Environmental influences on skin aging and ethnic-specific manifestations

Andrea Vierkötter* and Jean Krutmann
IUF–Leibniz Research Institute for Environmental Medicine; Düsseldorf, Germany

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Abbreviations: UV, ultraviolet; IR, infrared; ROS, reactive oxygen species; MMP, matrix metalloproteinases; mtDNA, mitochondrial DNA; AhR, arylhydrocarbon receptor; PM, particulate matter; PAH, polycyclic aromatic hydrocarbons

Skin aging does not only occur by passing time alone but also by the exposure to different environmental factors. The skin aging process, which is induced by environmental factors, is named premature or extrinsic skin aging process and can be distinguished from the chronologically (intrinsic) skin aging process by characteristic skin aging signs. Well known environmental factors leading to extrinsic skin aging are sun exposure and smoking. Recently, an epidemiological study could further discover an association between air pollution and skin aging. First of all the skin aging inducing effect of sun exposure was discovered and an own term (photoaging) was given to this special field of extrinsic skin aging. Mechanistic studies have further increased our knowledge about the molecular pathways by which environmental factors contribute to extrinsic skin aging. In this regard, profound knowledge how sun exposure leads to extrinsic skin aging were gained in the last years, and additionally there are also indications how smoking and air pollution might contribute to this process. Moreover it was realized that extrinsic skin aging manifests differently between different populations. Thus, in this review we summarize the influence of the different environmental factors: sun exposure, smoking and air pollution on skin aging and further present ethnic-specific manifestations of extrinsic skin aging.

Introduction

Aging of the skin is influenced by two separate processes. The general aging process, which is genetically determined and occurs by passing time alone, is called the intrinsic skin aging process, whereas the skin aging process induced by environmental factors is named extrinsic skin aging process. Each skin aging process leads to characteristic skin aging signs. The intrinsic skin aging process is characterized primarily by functional alterations than by gross morphological changes. The skin appears dry and pale with fine wrinkles displaying a certain degree of laxity and a variety of benign neoplasms. In contrast, the extrinsic skin aging process is characterized by striking morphologic and physiologic changes and in general leads to a premature aging of the skin. Prominent manifestations of the extrinsic skin aging process are coarse wrinkles, solar elastosis and pigment irregularities. These signs superimpose the intrinsic skin aging signs at chronically exposed areas of the body. The rate of extrinsic skin aging varies strikingly among individuals and among ethnic populations, which does not apply for the rate of intrinsic skin aging. On an individual basis the rate of extrinsic skin aging depends on the individual exposure pattern to different environmental factors and also on the individual genetic make-up. Some individuals might be more susceptible regarding skin damages by environmental exposure than other individuals. Furthermore, vast differences in regard to the manifestation of extrinsic skin aging between ethnic groups were observed. Here, one main difference between the ethnic groups, which might be most likely relevant, is the skin type. But also other genetic differences or habitual differences might be causal factors. The most important environmental factor leading to extrinsically aged skin is solar radiation. The detrimental effect of solar radiation on the facial appearance regarding skin aging was already recognized by the dermatologists Unna and Dubreuilh in the late 19th century, comparing the skin of sailors and farmers to that of indoor workers. Another important factor, which influences the appearance of the skin, was discovered in 1971 by Harry Daniell. He found striking associations between cigarette smoking and wrinkling. Recently, first observations indicate, that also airborne particle exposure leads to a premature skin aging.

In the following review, we will present the influence of environmental factors like solar radiation, smoking and air pollution on skin aging. Furthermore, we will describe the observed differences in the characteristic manifestation of extrinsic skin aging between different ethnic populations and underlying genetic and environmental factors.

Sun Exposure and Skin Aging

In the late 19th century the intimation that chronic sun exposure damages the skin leading finally to premature skin aging and skin cancer came from two dermatologists. Paul Gerson Unna observed severe degenerative changes in sun exposed areas of the...
skin of sailors in his clinic in the German seaport city Hamburg. Nearly at the same time William Auguste Dubreuilh observed a striking frequent incidence of keratoses and skin cancers in the vineyard workers in the Bordeaux region of France. However, this insight was temporarily lost since Albert M. Kligman published his findings on the structural changes that occur in human skin as a result of sun exposure, which was further distinguishable from the intrinsic skin aging process. This finding was strengthened by Lavker who also described profound structural differences between sun exposed and sun protected skin. Kligman and Kligman then coined the term “photoaging” in order to separate this special skin aging process from the general intrinsic skin aging process. From the whole spectrum of solar radiation it has been convincingly shown that the ultraviolet (UV) B (290–320 nm) and A (320–400 nm) fraction as well as the infrared (IR) A (770–1400 nm) fraction are able to induce the extrinsic skin aging process. UVB can penetrate through the upper layer of the skin, the epidermis; UVA even through the subjacent layer, the dermis and IRA is able to penetrate through all three layers of the skin, the epidermis, dermis and subcutis.

UV-induced skin aging process. The UV-induced skin aging process is complex and can be triggered by various pathways including receptor-initiated signaling, mitochondrial damage, protein oxidation, telomere-based DNA damage and arylhydrocarbon receptor (AhR) signaling (Fig. 1). The receptor-initiated signaling pathway is induced by photoproduction of reactive oxygen species (ROS). ROS activate cell surface receptors of cytokines and growth factors in keratinocytes as well as fibroblasts. Receptor activation then leads to intracellular signaling through stimulation of kinases inducing in a next step the transcription of nuclear transcription factor AP-1 and NFκB. Increased AP-1 transcription and activity on the one hand decreases the gene expression of the major dermal collagens I and III in fibroblasts leading to a reduced collagen synthesis. On the other hand AP-1 triggers the synthesis of matrix metalloproteinases (MMP) in keratinocytes and fibroblasts, which degrade mature dermal collagen. The other UV-induced transcription factor NFκB stimulates the transcription of inflammatory cytokines and is thus involved in the attraction of neutrophils containing neutrophil collagenases and thus is also involved in collagen degrading.

There is also a strong link between mitochondrial damage and photoaging. Mitochondrial damage or more precisely mitochondrial DNA (mtDNA) mutations can be induced in vitro and in vivo by repetitive sublethal UVA irradiation doses and are up to 10-fold more frequent in photoaged skin in comparison to sun-protected skin. The link to photoaging in regard to collagen destruction becomes even more obvious through the observation that mtDNA mutations are positively associated with MMP-1 levels without concomitant increase of MMP-1 specific tissue inhibitors. Mechanistically mtDNA damages are likely to be mediated through ROS. On the one hand, mitochondria continuously generate ROS themself during their main task of energy production (ATP) by consuming oxygen via the respiratory
chain. On the other hand, UVA exposure can further increase ROS generation. These ROS can then easily damage the mtDNA because it has only a limited capacity of base excision repair and is located near to the respiratory chain, where ROS is produced.35

UV radiation is also supposed to be a major contributor to protein oxidation and impairment of proteasomal function in skin,26 which are both hallmarks of aging. Oxidative protein damage may result in loss or gain of function, loss of protein structure and increased or decreased susceptibility for protein degradation.27 Further, the accumulation of oxidized proteins in the cell inhibits proteasomal function meaning the ability of the cell to successfully degrade damaged proteins. This pathway is supposed to be a potential reason for the accelerated dysfunction of skin tissue during aging38 and the maintenance of normal proteasome function is supposed to delay skin aging.29

Additionally, telomeres, the terminal portions of chromosomes, play an essential role in the general aging process. In the 1960th Leonard Hayflick discovered that human cells can only pass through a certain amount of cell divisions.30 This is due to the fact that telomer cannot be fully replicated and with each cell division the final 100–200 base pairs of the telomere are lost. When telomeres finally reach a critical length the cell will no longer divide and enters a state of replicative senescence or apoptosis. UV irradiation or other environmental exposures can also lead to telomere damage which induces similar aging processes like telomere shortening leading to a premature aging process.31

Furthermore, in the recent years evidence has increased that the arylhydrocarbon receptor (AhR) is an integral part of the UVB stress response and may have a role in photoaging as the MMP-1 gene is activated via the AhR signaling pathway.16

IRA-induced skin aging process. Accordingly to UV irradiation, IRA irradiation causes an increase in MMP-1 in vitro33 and in vivo44 without a concomitant upregulation of MMP-1 tissue inhibitor. Furthermore, IRA exposure also reduces collagen I expression.33 IRA irradiation of the skin is mainly absorbed by the surface of suspended PM in air of urban areas53 and are able to serve as carriers for organic chemicals and metals that are capable of localizing in mitochondria and generating ROS directly in the mitochondria and increases here the intra-mitochondrial production of ROS.34,35 These ROS then leave the mitochondria, alter intra-cytoplasmic calcium levels, activate the MAP kinases signaling pathway and lead to elevated MMP-1 expression.36 However, approximately 600 genes are IRA responsive36 and thus IRA radiation might further induce the extrinsic skin aging process through various other pathways. Up to now it is shown that IRA is able to induce angiogenesis36 and increases the number of mast cells in human skin in vivo,39 effects which are characteristic for photoaging.

Smoking and Skin Aging

In 1969 Harry Daniell recognized that smokers look older than non-smokers.39 Subsequently, he developed a wrinkle scoring system, which allowed him to analyze the association between smoking and wrinkled skin more objectively and with this scoring system he could validate his first impression.3 In the following years the association between smoking and skin wrinkling could be reproduced in various epidemiological studies.40–43 It was further elucidated that smoking is an independent skin aging-inducing environmental factor as the effect of sun exposure and smoking is multiplicative or additive.40–43 Once again the association between smoking and skin aging seems to be mediated through higher expression of MMP-1 and MMP-3 mRNA, but not of their specific inhibitors as well as a decrease of collagen I and III.43,44 Smoking seems also to be associated with increased elastosis and telangiectasia,45 indicating further molecular pathways in addition to the induction of MMP-1 expression. Recently, it was suggested that additionally the AhR pathway may play a role in the premature skin aging process of smoking-induced skin aging.46

Air Pollution and Skin Aging

Air pollution represents another environmental threat to which millions of humans worldwide are exposed. Adverse effects of air pollutants on human health are currently a serious concern and have been shown to include a higher risk for cancer, pulmonary and cardiovascular diseases.47–48 The skin is another organ which as outermost barrier is in direct contact with various air pollutants and thus the association between air pollution and skin damaging effects leading to skin aging is most likely. Some studies have already investigated in the effect of ozone on murine cutaneous tissue, which show evidence that ozone as a strong oxidative agent is capable of affecting the integrity of the skin.49,50 Furthermore, ozone was able to induce the expression of MMP-9 in murine skin indicating a role in matrix remodeling.50 A recent epidemiological study discovered a direct link between airborne particulate matter (PM) exposure and the occurrence of prominent skin aging signs especially pigment spots, but also wrinkles.50 One major mechanism by which ambient PM exerts its detrimental effects is through the generation of ROS.51 Furthermore, particles can serve as carriers for organic chemicals and metals that are capable of localizing in mitochondria and generating ROS directly in mitochondria52 leading to skin aging by mitochondrial damage. A third suggested skin aging inducing pathway might be through polycyclic aromatic hydrocarbons (PAHs) which are adsorbed on the surface of suspended PM in air of urban areas53 and are able to activate the xenobiotic metabolism via the AhR.

Ethnic Differences in the Manifestation of the Extrinsic Skin Aging Process

While the intrinsic skin aging process is rather a general process occurring similarly in all different populations, the extrinsic skin aging process manifests differently between populations regarding the time of development and also regarding prominent skin aging signs. Caucasians have an earlier onset and greater skin wrinkling than other populations and in general increased pigmentary problems are seen in Asians and in African-Americans.12,54 One main influencing factor for the ethnic-specific skin aging manifestation is the genetically determined skin type as there is an ethnic variation in melanin content and composition.55 Darker skin types are better protected regarding sun exposure due to the higher melanin content in their skin.56 The influence of the skin type can also be observed within one
population. In Caucasians, for example, two extrinsic skin aging manifestation forms are divided regarding their skin type. In fair-skinned persons the skin appears severely atrophic with multiple telangiectasis and a variety of premalignant lesions such as actinic keratosis, whereas in dark-skinned persons deep furrows and severe solar elastosis occur.57 Other underlying reasons for the ethnic-specific manifestation of skin aging might lay in further genetic variations beyond the skin type and/or in different exposure habits to environmental factors, which influence skin aging. Recently, an epidemiological study comparing the skin aging manifestation in Caucasian women from Düsseldorf in Germany with Japanese women from Nagoya in Japan discovered further underlying reasons for the ethnic-specific manifestation in these two populations. The first reason, which could explain a huge part why Japanese women expressed much less facial wrinkling than German women, was the higher antioxidant level in fast-growing blood of the Japanese women in comparison to the German women.58 The second reason was a difference in the distribution of a genetic marker in the SLC45A2 gene, which is involved in melanin synthesis. Here, Japanese women had a higher frequency of the allele which was positively associated with the occurrence of pigment spots and thus explained at least a part of the ethnic difference in the occurrence of pigment spots.29

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Conclusions
The previously described mechanisms by which the different environmental factors can contribute to premature/extrinsic skin aging are summarized in Figure 1. These mechanisms mainly lead to two processes, which disrupts the skin collagen matrix: (1) decreased collagen synthesis and (2) increased collagen degradation, leading to the characteristic appearance of extrinsically aged skin. All these mechanisms are also involved in the intrinsic skin aging process but they are increased by environmental exposure. Some of these environmental exposures are preventable by protecting the skin against sun exposure or by quitting smoking, but there are other environmental exposures like air pollution where up to now no protection is available. Here, new therapies have to be based on the molecular mechanism by which air pollutants induce extrinsic skin aging. Furthermore, it is important to investigate the extrinsic skin aging in different populations as environmental exposure lead to ethnic-specific skin aging manifestation. Through this, one can find the best therapy strategy for each population.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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