organ consisting of a complex epidermal layer, which includes appendages such as the hair follicle and a dermal layer consisting of a collagen matrix supported by fibroblasts that actively participate in physiological responses in the skin. The development and maintenance of skin are supported by direct communication between the dermal and epidermal layers, and it is thought that signaling from the dermal compartment is vital for the correct functioning of epidermal progenitor cells.[3] Important characteristics of skin aging are epidermal thinning, loss of elasticity in the dermis and progressive atrophy of the subcutaneous fat,[4] which lead to a deteriorating quality in the appearance of the skin. It has been proposed that the aged fibroblasts could propagate the epidermal aging by paracrine mechanisms.[5]

Changes in the appearance and structure of the skin are caused by not only chronological or intrinsic processes but also external factors including ultraviolet (UV) exposure, chemical air pollution and relative air humidity. Extrinsic aging factors elicit distinct and overlapping effects on the molecular and physiological responses that can lead to a cumulative macromolecular damage associated with long-term changes in skin barrier, pigmentation and dermal elasticity. The major cellular processes

Correspondence: Olusola Clement Idowu
Hexis Lab, Science Central, The Core, Bath Lane, Newcastle upon Tyne NE45TF, UK
Tel +44 191 495 7311
Email sola@hexislab.com

triggered by environmental damage, mostly caused by UV and chemical air pollution, are associated with DNA damage, inflammation, increased expression of reactive oxygen species (ROS), reduction in antioxidants and accumulation of oxidized proteins that impair the activity of proteasome. Both acute stress and chronic stress caused by the accumulation of macromolecular damage in response to low doses of the environmental stressors over time are thought to drive the skin-aging process. Current and future research aims at understanding the consequences of the interactions between these distinct environmental factors and their combined effect on the target organ.[5]

The nuclear lamina constitutes a main structural element of the cell nucleus that is also involved in signal transduction between nucleo-cytoplams and extracellular environment. A key component of the nuclear lamina, type V intermediate filament proteins lamins assemble into a higher order structure at the inner nuclear membrane and play a crucial role in signal transduction, oxidative stress and DNA damage response.[6,7] Gene mutations leading to systemic loss of the nuclear lamina protein function give rise to a broad range of human degenerative disorders affecting the tissues of mesenchymal origin and referred to as laminopathies.[8] One manifestation of the laminopathies is frequently occurring skin conditions that are consistent with premature aging and include cutaneous atrophy, wrinkles, inflammation, xerosis, hyperkeratosis, changes in pigmentation and hair loss. A number of studies have suggested that lamin deficiencies are linked to diminished capacities of tissue repair due to increased sensitivity to stress. In this review, we summarize the aspects of the molecular and clinical manifestations of the environmental stress on human skin and the likely mechanisms linked to the protective role of the nuclear lamina in extrinsic skin aging.

Cutaneous manifestations of the systemic loss of the nuclear lamina protein function

The nuclear envelope constitutes a main structural component of the cell nucleus, providing physical support and a functional barrier for an organized intermolecular exchange between nucleoplasmic and cytoplasmic compartments and extracellular environment. It is composed of a double-unit membrane and a fibrous network, the nuclear lamina. Based on the biochemical and physical properties, the proteins have been classified as A-type lamins (lamin A and C; the products of alternative splicing of the LMNA gene) and B-type lamins (lamin B1 and B2; the separate products of LMNB1 and

LMNB2 genes, respectively).[9] Both types of lamins undergo post-translational modifications that are slightly different for each lamin subtype and involve farnesylation, proteolysis and carboxymethylation (B-type lamins) or additional proteolytic cleavage (A-type lamins) at the C-terminal CAAX motif.[10]

In addition to the structural roles in the nucleus, the nuclear lamina is involved in a range of other important functions, including genome organization, coordination of DNA replication and repair, transcription, cellular proliferation, differentiation and stress response pathways.[11] Normal human skin is characterized by a defined pattern of the nuclear lamina protein expression, with A-type lamins mostly detected in dermal fibroblasts and suprabasal epithelial cells and B-type lamins present in all cell types.[12] Gene mutations leading to a systemic loss of the nuclear lamina protein function give rise to a broad range of human degenerative and premature aging disorders affecting the tissues of mesenchymal origin and referred to as laminopathies. The loss of the nuclear lamina function has been linked to deficiency in lamins and lamina-associated proteins or altered processing of lamin A and is currently thought to underlie a spectrum of disorders with strikingly overlapping clinical phenotypes. Among the frequently reported problems within the group of accelerated aging, lipodystrophy syndromes, peripheral nerve and bone disorders are also observed in skin, typically in the patients diagnosed with Hutchinson–Gilford progeria syndrome (HGPS), familial partial lipodystrophy of the Dunnigan type (FPLD), Charcot–Marie–Tooth disease (CMT), atypical Werner syndrome (atypical WS), mandibuloacral dysplasia (MAD), Barraquer–Simons syndrome (or acquired partial lipodystrophy [APL]) and Buschke–Ollendorff syndrome (BOS). The clinically defined skin problems linked to the nuclear envelope alterations involve dry skin (CMT, HGPS, WS), wrinkles (HGFP, WS), cutaneous atrophy (MAD), changes in pigmentation (HGPS, FPLD2, MAD, WS), hyperkeratosis (FPLD2, MAD), collagenoma (BOS), alopecia (CMT, HGPS, WS) and changes in the subcutaneous fat (HGPS, FPLD2, MAD, APL). In addition, significant abnormalities in the nuclear architecture and its dynamics have been routinely detected in fibroblasts from skin biopsies of the patients affected by these disorders.[8,11]

Molecular and clinical manifestations of the environmental stress on human skin
UV radiation

One of the most potent extrinsic factors in skin physiology is UV radiation, leading to cumulative damage that is

dependent on the degree of UV exposure and skin type.[13] The effects of UV on human skin are largely dependent on the wavelength. Based on electrophysical properties, UV is subdivided into UVA (320–400 nm, 90–95% of the solar UV), UVB (280–320 nm, 5–10% of the total solar UV) and UVC (100–280 nm, absorbed by atmospheric ozone). UV penetrates the skin in a wavelength-dependent manner, and human skin is exposed to both UVA and UVB simultaneously. Importantly, although each wavelength range is recognized to have distinct effects, UVA and UVB combined could exert the molecular signals that affect the skin in an overlapping manner.[14,15] Most of the alterations detected in the photo-damaged skin had been previously considered to be caused by UVB. UVB is the most energetic radiation but reaches only the epidermis because of its short wavelength. It is directly absorbed by DNA leading to mutagenic photoproducts[16] and induces a cascade of cytokines and neurohormonal mediators in an inflammatory response and sunburn.[17,18] Such responses can be associated further with increased cell divisions following the activation of the tumor protein p53 (p53) signaling pathway and DNA repair immediately after UV exposure, leading to an increase in the epidermal thickness.[19]

A number of studies have demonstrated that longer wavelength UVA penetrates deeply into the basal layer of the epidermis and dermis and induces profound alterations in the dermal connective tissue that are directly linked to the generation of ROS. The feedback between ROS production by mitochondria and mitochondrial DNA (mtDNA) damage leads to mtDNA mutations that are up to 10-fold more recurrent in photo-aged skin.[20] ROS affect a number of signal transduction pathways, for example, the activity of nuclear transcription factors NF-κB and AP-1 that trigger the synthesis of inflammatory cytokines and matrix metalloproteinases (MMPs) to decrease the expression of collagen I and III.[21–23] ROS can also contribute to the oxidative damage of DNA, cell membranes and proteins via indirect photosensitizing reactions.[24,25] The accumulation of oxidized proteins impairs proteasomal function and the cellular ability to dispose of damaged molecules.[26]

Skin sensitivity to UV light and susceptibility to photo-damage have been linked to constitutive pigmentation. UV stimulates an increase in the melanin production but melanin also plays an important role in protecting the skin keratinocytes against radiation, with DNA damage and cellular transformation occurring more frequently in lightly pigmented skin.[27] Interestingly, melanin was also shown

to reduce UV-induced DNA damage in cultured cells.[28] In addition, alpha-melanocyte-stimulating hormone (α-MSH), ligand of the melanocortin 1 receptor (MC1R), not only induces melanin synthesis but has also an ability to reduce UVB-induced DNA damage by enhanced nucleotide excision repair (NER) in melanocytes, therefore directly influencing UV resistance.[29] It is however recognized that UV exposure associates with significantly more pronounced occurrence of pigment spots in human skin.[31]

The changes associated with DNA damage, oxidative stress, inflammation, ECM degradation and melanogenesis are collectively responsible for early signs of photo-aging including solar elastosis, pigment irregularities and telangiectasias.[30–32] A schematic illustration of the molecular mechanisms for UV-induced skin aging is represented in Figure 1.

A-type lamins demonstrate increased expression in the epidermis of photo-exposed young human skin, suggestive of the likely photo-protective mechanism (Markiewicz, 2016 unpublished data). Recently, the A-type lamins have been implicated in DNA damage response pathways. Lamin-deficient progeroid fibroblasts demonstrate persistent levels of basal DNA damage, increase in DNA damage-responsive genes such as ataxia-telangiectasia mutated (ATM) kinase and sensitivity to genotoxic factors such as UV and ionizing radiation.[33,34] Importantly, the A-type lamins regulate the levels of DNA repair protein p53-binding protein 1 (53BP1) and facilitate its rapid recruitment to the sites of DNA damage, with the DNA repair significantly impaired due to delayed recruitment and proteasomal degradation of 53BP1 in laminopathy cells.[33–35] In addition to the impaired recruitment of the DNA repair components, the cells also demonstrate an abnormal accumulation of NER protein, xeroderma pigmentosum group A (XPA), at sites of DNA damage.[36] A deficiency in the mechanisms of repair of the DNA damage caused by UV light could also be closely linked with changes in pigmentation, such as hyperpigmentation and mottled pigmentation present in HGPS, FPLD2, MAD and atypical WS.

Recently, a novel role for A-type lamins has also emerged in the regulation of intracellular redox homeostasis. Lamin A-deficient and progeroid fibroblasts demonstrate increased basal levels of ROS together with upregulated expression and an impaired activity of ROS-detoxifying enzymes in response to oxidative stress.[37,38] Lamin A has been shown to be essential for an adaptive response to oxidative stress, with conserved C-terminal cysteine residues promoting the formation of inter- and intra-disulfide bonds upon mild oxidative stress.
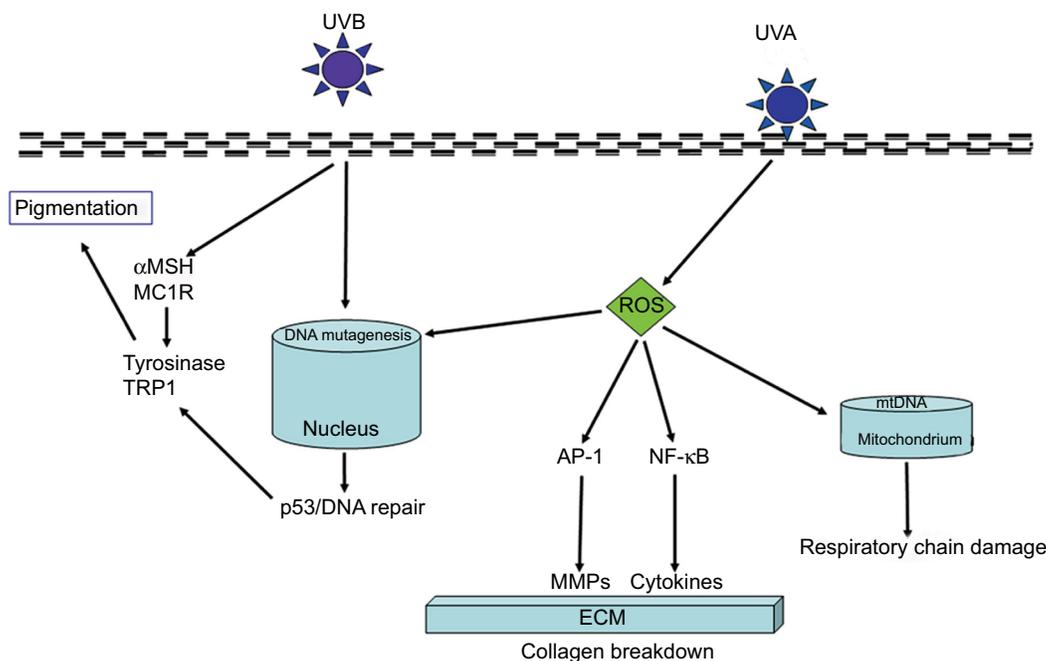
Figure 1 Schematic representation of the molecular mechanisms underlying the DNA damage, oxidative stress, inflammation, ECM degradation and pigmentation in UV-induced skin aging.
Abbreviations: ECM, extracellular matrix; ROS, reactive oxygen species; UV, ultraviolet.

Consequently, loss of these residues or lamin A deficiency promotes the nuclear disorganization and premature cellular aging concurrent with chronic ROS stimulation and enhanced sensitivity to oxidative stress.[6]

Enhanced inflammatory responses transmitted by the transcription factor NF-κB can also be triggered by defects in the nuclear lamina structure. The transcriptional activation of NF-κB and increased levels of pro-inflammatory cytokines or attenuated NF-κB activity in response to cytokine stimulation have been reported in the models of premature aging associated with lamin A.[39,40] In addition to the role in inflammation, NF-κB has been implicated in mechanotransduction, with the transcriptional activity highly affected by the elasticity of the extracellular matrix.[41] NF-κB also inhibits the expression of the collagen I (*COL*) gene.[42] Interestingly, collagen levels and matrix elasticity have been recently demonstrated to directly affect the cellular levels of lamin A, and lamin deficiency leads to defects in mechanotransduction and increased sensitivity to mechanical stress in the fibroblasts.[40,43] This mechanism could also play some role in the remodeling of the extracellular matrix and alterations in dermal elasticity underlying aging and premature aging of the skin. Wrinkles and cutaneous atrophy are typically present in HGPS, atypical WS and MAD syndrome.[8]

Chemical air pollution

The chemical air pollution has a major detrimental effect on human skin. Various air pollutants are generated from natural or human-made sources and include polycyclic aromatic hydrocarbons (PAHs; combustion of the organic material and automobile exhaust fumes), volatile organic compounds (VOCs; emissions from organic solvents and industrial facilities), particulate matter (PM; mixtures of particles from industrial sources), oxides (emitted from combustion sources) and ozone (O_3; interacts with UV, VOCs and nitrogen oxides to form active components of the photochemical smog).[44] The compounds mostly affect the outermost barrier of the skin but can also be absorbed via hair follicles and sebaceous glands or directly into the subcutaneous adipose tissue.[45,46] On the biochemical level and similarly to UV, chemical air pollutants interact with and activate the reactions associated with oxidative stress and DNA damage. PAHs are converted into redox-cyclic quinines that activate xenobiotic metabolism via ROS and epoxides and diols that bind DNA.[44,47] VOCs lead to the formation of photochemical oxidant products.[48] PM acts as a carrier for metals, ions and organic compounds with the capacities to localize in mitochondria and generate ROS.[49,50] Nitrogen dioxide (NO_2) leads to the generation of free radicals that stimulate oxidization of amino acids and lipid peroxidation.[51]

Most air pollutants act as unspecific irritants and immunomodulators, and levels of exposure that exceed the defensive capacities of the skin lead to the inflammatory and allergic conditions such as contact dermatitis, atopic dermatitis, telangiectasia and premature aging.[52–54] The primary target of ozone is the epidermis, and the oxidative damage is mediated by the formation of lipid peroxides and malondialdehyde and significant depletion of the nonenzymatic antioxidants such as vitamin E, vitamin C and glutathione (GSH) in the skin.[45,55,56] The impact of ozone on human skin in vivo has been analyzed using a specially designed exposure chamber with defined partial pressure corresponding to environmentally relevant, low doses of O_3. The exposure of skin samples to ozone in this system induced oxidative stress and 70% reduction in vitamin E in the stratum corneum.[56] Ozone is also capable of inducing inflammation, which is mediated by redox-sensitive transcription factors nuclear factor erythroid 2-related factor 2 (NRF2) and NF-kB in control of cellular detoxification.[57] Increased oxidative stress and impairment in the antioxidative responses associated with lamin A-associated premature aging phenotypes have also been recently attributed to the suppressed activity of the transcriptional factor NRF2.[58] Exposure to VOCs and NO_2 increases cytokines in the keratinocytes and oxidation of macromolecules in stratum corneum.[51,59] Clinical studies using a controlled climate chamber and involving control subjects and patients with atopic dermatitis evaluated the effects of short-term exposure and low concentration (0.1 ± 0.02 ppm) of NO_2 on skin in vivo. Exposure to NO_2 resulted in significant changes in skin surface and epidermal barrier function evidenced as an increase in transepidermal water loss (TEWL) in both groups.[51]

On the molecular level, one of the important mechanisms of the synergistic effects of air pollution is binding of the aryl hydrocarbon receptor (AhR) leading to the activation of xenobiotic metabolism and changes in skin pigmentation.[60,61] AhR ligands such as dioxin or PAH have a capacity to induce proliferation of melanocytes.[62] PM, especially the small-size airborne particles from traffic sources, is highly reactive toward skin surface and can also directly interact with melanocytes to affect their function. PM in association with bound PAHs can also generate oxidative stress that contributes to extrinsic skin aging. A recent detailed epidemiological study involving 400 volunteers demonstrated a significant impact of PM air pollution, particularly pigment spots and to less extent wrinkles that occur independently on UV radiation or in the absence of UV overexposure.[50] The study was based on the objective determination of traffic-related PM and PAH exposure by measurements of ambient particles and estimation of soot in fine dust at fixed monitoring sites in rural and urban areas of residence. The clinical assessment of skin aging was performed using validated score of intrinsic and extrinsic skin aging, Scinexa, with extrinsic aging represented by pigment spots, coarse wrinkles, elastosis and telangiectasia. Exposure to traffic-related air pollution correlated with the signs of extrinsic skin aging, in particular increased numbers of facial pigment spots, which had scores higher by up to 20% on forehead and cheeks, and less pronounced but still evident effect of wrinkles.[50]

Relative air humidity

The proper function of the skin depends on the intact, waterproof barrier that is composed of protein-rich corneocytes surrounded by the intercellular lipids in stratum corneum and crucial to the maintenance of healthy skin.[63] Epidermal keratinocytes undergo cell divisions and differentiation while migrating toward the surface of the skin to form the outermost barrier comprising the corneocytes.[64] Natural moisturizing factor (NMF) is composed of free amino acids and their derivatives such as urocanic acid, sugars, inorganic salts, lactic acid and urea that attract and bind water from the atmosphere into the corneocytes even at a low relative air humidity.[65,66] This mechanism facilitates hydration, maintenance of the osmotic pressure and activities of the enzymes involved in desquamation as well as increases the elasticity of the stratum corneum.[67] The free amino acids are derived from the proteolysis of the filaggrin protein, making up to 70–100% of the amino acid content in the stratum corneum. This processing is dependent on the water content within the corneocytes and external relative humidity, occurring at the outermost surface in humid environment and in deeper layers in low humidity. In addition, low air humidity impairs the ability of hydrolytic enzymes to break down filaggrin into NMF.[68,69] Low humidity leads further to changes in the values of TEWL and skin roughness, which is a measure of the integrity of the skin barrier function. The rapid alterations in skin properties, such as decrease in skin surface conductance and elasticity, can manifest at a low difference in relative air humidity.[70,71] Reduced levels or loss of NMF and damage to the skin barrier are associated with a number of chronic and age-related skin conditions. Xerosis manifests as scaling and flaking of the skin that can be experienced in low-humidity environment and becomes more prevalent with age. Localized areas of xerotic skin accompany a range of inflammatory skin conditions such as atopic dermatitis, irritant contact dermatitis, psoriasis and ichthyosis.[72–74]

The normal epidermal barrier function relies on the maintenance of the properly organized cornified envelope formed in the terminal stages of the keratinocyte differentiation program. A key stage to this process, a degradation of cell nucleus in the upper layers of the epidermis, is mediated by protein kinase B (AKT)-dependent phosphorylation and degradation of lamin A/C. The inhibition of this mechanism contributes to the nuclear retention in the cornified layer of the epidermis (parakeratosis), which is commonly associated with dry skin conditions and profound changes in the expression of terminal differentiation markers including filaggrin.[75] Changes in skin moisture can reflect both the relative air humidity and the mechanisms linked to the maintenance of epidermal cell turnover and the mechanical properties of the skin such as epidermal elasticity. Interestingly, the skin of lamin-deficient animal models characterized by an absence of all nuclear lamins (lamin A/C, B1 and B2) in keratinocytes demonstrates impaired development and profound disorganization of stratum corneum due to parakeratosis and accumulation of neutral lipid droplets, which is accompanied by thickened stratum granulosum and hyperkeratosis. Skin barrier defects are additionally evidenced by ichthyosis and severe epidermal water loss leading to dehydration.[76] A deficiency in the mechanisms responsible for the maintenance of the skin barrier properties, skin hydration and desquamation could be also underlying some of the phenotypes characterizing laminopathies, with dry skin frequently present in CMT, FPLD2 and atypical WS.

Molecular mechanisms of repair in extrinsically aged skin

Environmental factors associated with extrinsic skin aging exert a broad range of molecular and cellular effects that fall into distinct categories; nevertheless, they can also demonstrate inevitable overlapping outcomes. Some chemical air pollutants (ozone, nitrogen dioxide and sulfur dioxide) significantly reduce the effects of shorter wavelength UV; therefore, the ratio of UVB/UVA and their biological influence are highly dependent on the thickness of the ozone layer and air pollution. UVA in combination with chemical air pollutants significantly increases photo-damage in the skin through overlapping effects and cross-talk reactions of photochemical processes.[77,78] Chemical air pollution not only induces xenobiotic metabolism in the skin but also has a well-documented effect on pigmentation, oxidative stress response and inflammation that are the common physiological outcomes of UV radiation. Similarly, UV radiation affects the epidermal thickness and skin elasticity, and both parameters are also strongly associated with reciprocal responses to relative air humidity (Figure 2).

Genotoxic stress and molecular damage trigger the corresponding defense mechanisms involving DNA repair factors and ROS-detoxifying enzymes that play a crucial role in restoring the cellular structure and function. The main UV-induced DNA damage cellular response is the NER pathway involving several major repair components that include RAD, replication protein A, excision repair 1 (or ERCC1) and
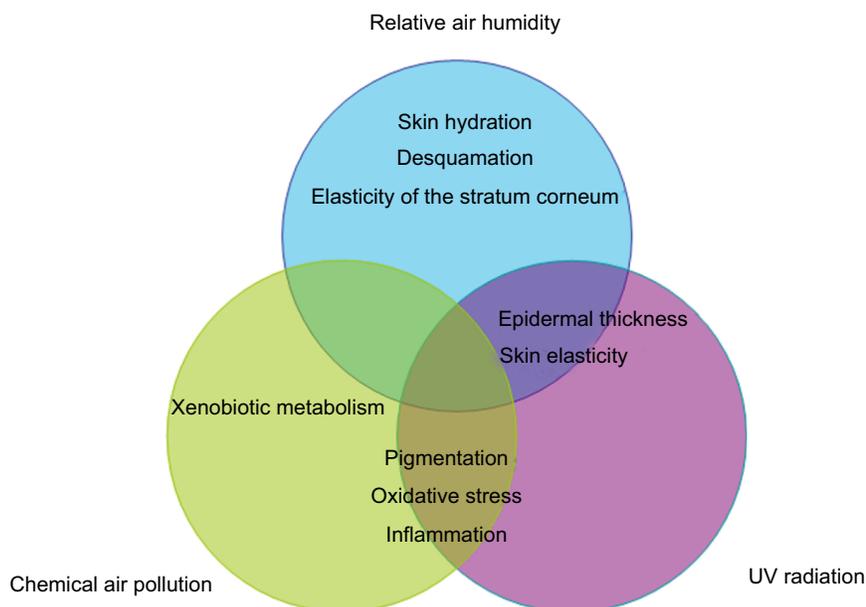

Figure 2 Schematic diagram representing the distinct and overlapping effects of relative air humidity, air pollution and UV radiation on human skin.
Abbreviation: UV, ultraviolet.

xeroderma pigmentosum complementation group E protein (or XPE/DDB2).[79–81] DNA damage also triggers the activation of checkpoint pathways, which initiate a temporary cell cycle arrest to allow the DNA repair. The cell cycle checkpoints are activated by transcription factor p53 in response to its phosphorylation by kinases ATM, ATM-related (ATR) and checkpoint kinase ½ (CHK1/2) and expression of the genes involved in the NER pathway, cell cycle inhibitors and pro-apoptotic proteins.[81–83]

In addition to the DNA repair, the second crucial mechanism of protection of skin cells against the damage and stimulation of repair involves a network of endogenous antioxidants that maintain ROS scavenging reactions and optimum redox balance. The system includes both nonenzymatic antioxidants such as ascorbate, GSH and α-tocopherol and antioxidant/detoxification enzymes such as catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), thioredoxin reductase (TrxR), glutamate cysteine ligase (*GCL*), glutathione transferase (*GST*), heme oxygenase-1 (*HO-1*) and NAD(P)H quinine oxidoreductase-1 (*NQO1*).[84–87] Expression of the genes involved in adaptive responses of skin to oxidative stress and damage is regulated by redox transcription factors NRF2 and FoxO (Forkhead box) family.[87,88]

Endogenous antioxidants and DNA repair can be influenced by several precursors and intermediates of melanogenesis, which could have other important functions in skin environment in addition to the biosynthesis of melanin.[89] For example, the eumelanin intermediate, 5,6-dihydroxyindole-2-carboxylic acid can stimulate the expression and activity of SOD and CAT upon entry into keratinocytes.[90] The main enzyme in the melanin synthesis pathway, dopachrome tautomerase, has been also demonstrated to regulate the p53 signaling pathway, which has a direct effect on the induction of hormonal agonists of MCR1 in melanocytes in response to UV-induced DNA damage.[91] Finally, tyrosinase and dopaquinone are involved in the interactions with antioxidant GSH, indicating a crucial role of the oxidative stress in the switch between eumelanogenesis and pheomelanogenesis.[92,93]

Premature aging of the skin characterized by skin atrophy and abnormal pigmentation is associated with deficiencies in the proteins involved in DNA repair and antioxidant defense.[94] Defects in NER are present in progeroid syndromes WS, HGPS and XP, with XP additionally demonstrating hypersensitivity to solar UV.[95–97] Premature skin aging is also linked with mutations in the ATM gene, resulting in inherited deficiencies in the checkpoint pathways and gradual accumulation of DNA damage.[98] Research of the past several

years demonstrated that the multiple components essential in the repair of the molecular damage are also functionally associated with the nuclear lamina proteins. A-type lamins control the expression levels and recruitment of DNA repair factors 53BP1, ATM, RAD and A(XPA) and the basal levels of DNA damage.[33–36] Lamin A also regulates the activity of redox transcription factor NRF2[58] and expression and activity of ROS-detoxifying enzymes SOD, CAT, GST and GPX in response to oxidative stress.[6,37,38] The accumulation of DNA damage, impaired redox homeostasis and inflammation could be responsible for the overlapping phenotypes associated with premature skin aging, such as decreased elasticity, hyperkeratosis and changes in pigmentation observed in laminopathies (Table 1).

Conclusion

The nuclear lamina proteins play important role in the maintenance of the structural properties of cell nuclei. The functional importance of the nuclear lamins and lamina-associated proteins has been recently highlighted by the reports indicating lamina involvement in the stabilization and recruitment of DNA repair proteins as well as transcription factors central to inflammatory response and redox homeostasis. Consequently, gene deficiencies leading to the loss of the nuclear lamina protein functions underlie a broad spectrum of degenerative disorders with frequent manifestations of prematurely aged skin. Typically, the abnormalities in nuclear morphology and chromatin organization characterizing the fibroblasts obtained from skin biopsies of laminopathy patients are accompanied by impaired growth, increased basal levels of DNA damage and ROS as well as enhanced sensitivity to oxidative and genotoxic stress. Environmental factors such as UV radiation, chemical air pollution and relative air humidity have both distinct and overlapping effects on skin characteristics associated with extrinsic aging including loss of elasticity, changes in epidermal thickness and pigmentation that are also evident in many degenerative disorders harboring lamin mutations. On the molecular level, analysis of the biological markers and signaling pathways indicates the extrinsic aging factors trigger many repair mechanisms or cellular damage phenotypes that are also regulated by the nuclear lamina proteins. This leads to the likely suggestion that the clinical manifestations of skin problems associated with laminopathies, and particularly with progeroid syndromes, arise because of impaired capacity to neutralize the damage caused by environmental factors and point at the nuclear lamina as a cellular safeguard against the stress.

Table 1 Summary of the molecular interactions and skin phenotypes associated with the nuclear lamina proteins

Molecular interactions	Roles	Related genes and proteins	References
DNA damage response	Control of the levels of basal DNA damage, expression levels and recruitment of DNA repair factors	53BP1	33–35
		ATM	33,34
		RAD	33
		A(XPA)	36
Oxidative stress and intracellular redox homeostasis	Control of the basal levels of ROS, expression and activity of ROS-detoxifying enzymes in response to oxidative stress	CAT	6,37
		SOD	37,38
		GST	6,38
		PRDX	38
	Adaptive response to oxidative stress through conserved cysteine residues and cellular sensitivity to oxidative stress	LMNA	6
	Lamin A-dependent regulation of activity of redox transcription factors	NRF2	58
Inflammation	Control of the inflammatory responses via transcription	NF-kB	39,40
Mechanotransduction	Reciprocal association between lamin A and collagen levels (ECM elasticity)	LMNA *COL*	40,43
	Skin phenotype: wrinkles, cutaneous atrophy present in HGPS, atypical WS, MAD	LMNA	
Epidermal thickness and differentiation	Absence of all nuclear lamins in keratinocytes leads to hyperkeratosis in the animal models	LMNA, LMNB1, LMNB2	76
	Skin phenotype: hyperkeratosis present in FPLD2, MAD	LMNA	
Skin hydration and desquamation	Absence of all nuclear lamins in keratinocytes leads to ichthyosis and dehydration in the animal models	LMNA, LMNB1, LMNB2	75,76
	Abnormal accumulation of lamin A/C in the epidermis prevents the formation of the stratum corneum in the animal models	AKT-1	
	Skin phenotype: dry skin present in CMT, FPLD2, atypical WS	LMNA	
Pigmentation	Indirect: functional interactions between ROS scavenging enzymes and the intermediates of melanogenesis	DHICA, SOD, CAT DCT, p53 TYR, dopaquinone, GSH	90–93
	Skin phenotype: hyperpigmentation, mottled pigmentation present in HGPS, FPLD2, MAD, atypical WS	LMNA	

Abbreviations: AhR, aryl hydrocarbon receptor; AP-1, activator protein 1; APL, acquired partial lipodystrophy; ATM, ataxia-telangiectasia mutated; ATR, ATM-related; BOS, Buschke–Ollendorff syndrome; CAT, catalase; CHK1/2, checkpoint kinase 1/2; CMT, Charcot–Marie–Tooth disease; *COL*, collagen; DCT, dopachrome tautomerase; DHICA, 5,6-dihydroxyindole-2-carboxylic acid; ECM, extracellular matrix; FoxO, Forkhead box; FPLD, familial partial lipodystrophy of the Dunnigan type; GCL, glutamate cysteine ligase; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, glutathione; GST, glutathione transferase; HGPS, Hutchinson–Gilford progeria syndrome; HO-1, heme oxygenase-1; LMNA, lamin A/C; LMNB1, lamin B1; LMNB2, lamin B2; MAD, mandibuloacral dysplasia; MC1R, melanocortin 1 receptor; MMP, matrix metalloproteinase; a-MSH, alpha-melanocyte-stimulating hormone; mtDNA, mitochondrial DNA; NER, nucleotide excision repair; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; NMF, natural moisturizing factor; NQO1, NAD(P)H quinine oxidoreductase-1; NO$_2$, nitrogen dioxide; NRF2, nuclear factor erythroid 2-related factor 2; p53, tumor protein 53; 53BP1, p53-binding protein 1; PAH, polycyclic aromatic hydrocarbon; PM, particulate matter; *PRDX*, peroxiredoxin; ROS, reactive oxygen species; RPA, replication protein A, SOD, superoxide dismutase; SNP, single nucleotide polymorphism; TEWL, transepidermal water loss; TrxR, thioredoxin reductase; TYR, tyrosinase; UV, ultraviolet; VOC, volatile organic compound; WS, Werner syndrome; XPA, xeroderma pigmentosum group A; XPE/DDB2, xeroderma pigmentosum complementation group E protein.

Addressing the roles of the DNA repair pathways, activity of antioxidant proteins and inflammatory responses in the context of both intrinsic and extrinsic aging will add a novel dimension to understand the laminopathies and aging. Furthermore, this also leads to the outstanding questions on the influence of the environment on the expression and activity of the nuclear lamina proteins, which remain unresolved challenge. Studies on these aspects, bringing the focus onto the association between cell nucleus and cellular environment, will facilitate a search for effective therapeutic agents such as bioactive molecules for DNA repair, ROS scavengers and anti-inflammatory factors, with a practical impact not only in dermatology but also in better understanding of aging.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Slominski A, Wortsman J. Neuroendocrinology of the skin. *Endocr Rev.* 2000;21(5):457–487.
2. Fuchs E. Scratching the surface of skin development. *Nature.* 2007;445(7130):834–842.
3. Jahoda CA, Reynolds AJ. Hair follicle dermal sheath cells: unsung participants in wound healing. *Lancet.* 2001;358(9291):1445–1448.
4. Zouboulis CC, Makrantonaki E. Clinical aspects and molecular diagnostics of skin aging. *Clin Dermatol.* 2011;29(1):3–14.
5. Krutmann J, Bouloc A, Sore G, Bernard BA, Passerone T. The skin aging exposome. *J Dermatol Sci.* 2017;85(3):152–161.
6. Pekovic V, Gibbs-Seymour I, Markiewicz E, et al. Conserved cysteine residues in the mammalian lamin A tail are essential for cellular responses to ROS generation. *Aging Cell.* 2011;10(6):1067–1079.

7. Gonzalo S. DNA damage and lamins. *Adv Exp Med Biol.* 2014;773: 377–399.

8. Schreiber KH, Kennedy BK. When lamins go bad: nuclear structure and disease. *Cell.* 2013;152(6):1365–1375.

9. Gerace L, Blum A, Blobel G. Immunocytochemical localization of the major polypeptides of the nuclear pore complex-lamina fraction. Interphase and mitotic distribution. *J Cell Biol.* 1998;79(2 Pt 1):546–566.

10. Weber K, Plessmann U, Traub P. Maturation of nuclear lamin A involves a specific carboxy-terminal trimming, which removes the polyisoprenylation site from the precursor; implications for the structure of the nuclear lamina. *FEBS Lett.* 1989;257(2):411–414.

11. Broers JL, Ramaekers FC, Bonne G, Yaou RB, Hutchison CJ. Nuclear lamins: laminopathies and their role in premature ageing. *Physiol Rev.* 2006;86(3):967–1008.

12. Venables RS, McLean S, Luny D, et al. Expression of individual lamins in basal cell carcinomas of the skin. *Br J Cancer.* 2001;84(4):512–519.

13. D'Orazio JA, Nobuhisa T, Cui R, et al. Topical drug rescue strategy and skin protection based on the role of Mc1r in UV-induced tanning. *Nature.* 2006;443(7109):340–344.

14. Schieke K, Ruwiedel H, Gers-Barlag S, Grether-Beck S, Krutmann J. Molecular crosstalk of the ultraviolet A and ultraviolet B signaling responses at the level of mitogen-activated protein kinases. *J Invest Dermatol.* 2005;124(4):857–859.

15. Polefka TG, Meyer TA, Agin PP, Bianchini RJ. Effects of solar radiation on the skin. *J Cosmet Dermatol.* 2012;11(2):134–143.

16. Pfeifer GP, You YH, Besaratinia A. Mutations induced by ultraviolet light. *Mutat Res.* 2005;571(1–2):19–31.

17. Clydesdale GJ, Dandie GW, Muller HK. Ultraviolet light induced injury: immunological and inflammatory effects. *Immunol Cell Biol.* 2001;79(6):547–568.

18. Matsumura Y, Ananthaswamy HN. Toxic effects of ultraviolet radiation on the skin. *Toxicol Appl Pharmacol.* 2004;195(3):298–308.

19. Coelho SG, Choi W, Brenner M, et al. Short- and long-term effects of UV radiation on the pigmentation of human skin. *J Investig Dermatol Symp Proc.* 2009;14(1):32–35.

20. Berneburg M and Krutmann J. Mitochondrial DNA deletions in human skin reflect photo- rather than chronologic aging. *J Invest Dermatol.* 1998;111(4):709–710.

21. Fisher GJ, Voorhees JJ. Molecular mechanisms of photoaging and its prevention by retinoic acid: ultraviolet irradiation induces MAP kinase signal transduction cascades that induce Ap-1-regulated matrix metalloproteinases that degrade human skin in vivo. *J Investig Dermatol Symp Proc.* 1998;3(1):61–68.

22. Fisher GJ, Datta SC, Talwar HS, et al. Molecular basis of sun-induced premature skin ageing and retinoid antagonism. *Nature.* 1996;379(6563):335–339.

23. Fisher GJ, Choi HC, Bata-Csorgo Z, et al. Ultraviolet irradiation increases matrix metalloproteinase-8 protein in human skin in vivo. *J Invest Dermatol.* 2001;117(2):219–226.

24. Tyrrell RM. Ultraviolet radiation and free radical damage to skin. *Biochem Soc Symp.* 1995;61:47–53.

25. Sander CS, Chang H, Hamm F, Elsner P, Thiele JJ. Role of oxidative stress and the antioxidant network in cutaneous carcinogenesis. *Int J Dermatol.* 2004;43(5):326–335.

26. Widmer R, Ziaja I, Grune T. Protein oxidation and degradation during aging: role in skin aging and neurodegeneration. *Free Radic Res.* 2006;40(12):1259–1268.

27. Situm M, Buljan M, Cavka V, Bulat V, Krolo I, Mihić LL. Skin changes in the elderly people—how strong is the influence of the UV radiation on skin aging? *Coll Antropol.* 2010; 34 Suppl 2:9–13.

28. Kobayashi N, Muramatsu T, Yamashina Y, Shirai T, Ohnishi T, Mori T. Melanin reduces ultraviolet-induced DNA damage formation and killing rate in cultured human melanoma cells. *J Invest Dermatol.* 1993;101(5):685–689.

29. Bohm M, Wolff I, Scholzen TE, et al. Alpha-melanocyte-stimulating hormone protects from ultraviolet radiation-induced apoptosis and DNA damage. *J Biol Chem.* 2005;280(7):5795–5802.

30. Flament F, Bazin R, Laquieze S, Rubert V, Simonpietri E, Piot B. Effect of the sun on visible clinical signs of aging in Caucasian skin. *Clin Cosmet Investig Dermatol.* 2013;6:221–232.

31. Fisher GJ, Wang ZQ, Datta SC, Varani J, Kang S, Voorhees JJ. Pathophysiology of premature skin aging induced by ultraviolet light. *N Engl J Med.* 1997;337(20):1419–1428.

32. 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.

33. Liu B, Wang J, Chan KM, et al. Genomic instability in laminopathy-based premature aging. *Nat Med.* 2005;11(7):780–785.

34. Gibbs-Seymour I, Markiewicz E, Bekker-Jensen S, Mailand N, Hutchison CJ. Lamin A/C-dependent interaction with 53BP1 promotes cellular responses to DNA damage. *Aging Cell.* 2015;14(2):162–199.

35. Gonzalez-Suarez I, Redwood AB, Perkins SM, et al. Novel roles for A-type lamins in telomere biology and the DNA damage response pathway. *EMBO J.* 2009;28(16):2414–2427.

36. Liu Y, Wang Y, Rusinol AE, et al. Involvement of xeroderma pigmentosum group A (XPA) in progeria arising from defective maturation of prelamin A. *FASEB J.* 2008;22(2):603–611.

37. Viteri G, Chung YW, Stadtman ER. Effect of progerin on the accumulation of oxidized proteins in fibroblasts from Hutchinson Gilford progeria patients. *Mech Ageing Dev.* 2010;131(1):2–8.

38. Sieprath T, Corne TD, Nooteboom M, et al. Sustained accumulation of prelamin A and depletion of lamin A/C both cause oxidative stress and mitochondrial dysfunction but induce different cell fates. *Nucleus.* 2015;6(3):236–246.

39. Osorio FG, Barcena C, Soria-Valles C, et al. Nuclear lamina defects cause ATM-dependent NF-kB activation and link accelerated aging to a systemic inflammatory response. *Genes Dev.* 2012;26(20):2311–2324.

40. Lammerding J, Schulze PC, Takahashi T, et al. Lamin A/C deficiency causes defective nuclear mechanics and mechanotransduction. *J Clin Invest.* 2004;113(3):370–378.

41. Ishihara S, Yasuda M, Harada I, Mizutani T, Kawabata K, Haga H. Substrate stiffness regulates temporary NF-κB activation via actomyosin contractions. *Exp Cell Res.* 2013;319(19):2916–2927.

42. Rippe RA, Schrum LW, Stefanovic B, Solís-Herruzo JA, Brenner DA. NF-kappaB inhibits expression of the alpha1(I) collagen gene. *DNA Cell Biol.* 1999;(10):751–761.

43. Swift J, Ivanovska IL, Buxboim A, et al. Nuclear lamin-A scales with tissue stiffness and enhances matrix-directed differentiation. *Science.* 2013;341(6149):1240104.

44. Baudouin C, Charveron M, Tarroux R, Gall Y. Environmental pollutants and skin cancer. *Cell Biol Toxicol* 2002;18(5):341–348.

45. Drakaki E, Dessinioti C, Antoniou CV. Air pollution and the skin. *Front. Environ. Sci.* 2014;2:11.

46. Puri P, Nandar SK, Kathuria S, Ramesh V. Effects of air pollution on the skin: A review. *Indian J Dermatol Venereol Leprol.* 2017;83(4): 415–423.

47. Penning TM, Burcynski ME, Hung CF, McCoull KD, Palackal NT, Tsuruda LS. Dihydrodiol dehydrogenase and polycyclic aromatic hydrocarbon activation: generation of reactive and redox active o-quinones. *Chem Res Toxicol.* 1999;12(1):1–18.

48. Schroeder P, Schieke SM, Morita A. Premature skin aging by infrared radiation, tobacco smoke and ozone. In: Gilchrest BA, Krutmann J, editors. *Skin Aging*. Berlin: Springer; 2006:45–53.

49. Kampa M and Castanas E. Human health effects of air pollution. *Environ Pollut.* 2008;151(2):362–367.

50. Vierkötter A, Schikowski T, Ranft U, et al. Airborne particle exposure and extrinsic skin aging. *J Invest Dermatol.* 2010;130(12):2719–2726.

51. Eberlein-König B, Przybilla B, Kûhnl P, et al. Influence of airborne nitrogen dioxide or formaldehyde on parameters of skin function and cellular activation in patients with atopic eczema and control subjects. *J Allergy Clin Immunol.* 1998; 101(1 Pt 1):141–143.

52. Halliwell B and Cross CE. Oxygen-derived species: their relation to human disease and environmental stress. *Environ Health Perspect.* 1994;102 Suppl 10:5–12.

53. Xu F, Yan S, Wu M, et al. Ambient ozone pollution as a risk factor for skin disorders. *Br J Dermatol.* 2011;165(1):224–225.

54. Valacchi G, Sticozzi C, Pecorelli A, Cervellati F, Cervellati C, Maioli E. Cutaneous responses to environmental stressors. *Ann N Y Acad Sci.* 2012;1271:75–81.

55. Thiele JJ, Traber MG, Tsang K, Cross CE, Packer L. In vivo exposure to ozone depletes Vitamins C and E and induces lipid peroxidation in epidermal layers of murine skin. *Free Radic Biol Med.* 1997;23(3):385–391.

56. He QC, Tavakkol A, Wietecha K, Begum-Gafur R, Ansari SA, Polefka T. Effects of environmentally realistic levels of ozone on stratum corneum function. *Int J Cosmet Sci.* 2006;28(5):349–357.

57. Valacchi G, Sticozzi C, Belmonte G, et al. Vitamin C compound mixtures prevent ozone-induced oxidative damage in human keratinocytes as initial assessment of pollution protection. *PLoS One* 2015;10(8):e0131097.

58. Kubben N, Zhang W, Wang L, et al. Repression of the antioxidant NRF2 pathway in premature aging. *Cell.* 2016;165(6):1361–1374.

59. Ushio H, Nohara K, Fujimaki H. Effect of environmental pollutants on the production of pro-inflammatory cytokines by normal human dermal keratinocytes. *Toxicol Lett.* 1999;105(1):17–24.

60. Afaq F, Zaid MA, Pelle E, et al. Aryl hydrocarbon receptor is an ozone sensor in human skin. *J Invest Dermatol.* 2009;129(10):2396–2403.

61. Hüls A, Vierkötter A, Gao W, et al. Traffic-related air pollution contributes to development of facial lentigines: further epidemiological evidence from Caucasians and Asians. *J Invest Dermatol.* 2016;136(5):1053–1056.

62. Krutmann J, Jux B, Luecke S, et al. Involvement of aryl hydrocarbon receptor (AhR-) signaling in skin melanogenesis. *J Investig Dermatol.* 2003;128:S220.

63. Schwartz J, Friedman AJ. Exogenous factors in skin barrier Repair. *J Drugs Dermatol.* 2016;15(11):1289–1294.

64. Proksch E, Brandner JM, Jensen JM. The skin: an indispensable barrier. *Exp Dermatol.* 2008;17:1063–1072.

65. Harding CR, Watkinson A, Rawlings AV, Scott IR. Dry skin, moisturization and corneodesmolysis. *Int J Cosmet Sci.* 2000;22(1):21–52.

66. Rawlings AV, Scott IR, Harding CR, Bowser PA. Stratum corneum moisturization at the molecular level. *J Invest Dermatol.* 1994;103(5):731–741.

67. Sato J, Katagiri C, Nomura J, Denda M. Drastic decrease in environmental humidity decreases water-holding capacity and free amino acid content of the stratum corneum. *Arch Dermatol Res.* 2001:293:477–480.

68. Scott IR, Harding CR, Barrett JG. Histidine-rich protein of the keratohyalin granules. Source of the free amino acids, urocanic acid, and pyrrolidone carboxylic acid in the stratum corneum. *Biochim Biophys Acta.* 1982;719(1):110–117.

69. Scott IR, Harding CR. Filaggrin breakdown to water binding compounds during development of the rat stratum corneum is controlled by the water activity of the environment. *Dev Biol.* 1986;115(1):84–92.

70. Sato J, Denda M, Nakanishi J, Koyama J. Dry condition affects desquamation of stratum corneum in vivo. *J Derm Sci.* 1998;18(3):163–169.

71. Egawa M, Oguri M, Kuwahara T, Takahashi M. Effect of exposure of human skin to a dry environment. *Skin Res Technol.* 2002;8(4):212–218.

72. Horii I, Nakayama Y, Obata M, Tagami H. Stratum corneum hydration and amino acid content in xerotic skin. *Br J Dermatol.* 1989;121(5):587–592.

73. Jacobson TM, Yüksel KU, Geesin JC, Gordon JS, Lane AT, Gracy RW. Effects of aging and xerosis on the amino acid composition of human skin. *J Invest Dermatol.* 1990;95(3):296–300.

74. Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet.* 2006;38(4):441–446.

75. Naeem AS, Zhu Y, Di WL, Marmiroli S, O'Shaughnessy RF. AKT1-mediated Lamin A/C degradation is required for nuclear degradation and normal epidermal terminal differentiation. *Cell Death Differ.* 2015;22(12):2123–2132.

76. Jung HJ, Tatar A, Tu Y, et al. An absence of nuclear lamins in keratinocytes leads to ichthyosis, defective epidermal barrier function, and intrusion of nuclear membranes and endoplasmic reticulum into the nuclear chromatin. *Mol Cell Biol.* 2014;34(24):4534–4544.

77. Thiele JJ, Podda M, Packer L. Tropospheric ozone: an emerging environmental stress to skin. *Biol Chem.* 1997;378(11):1299–1305.

78. Burke KE and Wei H. Synergistic damage by UVA radiation and pollutants. *Toxicol Ind Health.* 2009;25:219–224.

79. Kamileri I, Karakasilioti I, Garinis GA. Nucleotide excision repair: new tricks with old bricks. *Trends in Genetics.* 2012;28(11):566–573.

80. de Laat WL, Jaspers NG, Hoeijmakers JH. Molecular mechanism of nucleotide excision repair. *Genes Dev.* 1999;13(7):768–785.

81. Kulaksiz G, Reardon J, Sancar A. Xeroderma pigmentosum complementation group E protein (XPE/DDB2): purification of various complexes of XPE and analyses of their damaged DNA binding and putative DNA repair proteins. *Mol Cell Biol.* 2005;25(22):9784–9792.

82. Lakin ND, Jackson SP. Regulation of p53 in response to DNA damage. *Oncogene.* 1999;18(53):7644–7655.

83. Sax JK, Fei P, Murphy ME, Bernhard E, Korsmeyer SJ, El-Deiry WS. BID regulation by p53 contributes to chemosensitivity. *Nat Cell Biol.* 2002;4(11):842–849.

84. Wood JM and Schallreuter KU. A plaidoyer for cutaneous enzymology: our view of some important unanswered questions on the contributions of selected key enzymes to epidermal homeostasis. *Exp Dermatol.* 2008;17(7):569–578.

85. Pinnell SR. Cutaneous photodamage, oxidative stress and topical antioxidant protection. *J Am. Acad Dermatol.* 2003;48(1):1–22.

86. Wolfle U, Seelinger G, Bauer G, Meinke MC, Lademann J, Schempp CM. Reactive molecule species and antioxidative mechanisms in normal skin and skin aging. *Skin Pharmacol Physiol.* 2014;27(6):316–332.

87. Schafer M, Werner S. Nrf2-A regulator of keratinocyte redox signaling. *Free Radic Biol Med.* 2015;88(Pt B):243–252.

88. Klotz LO, Sanchez-Ramos C, Prieto-Arroyo I, Urbánek P, Steinbrenner H, Monsalve M. Redox regulation of FoxO transcription factors. *Redox Biol.* 2015;6:51–72.

89. Slominski A, Zmijewski MA, Pawelek J. l-tyrosine and l-dihydroxy-phenylalanine as hormone-like regulators of melanocyte functions. *Pigment Cell Melanoma Res.* 2012;25(1):14–27.

90. Kovacs D, Flori E, Maresca V, et al. The eumelanin intermediate 5,6-dihydroxyindole-2-carboxylic acid is a messenger in the cross-talk among epidermal cells. *J Invest Dermatol.* 2012;132(4):1196–1205.

91. Sendoel A, Kohler I, Fellmann C, Lowe SW, Hengartner MO. HIF-1 antagonizes p53-mediated apoptosis through a secreted neuronal tyrosinase. *Nature.* 2010;465(7298):577–583.

92. del Marmol V, Solano F, Sels A, et al. Glutathione depletion increases tyrosinase activity in human melanoma cells. *J Invest Dermatol.* 1993;101(6):871–874.

93. Jara JR, Aroca P, Solano F, Martinez JH, Lozano JA. The role of sulfhydryl compounds in mammalian melanogenesis: the effect of cysteine and glutathione upon tyrosinase and the intermediates of the pathway. *Biochim Biophys Acta.* 1988;967(2):296–303.

94. Kamenisch Y, Berneburg M. Progeroid syndromes and UV-induced oxidative DNA damage. *J Invest Dermatol.* 2009;14(1):8–14.

95. Bergoglio V, Magnaldo T. Nucleotide excision repair and related human diseases. *Genome Dyn.* 2006;1:35–52.

96. Davis T, Kipling D. Werner Syndrome as an example of inflamm-aging: possible therapeutic opportunities for a progeroid syndrome? *Rejuvenation Res.* 2006;9(3):402–407.

97. Cleaver JE, Lam ET, Revet I. Disorders of nucleotide excision repair: the genetic and molecular basis of heterogeneity. *Nat Rev Genet.* 2009;10(11):756–768.

98. Behrens A, van Deursen JM, Rudolph KL, Schumacher B. Impact of genomic damage and ageing on stem cell function. *Nat Cell Biol.* 2014;16(3):201–207.