Pearl Chapter: Basis of Photoaging and the Use of Chemical Peelings

2

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2.1 Intrinsic Aging

Intrinsic aging is the process of senescence that affects all body organs, and the skin clearly shows the action of time and is transformed by it [1]. In 1990, there were more than 300 theories of aging. Today, the situation is even more complicated [2].

Intrinsic skin aging or chronologic aging is characterized by physiological changes genetically determined and includes structural, biochemical, and functional alterations [3, 4]. These changes are complex, and there are many theories of skin pathophysiology, like shortening of telomeres, reduction of cellular DNA repair capacity [5], cellular senescence, and decreased proliferative ability [6] mutations of extranuclear mitochondrial DNA [7]. Some of them are highlighted.

2.1.1 Shortening of Telomeres

Telomeres are sequences of repeating nucleopeptides present at the end of chromosomes (Fig. 2.1) [8]. Because DNA polymerase cannot transcribe the final sequence of bases present in the DNA ribbon during replication, the telomeric size is reduced at each mitotic cycle [9]. This telomere reduction is associated with cellular aging [10–13]. This mechanism contributes to the regulation of growth arrest in senescent human cell cultures the same way as stress or aberrant signaling-induced senescence (STASIS) [14]. Telomeres themselves are regarded as possible biomarkers of biological aging and cellular senescence. Other possible biomarkers are the free radicals [15].

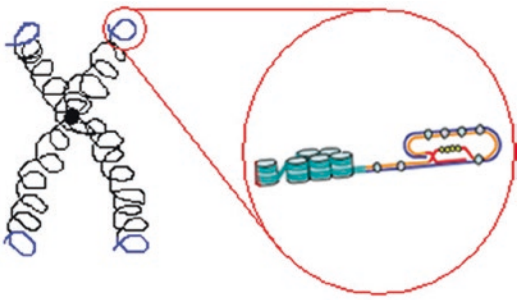

Fig. 2.1 Representation of a telomere, highlighted

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2.1.2 Free Radicals and Antioxidizing Ability

In 1956, Denham Harman proposed a theory that free radicals are also involved in this aging process: they would cause cellular damage, which would accumulate over the course of life and result in acceleration of dysfunctions [16]. Later, Yu and Yang described that not only the overexpressed production of reactive oxygen species (ROS) but also other oxidants, such as the reactive nitrogen species and reactive lipid species, cause oxidative damage [17].

In other studies, the degradation of oxidized products was unraveled. The body can neutralize ROS through the production of antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase, by an innate antioxidant defense system [18, 19]. This function is exerted by proteasome (multicatalyctic protease), whose activity seems to diminish over the course of life. With this, an incomplete degradation of oxidized proteins, increased protein aggregates, and the acceleration of cell dysfunction are observed, which, ultimately, lead to cellular aging [16, 20].

2.1.3 Cellular Senescence

The theory of cellular senescence has been demonstrated in keratinocytes, fibroblasts, and melanocytes [21]. There is a reduction in the proliferative potential of cells after a certain amount of division [22–24]. Senescent cells can also produce several cytokines, chemokines, growth factors, proteases, and matrix metalloproteases, a phenomenon described as senescence-associated secretory phenotype (SASP) [25]. A hallmark of skin aging is the degradation of collagen and other extracellular matrix components in the dermal connective tissue and can be induced through chronic MMPs secretion by senescent cells [26].

2.2 Intrinsic Factors

2.2.1 Genetic Characteristics

Many studies correlated genomes with the aging process [27, 28]. According to one of them, of all genes studied, 39 were regulated overlappingly in both sexes. They could serve as gender-independent biomarkers of endogenous skin aging. On the other hand, Wnt signaling pathway showed to be significantly downregulated in aged skin with decreased gene and protein expression for males and females [29].

Genic expression studies from aged sun-protected skins showed differential expression, possibly responsible for dysregulation of the insulin and STAT3 signaling pathway, the extracellular matrix (PI3, S100A2, A7, A9, SPRR2B), and the cell cycle (CDKs, GOS2). There was also evidence of a high regulation of proapoptotic genes, in part by a dysregulation of FOXO1. An under-expression of the JUN and FOS family members and cytoskeleton genes (KRT2A, KRT6A, and KRT16A) is also affected by intrinsic aging [30].

Another alteration observed in skin aging is the reduced expression of type I collagen due to downregulation of the transcription growth factor (TGF) β-1 and the connective tissue growth factor (CTGF). This reduced collagen expression is even associated with increased nuclear factor-κB (NF-κB) activity and increased expression of matrix metalloproteinase (MMP)-1 [31, 32].

An interesting discovery is that DNA methylation measures the cumulative effect of an epigenetic maintenance system, like a “clock of aging,” and can determine the individual age with an error of less than 3.6 years. This additional information can be used to address a host of questions in developmental biology, cancer, and aging research [33].

2.2.2 Sexual Hormones

With aging, the functional reserves of the endocrine system are reduced. As a result, the levels of sexual hormones decline. In females, hormonal changes are well documented. Women have a rapid decline of estrogen during menopause [34]. Estrogen is related to the stimulus of keratinocyte proliferation, which leads to the thickening of the epidermis, avoiding its atrophy [35]. In the dermis, the stimulus is of blood vessels and fibroblast production, thereby preserving collagen, elastic fibers, and glycosaminoglycans [36, 37]. With the

reduction of this hormone, the maintenance of these processes would be compromised.

The characterization of hormonal changes in males is a challenge, as there is not a remarkable hormonal decrease when compared with females. During the aging process, most men show a gradual reduction of circulating testosterone—something around 1% a year after 30 years of age. However, this number substantially varies among men [38]. Testosterone reduction is related to intrinsic aging because it broadly interacts with the skin, the whole body, and the male behavior itself [39].

2.3 Extrinsic Aging

Extrinsic aging results from the exposure to environmental factors—critical for the final result of the process [35]. Sun exposure intensifies skin aging due to ultraviolet radiation, a process referred to as photoaging [40]. Factors such as smoking and pollution may also lead to aging [41]. All these factors can lead to ROS generation, reducing collagen synthesis and increasing its degradation, contributing to premature skin aging (Fig. 2.2).

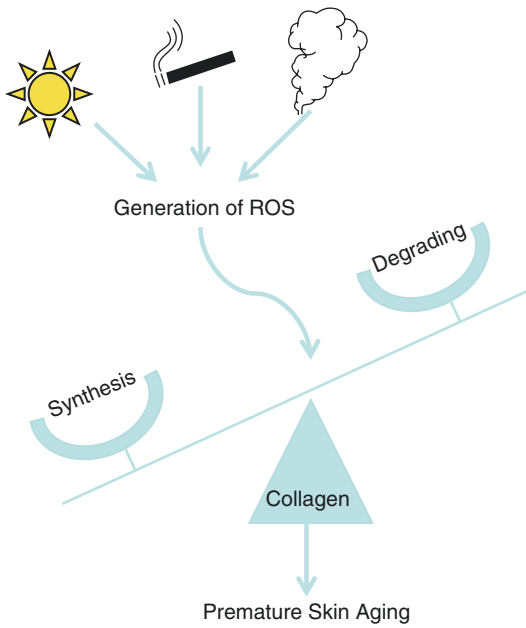

Fig. 2.2 Air pollution, smoking, and sun exposure leading to ROS generation, reducing collagen synthesis and increasing its degradation, contributing to premature aging

2.4 Extrinsic Factors

2.4.1 Air Pollution

The World Health Organization defines air pollution as contamination of the indoor or outdoor environment by any chemical, physical, or biological agent that modifies the natural characteristics of the atmosphere [42]. The skin acts as a physical, chemical, and immunological barrier against the environmental factors. This barrier can fail when the exposure to stressors is prolonged and repetitive, leading to the development of various skin diseases [43]. Major air pollutants which affect the skin are solar ultraviolet radiation, polycyclic aromatic hydrocarbons, volatile organic compounds, nitrogen oxides, particulate matter, cigarette smoke, heavy metals, and arsenic [44]. Air pollutants damage the skin by inducing oxidative stress and can lead to aging of the skin [41, 44].

Some pollutants stand out, such as ozone, particulate matter (PM), and polycyclic aromatic hydrocarbons. Ozone can affect the integrity of the skin on murine cutaneous tissue, can act as a strong oxidative agent, and can induce the expression of MMP-9, indicating a role in matrix remodeling [45, 46]. Oxidation of epidermal lipids and disturbed activity of matrix metalloproteinases contribute to wrinkling and extrinsic skin aging [47].

Particulate matter in the air consists of complex and varying mixtures of different sizes and composition. After penetrating the skin either through hair follicles or transdermally, PM exerts its detrimental effects through the generation of oxidative stress, contributing to extrinsic skin aging, characterized particularly by pigment spots on the face and nasolabial folds and less so by coarse wrinkles, solar elastosis, and telangiectasia [48–50]. Furthermore, particles can serve as carriers for organic chemicals and metals that are capable of localizing in mitochondria and generating ROS directly in mitochondria [51], leading to skin aging by mitochondrial damage [41].

Polycyclic aromatic hydrocarbons (PAHs) are adsorbed on the surface of suspended PM in the air of urban areas [52] and are converted into quinines, redox-cycling chemicals that produce reactive oxygen species [53]. They are associated with extrinsic skin aging, pigmentation, cancers, and acneiform eruption [52].

2.4.2 Smoking

In 1969 it was recognized that smokers look older than non-smokers [54]. Later, smoking was found to be an independent risk factor for premature facial wrinkling even after controlling for sun exposure, age, sex, and skin pigmentation [55]. A dose–response relationship between wrinkling and smoking has been identified, with smoking being a greater contributor to facial wrinkling than sun exposure [56].

Reactive oxidants and free radicals from cigarette smoke cause oxidative stress or secondary oxidative events and inhibition of antioxidant mechanisms [57–59]. Components of cigarette smoke increase transepidermal water loss, degeneration of connective tissue in the skin, and upregulation of matrix metalloproteinases-1 and -3 which degrade collagen and elastic fibers, which causes skin to become less elastic [43, 60, 61].

2.4.3 Ultraviolet Radiation and Photoaging

Photoaging is a cumulative process that is dependent on sun exposure degree and skin pigmentation level. Clinical presentation of sun-aged skin includes dryness of the skin; yellowish, wrinkled, atrophic, irregular pigmentation; telangiectasias; and pre-malignant lesions [62, 63]. Histologically there is thinning of the stratum spinosum, increased thickness of granular cell layer, flattening of the dermoepidermal junction, and an increased number of hypertrophic dopa-positive melanocytes [62, 64].

In aging process it is observed that keratinocytes become resistant to apoptosis and susceptible to DNA mutations. The number of melanocytes is also reduced, and the melanocytic density is altered. Langerhans cells also decrease in number with aging, resulting in loss of antigenic ability [62].

The immediate effect of sun exposure on the skin is cutaneous hyperpigmentation with delay in the formation of new melanin, which is reversible. The prolonged, recurrent sun exposure implies definitive changes in the quantity and distribution of melanin in the skin. The deposition of amorphous material in the papillary dermis, in place of conjunctive tissue, is the main element in differentiating chronologic aging and photoaging [62].

The morphological changes resulting from photoaging are, essentially, different from those observed in intrinsic aging. A parallel between such changes is shown in Table 2.1 [62, 40, 64, 65].

Table 2.1 Skin changes caused by intrinsic and extrinsic aging

	Intrinsic aging (chronologic)	Extrinsic aging (environmental factors)
Wrinkles	Thin	Deep
Stratum corneum	Unchanged	Tapered
Dysplastic cells	Few	Many
Collagen fibers	Slight change in size and organization	Great change in size and organization
Elastic fibers	Reorganized	↓ production and ↑ degeneration
Capillary follicle	↓ number and thinning	↓ number and structure: hair loss
Melanocytes	Normal	↓ number and melanin
Sebaceous and sweat glands	↓ number	↓ number: dry skin
Dermoepidermal junction	Slight flattening	Major flattening
Microvasculature	Reduced area	Telangiectasias, ecchymoses, inflammatory perivascular infiltrate.
Benign changes	Seborrheic keratosis	Seborrheic keratosis
Pre-malignant changes	_	Actinic keratosis
Malignant changes	_	Basal cell carcinoma Spindle cell carcinoma

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Table 2.2 Main mechanisms involved in aging

Intrinsic aging
Shortening of telomeres
Reduction of cellular DNA repair capacity
Cellular senescence and decreased proliferative ability
Mutations of extranuclear mitochondrial DNA
Extrinsic aging
Receptor-initiated signaling
Mitochondrial damage
Protein oxidation
DNA damage
Arylhydrocarbon receptor signaling

The ultraviolet (UV) B (290–320 nm) and A (320–400 nm) fractions [66] as well as the infrared (IR) A (770–1400 nm) fraction [67–69] can induce the extrinsic skin aging process [41].

Ultraviolet radiation penetrates the skin, and in accordance with the wavelength, it interacts with the different cells located in the different strata. Shortwave radiation (UVB) is more absorbed in the epidermis and predominantly affects keratinocytes but is also able to cross this layer and reach the papillary dermis [70]. Longer waves (UVA) penetrate more deeply and hit epidermal keratinocytes and dermal fibroblasts [71, 72]. IRA is able to penetrate through all three layers of the skin: the epidermis, dermis, and subcutis [41].

The UV-induced skin aging process is complex and can occur by various pathways including receptor-initiated signaling, mitochondrial damage, protein oxidation, DNA damage, and arylhydrocarbon receptor (AhR) signaling [41]. Table 2.2 compares the main mechanisms of intrinsic and extrinsic aging.

2.4.4 Receptor-Initiated Signaling Pathway

The reactive oxygen species produced by ultraviolet radiation activate cell surface receptors of cytokines and growth factors in keratinocytes and fibroblasts, which activate kinases, that induce expression and transcription factors such as nuclear κB transcription factor (NF-κB) and protein 1 (AP-1) [41, 63].

The activated NFkB stimulates the transcription of inflammatory cytokines (IL1, IL6, TNFa), attracting neutrophils and collagenases, associated in collagen degrading [73].

Increased AP-1, in turn, decreases the gene expression of dermal collagens I and III in fibroblasts, reducing collagen synthesis. Besides that, AP-1 stimulates the transcription of genes of matrix-disintegrating enzymes, such as metalloproteins (MMP-1, MMP-3, MMP-9), degrading mature dermal collagen [74, 75]. The radiation is not only related to collagen degradation but also contributes to reducing its synthesis. UVA ray exposure triggers two factors related to photoaging: induction of matrix metalloproteinases (MMPs) and mitochondrial mutation [72, 76, 77].

2.4.5 Mitochondrial Damage

Actually, mitochondrial DNA damages are likely to be mediated through ROS. Mitochondria contain multiple DNA copies and generate ROS during energy production (adenosine triphosphate—ATP), by consuming oxygen via the respiratory chain. ROS can easily damage lipids, proteins, and even the mtDNA itself [78, 79]. The mitochondrial DNA shows a high mutation rate due to its histone deficiency, limited capacity of base excision repair, and proximity to ROS [79, 80].

UVA exposure can further increase ROS generation and induce mutations at the mitochondrial DNA [72, 81], like deletion of 4977 bp (base pair), the most often found mutation in aged tissues [63, 82–87]. While this genic change can be detected in tissues that are non-susceptible to solar rays [83], mtDNA mutations can be tenfold more frequent in photoaged skin in comparison to sun-protected skin [64, 78, 79, 88–92].

2.4.6 DNA Damage

Sunlight-induced DNA damage is considered the main cause for the genetic changes leading to skin lesions and carcinogenesis including malignant melanoma [93]. DNA, the main intracellular

chromophore for UVB [70], absorbs photons from UVB. This interaction increases ROS production and creates dimeric photoproducts, such as pyrimidines, which may be related to premalignant skin lesions [94, 95]. The DNA photoproducts that are induced by UVA are potentially more mutagenic than those induced by UVB, although UVB induces more cyclobutane pyrimidine dimers than UVA [96].

Ultraviolet radiation also alters RNA and implies the formation of dysfunction-causing proteins. A blockade in RNA transcription by a DNA photoproduct allows p53 activation, thereby inducing the apoptosis of irradiated keratinocytes [94].

These events activate multiple important signaling pathways related to cell growth, differentiation, senescence, DNA damage repair, connective tissue degradation, and inflammation [97]. This is followed by an irreversible blocking of cell cycle progression to prevent further DNA damage and increase the expression of senescence-associated genes [97, 98].

2.4.7 Arylhydrocarbon Receptor Signaling

It is known that UVB also generates ROS species [99] initiating DNA damage, in the nucleus, once DNA is chromophore of UVB [100]. But, in the recent years, arylhydrocarbon receptor (AhR) was demonstrated to integrate part of the UVB stress response associated with photoaging.

This DNA damage-independent pathway is initiated outside the nucleus by the cluster ring and the internalization of cell membrane-bound growth factor receptors, such as the epidermal growth factor receptor (EGFR) [101]. AhR is activated in human epidermal keratinocytes upon exposure to UVB radiation, producing a series of photoproducts from tryptophan, which is free in the cytoplasm. These photoproducts are ligands of the AhR and activate it. This process leads to regulation of inflammation-associated genes, such as cyclooxygenase2 (COX2), that increase the expression of matrix metalloproteinases such as MMP-1 and MMP-3, among other proteases [102–105], melanocyte proliferation, and melanin synthesis [58, 106]. In this scenario, the molecular response to solar aggression is evident. These mechanisms are briefly illustrated in Fig. 2.3.

2.4.8 Infrared Radiation

IRA irradiation is mainly absorbed by mitochondria, where copper could serve as a chromophore [107], and increases intra-mitochondrial production of ROS [108, 109]. ROS can increase intra-cytoplasmic calcium levels, activate the MAP kinases signaling pathway, and lead to elevated MMP-1 expression. Approximately 600 genes are IRA responsive [110], and thus IRA radiation might further induce the extrinsic skin aging process through various other pathways. Important functions of the human skin which are characteristic for photoaging, such as angiogenesis [111] and production of mast cells [54], can be induced by IRA. Though IR does not induce tumorigenesis in the skin to the same extent as UVB, it is associated with a more aggressive tumor growth [112].

2.5 Conclusion

Ultimately, simply put, aging results from the modulation imbalance of collagen (with higher degradation and reduction of its synthesis) caused by excessive free radicals. Exposure to certain environmental factors, such as ultraviolet radiation, smoking, and air pollution, induces or enhances this process, thereby leading to premature or exogenous aging.

Even with all biomolecular advances, prevention is still the best way to fight aging and its consequences, by avoiding the exposure to well-known exogenous factors. Endogenous and exogenous aging are objects of many research studies involving diet components in order to avoid or minimize the signs of time; however, there is still a lot to be proven. The advance in the knowledge of its pathogenesis is expected to corroborate with new therapeutic findings.

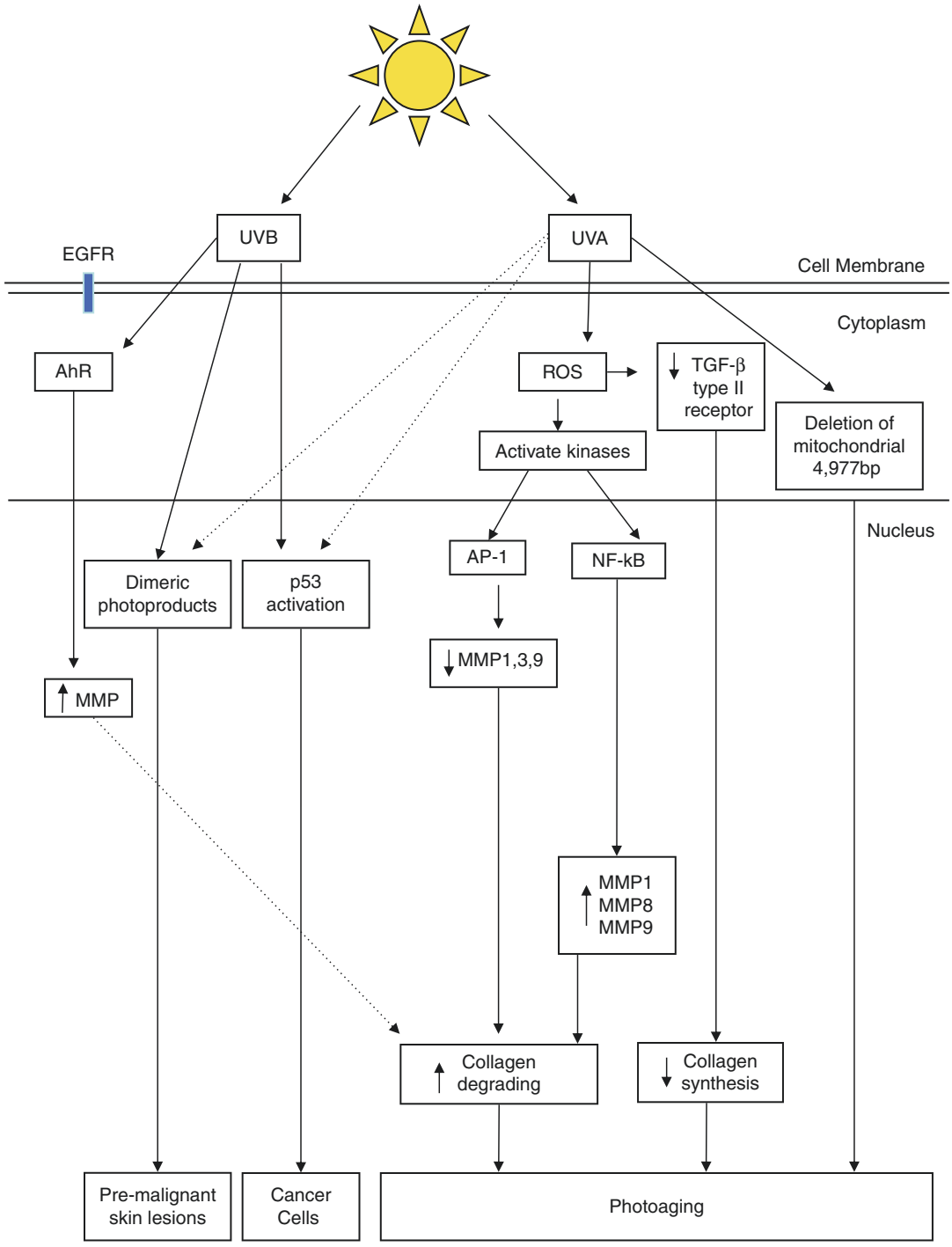

Fig. 2.3 Cellular effects of ultraviolet radiation. AhR signaling pathway. UVB forming photoproducts that lead to pre-malignant lesions. UVA/UVB action on p53, producing cancer cells. Deletion of mitochondrial 4977 bp and ROS production by UVA radiation, ultimately, resulting in photoaging. (Adapted with permission from Montagner and Costa [65])

References

1. Noh EM, Park J, Song HR, Kim JM, Lee M, Song HK, Hong OY, Whang PH, Han MK. Skin aging-dependent activation of the PI3K signaling pathway via downregulation of PTEN increases intracellular ROS in human dermal fibroblasts. Oxidative Med Cell Longev. 2016;2016:6354261.
2. Kanaki T, Makrantonaki E, Zouboulis CC. Biomarkers of skin aging. Rev Endocr Metab Disord. 2016;17(3):433–42.
3. Farage MA, Miler KW, Elsner P, Maibach HI. Intrinsic and extrinsic factors in skin ageing: a review. Int J Cosm Sci. 2008;30:87–95.
4. Farage MA, Miler KW, Elsner P, Maibach HI. Characteristics of the aging skin. Adv Wound Care. 2013;2:5–10.
5. Allsopp RC, Vaziri H, Patterson C, Goldstein S, Younglai EV, Futcher AB, et al. Telomere length predicts replicative capacity of human fibroblasts. Proc Natl Acad Sci U S A. 1992;89:10114–8.
6. Smith JR, Pereira-Smith OM. Replicative senescence: implications for in vivo aging and tumor suppression. Science. 1996;273:63–7.
7. Michikawa Y, Mazzucchelli F, Bresolin N, Scarlato G, Attardi G. Aging-dependent large accumulation of point mutations in the human mtDNA control region for replication. Science. 1999;286:774–9.
8. Meyne J, Ratliff R, Moyzis R. Conservation of the human telomere sequence (TTAGGC)n among vertebrates. Proc Natl Acad Sci U S A. 1989;86:7049–53.
9. Yaar M, Eller MS, Gilchrest BA. Fifty years of skin aging. J Investig Dermatol Symp Proc. 2002;7:51–8.
10. Kosmadari MG, Gilchrest BA. The role of telomeres in skin aging/photoaging. Micron. 2004;35:155–9.
11. Dimri GP, Lee X, Basile G, Acosta M, Scott G, Roskelley C, et al. A biomarker that identifies senescent human cells in culture and in aging skin in vivo. Proc Natl Acad Sci U S A. 1995;92:9363–7.
12. Yaar M, Gilchrest BA. Skin aging: postulated mechanisms and consequent changes in structure and function. Clin Geriatr Med. 2001;17:617–30.
13. Rabe JH, Mamelak AJ, McElgunn PJ, Morison WL, Sauder DN. Photoaging: mechanisms and repair. J Am Acad Dermatol. 2006;55:1–19.
14. Herbig U, Ferreira M, Condel L, Carey D, Sedivy JM. Cellular senescence in aging primates. Science. 2006;311:1257.
15. Green DR, Galluzzi L, Kroemer G. Mitochondria and the autophagy-inflammation-cell death axis in organismal aging. Science. 2011;333:1109–12.
16. Widmer R, Ziaja I, Grune T. Protein oxidation and degradation during aging: role in skin aging and neurodegeneration. Free Radic Res. 2006;40:1259–68.
17. Yu BP, Yang R. Critical evaluation of the free radical theory of aging. A proposal for the oxidative stress hypothesis. Ann N Y Acad Sci. 1996;786:1–11.
18. Callaghan TM, Wilhelm KP. A review of ageing and an examination of clinical methods in the assessment of ageing skin. Part I: cellular and molecular perspectives of skin ageing. Int J Cosmet Sci. 2008;30:313–22.
19. Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of aging. Nature. 2000;408:239–47.
20. Kraft DC, Deacaris CC, Rattan SI. Proteasomal oscillation during mild heat shock in aging human skin fibroblasts. Ann N Y Acad Sci. 2006;1067:224–7.
21. Hayflick L. The limited in vitro lifetime of human diploid cell strains. Exp Cell Res. 1965;37:614–36.
22. Gilchrest BA. In vitro assessment of keratinocyte aging. J Invest Dermatol. 1983;81:184s–9s.
23. Cristofalo VJ, Pignolo RJ. Replicative senescence of human fibroblast-like cells in culture. Physiol Rev. 1993;73:617–38.
24. Gilchrest BA, Vrabel MA, Flynn E, Szabo G. Selective cultivation of human melanocytes from newborn and adult epidermis. J Invest Dermatol. 1984;83:370–6.
25. Waldera Lupa DM, Kalfalah F, Safferling K, Boukamp P, Poschmann G, Volpi E, Götz- Rösch C, Bernerd F, Haag L, Huebenthal U, Fritsche E, Boege F, Grabe N, Tigges J, Stühler K, Krutmann J. Characterization of skin aging-associated secreted proteins (SAASP) produced by dermal fibroblasts isolated from intrinsically aged human skin. J Invest Dermatol. 2015;135:1954–68.
26. Velarde MC, Demaria M. Targeting senescent cells: possible implications for delaying skin aging: a mini-review. Gerontology. 2016;62(5):513–8.
27. Kennedy SR, Loeb LA, Herr AJ. Somatic mutations in aging, cancer and neuro- degeneration. Mech Ageing Dev. 2012;133:118–26.
28. Makrantonaki E, Pfeifer GP, Zouboulis CC. [Intrinsic factors, genes, and skin aging]. Hautarzt. 2016;67(2):103–6.
29. Makrantonaki E, Brink TC, Zampeli V, Elewa RM, Mlody B, Hossini AM, Hermes B, Krause U, Knolle J, Abdallah M, Adjaye J, Zouboulis CC. Identification of biomarkers of human skin ageing in both genders. Wnt signalling – a label of skin ageing? PLoS One. 2012;7(11):e50393. https://doi.org/10.1371/journal.pone.0050393.
30. Lener T, Moll PR, Rinnerthaler M, Bauer J, Aberger F, Richter K. Expression profiling of aging in the human skin. Exp Gerontol. 2006;41:387–97.
31. Makrantonaki E, Zouboulis CC. William J. Cunliffe Scientific Awards. Characteristics and pathomechanisms of endogenously aged skin. Dermatology. 2007;214:352–60.
32. Makrantonaki E, Bekou V, Zouboulis CC. Genetics and skin aging. Dermatoendocrinology. 2012;4:280–4.
33. Horvath S. DNA methylation age of human tissues and cell types. Genome Biol. 2013;14:R115.
34. Labrie F, Belanger A, Cusan L, Gomez JL, Candas B. Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. J Clin Endocrinol Metab. 1997;82:2396–402.

35. Pereira S. Dermatoses no idoso. In: Rotta O, editor. Guia de Dermatologia: clínica, cirúrgica e cosmiátrica. São Paulo: Manole; 2008. p. 567–91.
36. Verdier-Sevrain S, Bontè F, Gilchrest B. Biology of estrogens in skin: implications for skin aging. Exp Dermatol. 2006;15:83–94.
37. Wolff EF, Narayan D, Taylor HS. Long-term effects of hormone therapy on skin rigidity and wrinkles. Fertil Steril. 2005;84:285–8.
38. Bain J. Epidemiology, evaluation and diagnosis of andropause. Geriatr Aging. 2003;6(Suppl 10):4–8.
39. Tenover JL. Testosterone and the aging male. J Androl. 1997;18:103–6.
40. Wulf HC, Sandby-Møller J, Kobayasi T, Gniadecki R. Skin aging and natural photoprotection. Micron. 2004;35:185–91.
41. Vierkötter A, Krutmann J. Environmental influences on skin aging and ethnic-specific manifestations. Dermato-Endocrinology. 2012;4(3):227–31.
42. WHO air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide, global update 2005, summary of risk assessment; 2006. Available from: http://www.who.int/phe/health_topics/outdoorair/outdoorair_aqg/en/. Last accessed on 4 Apr 2016.
43. 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.
44. Puri P, Nandar SK, Kathuria S, Ramesh V. Effects of air pollution on the skin: a review. Indian J Dermatol Venereol Leprol. 2017;83:415–23.
45. Thiele JJ, Traber MG, Polefka TG, Cross CE, Packer L. Ozone-exposure depletes vitamin E and induces lipid peroxidation in murine stratum corneum. J Invest Dermatol. 1997;108:753–7.
46. Valacchi G, Pagnin E, Okamoto T, Corbacho AM, Olano E, Davis PA, et al. Induction of stress proteins and MMP-9 by 0.8 ppm of ozone in murine skin. Biochem Biophys Res Commun. 2003;305:741–6.
47. Rittié L, Fisher GJ. UV-light-induced signal cascades and skin aging. Ageing Res Rev. 2002;1:705–20.
48. Lademann J, Schaefer H, Otberg N, Teichmann A, Blume-Peytavi U, Sterry W. Penetration of microparticles into human skin. Hautarzt. 2004;55:1117–9.
49. Vierkötter A, Schikowski T, Ranft U, Sugiri D, Matsui M, Krämer U, et al. Airborne particle exposure and extrinsic skin aging. J Invest Dermatol. 2010;130:2719–26.
50. Mills NL, Miller MR, Lucking AJ, Beveridge J, Flint L, Boere AJ, et al. Combustion-derived nanoparticulate induces the adverse vascular effects of diesel exhaust inhalation. Eur Heart J. 2011;32:2660–71.
51. Li N, Sioutas C, Cho A, Schmitz D, Misra C, Sempf J, et al. Ultrafine particulate pollutants induce oxidative stress and mitochondrial damage. Environ Health Perspect. 2003;111:455–60.
52. Krutmann J, Jux B, Luecke S, Fritsche E, Abel J, Essel C, Rannug A. Involvement of arylhydrocarbon receptor (AhR-) signaling in skin melanogenesis. J Invest Dermatol. 2008;128:S220.
53. Penning TM. Dihydrodiol dehydrogenase and its role in polycyclic aromatic hydrocarbon metabolism. Chem Biol Interact. 1993;89:1–34.
54. Daniell HW. Smooth tobacco and wrinkled skin. N Engl J Med. 1969;280:53.
55. Kadunce DP, Burr R, Gress R, Kanner R, et al. Cigarette smoking: risk factor for premature facial wrinkling. Ann Intern Med. 1991;114:840–4.
56. Kennedy C, Bastiaens MT, Bajdik CD, Willemze R, et al. Leiden skin cancer study. Effect of smoking and sun on the aging skin. J Invest Dermatol. 2003;120:548–54.
57. Chow CK. Cigarette smoking and oxidative damage in the lung. Ann N Y Acad Sci. 1993;686:289–98.
58. Boyd AS, Shyr Y, King LE Jr. Basal cell carcinoma in young women: an evaluation of the association of tanning bed use and smoking. J Am Acad Dermatol. 2002;46:706–9.
59. Dietrich M, Block G, Norkus EP, Hudes M, Traber MG, Cross CE, et al. Smoking and exposure to environmental tobacco smoke decrease some plasma antioxidants and increase gamma-tocopherol *in vivo* after adjustment for dietary antioxidant intakes. Am J Clin Nutr. 2003;77:160–6.
60. Jorgensen LN, Kallehave F, Christensen E, Siana JE, Gottrup F. Less collagen production in smokers. Surgery. 1998;123:450–5.
61. Just M, Ribera M, Monsó E, Lorenzo JC, Ferrándiz C. Effect of smoking on skin elastic fibres: morphometric and immunohistochemical analysis. Br J Dermatol. 2007;156:85–91.
62. Binic I, Lazarevic V, Ljubenovic M, Mojsa J, Sokolovic D. Skin ageing: natural weapons and strategies. Evid Based Complement Alternat Med. 2013;2013:1–10.
63. Landau M. Exogenous factors in skin aging. Curr Probl Dermatol. 2007;35:1–13.
64. Berneburg M, Grether-Beck S, Kürten V, Ruzicka T, Briviba K, Sies H, et al. Singlet oxygen mediates the UVA-induced generation of the photoaging-associated mitochondrial common deletion. J Biol Chem. 1999;274:15345–9.
65. Montagner S, Costa A. Molecular basis of photoaging. An Bras Dermatol. 2009;84(3):263–9.
66. Kligman LH. Intensification of ultraviolet-induced dermal damage by infrared radiation. Arch Dermatol Res. 1982;272:229–38.
67. Schieke SM, Schroeder P, Krutmann J. Cutaneous effects of infrared radiation: from clinical observations to molecular response mechanisms. Photodermatol Photoimmunol Photomed. 2003;19:228–34.
68. Schroeder P, Haendeler J, Krutmann J. The role of near infrared radiation in photoaging of the skin. Exp Gerontol. 2008;43:629–32.
69. Schroeder P, Calles C, Benesova T, Macaluso F, Krutmann J. Photoprotection beyond ultraviolet radiation--effective sun protection has to include

protection against infrared A radiation-induced skin damage. Skin Pharmacol Physiol. 2010;23:15–7.
70. Sanches Silveira JEP, Myaki Pedroso DM. UV light and skin aging. Rev Environ Health. 2014;29:243–54. https://doi.org/10.1515/reveh-2014-0058.
71. Debacq-Chainiaux F, Leduc C, Verbeke A, Toussaint O. UV, stress and aging. Dermatoendocrinology. 2012;4:236–40.
72. Krutmann J. The role of UVA rays in skin aging. Eur J Dermatol. 2001;11:170–1.
73. Reelfs O, Tyrrel RM, Pourzand C. Ultraviolet a radiation-induced immediate iron release is a key modulator of the activation of NF-kappaB in human skin fibroblasts. J Invest Dermatol. 2004;122:1440–7.
74. Angel P, Szabowski A, Schorpp-Kistner M. Function and regulation of AP-1 subunits in skin physiology and pathology. Oncogene. 2001;20:2413–23.
75. Fisher GJ, Kang S, Varani J, Bata-Csorgo Z, Wan Y, Datta S, et al. Mechanisms of photoaging and chronological skin aging. Arch Dermatol. 2002;138:1462–70.
76. Wang XY, Bi ZG. UVB-irradiated human keratinocytes and interleukin-1alpha indirectly increase MAP kinase/AP-1 activation and MMP-1 production in UVAirradiated dermal fibroblasts. Chin Med J (Engl). 2006;119:827–31.
77. Watanabe H, Shindo K, Ida H, Tanaka H, Nagasaka T, Shiozawa Z. Aging effects of sympathetic reflex activities on skin nerves. Gerontology. 2003;49:366–73.
78. Ray AJ, Turner R, Nikaido O, Rees JL, Birch-Machin MA. The spectrum of mitochondrial DNA deletions is a ubiquitous marker of ultraviolet radiation exposure in human skin. J Invest Dermatol. 2000;115:674–9.
79. Koch H, Wittern KP, Bergemann J. In human keratinocytes the common deletion reflects donor variabilities rather than chronologic aging and can be induced by ultraviolet A irradiation. J Invest Dermatol. 2000;117:892–7.
80. Ballard JW, Dean MD. The mitochondrial genome: mutation, selection and recombination. Curr Opin Genet Dev. 2001;11:667–72.
81. Hernandez-Pigeon H, Jean C, Charruyer A, Haure MJ, Baudouin C, Charveron M, et al. UVA induces granzyme B in human keratinocytes through MIF: implication in extracellular matrix remodeling. J Biol Chem. 2007;282:8157–64.
82. Shigenaga MK, Hagen TM, Ames BN. Oxidative damage and mitochondrial decay in aging. Proc Natl Acad Sci U S A. 1994;91:10771–8.
83. Eshaghian A, Vleugels R, Canter JA, McDonald MA, Stasko T, Sligh JE. Mitochondrial DNA deletions serve as biomarkers of aging in the skin, but are typically absent in nonmelanoma skin cancers. J Invest Dermatol. 2006;126:336–44.
84. Shoffner JM, Lott MT, Voljavec AS, Soueidan SA, Costigan DA, Wallace DC. Spontaneous Kearns–Sayre/chronic external ophthalmoplegia plus syndrome associated with a mitochondrial DNA deletion: a slip-replication model and metabolic therapy. Proc Natl Acad Sci U S A. 1989;86:7952–6.
85. Lu CY, Lee HC, Fahn HJ, Wei YH. Oxidative damage elicited by imbalance of free radical scavenging enzymes is associated with largescale mtDNA deletions in aging human skin. Mutat Res. 1999;423:11–21.
86. Cortopassi GA, Arnheim N. Detection of a specific mitochondrial DNA deletion in tissues of older humans. Nucleic Acids Res. 1990;18:6927–33.
87. Cortopassi GA, Shibata D, Soong NW, Arnheim N. A pattern of accumulation of a somatic deletion of mitochondrial DNA in aging human tissues. Proc Natl Acad Sci U S A. 1992;89:7370–4.
88. Harbottle A, Krishnan KJ, Birch-Machin MA. Implications of using the ND1 gene as a control region for real-time PCR analysis of mitochondrial DNA deletions in human skin. J Invest Dermatol. 2004;122:1518–21.
89. Krishnan KJ, Harbottle A, Birch-Machin MA. The use of a 3895 bp mitochondrial DNA deletion as a marker for sunlight exposure in human skin. J Invest Dermatol. 2004;123:1020–4.
90. Berneburg M, Gattermann N, Stege H, Grewe M, Vogelsang K, Ruzicka T, et al. Chronically ultraviolet- exposed human skin shows a higher mutation frequency of mitochondrial DNA as compared to unexposed skin and the hematopoietic system. Photochem Photobiol. 1997;66:271–5.
91. Berneburg M, Krutmann J. Mitochondrial DNA deletions in human skin reflect photo rather than chronologic aging. J Invest Dermatol. 1998;111:709–10.
92. Berneburg M, Plettenberg H, Medve-König K, Pfahlberg A, Gers-Barlag H, Gefeller O, et al. Induction of the photoaging-associated mitochondrial common deletion in vivo in normal human skin. J Invest Dermatol. 2004;122:1277–83.
93. Schuch AP, Moreno NC, Schuch NJ, Menck CFM, Garcia CCM. Sunlight damage to cellular DNA: focus on oxidatively generated lesions. Free Radic Biol Med. 2017;107:110–24.
94. Svobodova A, Walterova D, Vostalova J. Ultraviolet light induced alteration to the skin. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2006;150:25–38.
95. Gilchrest BA. Photoaging. J Invest Dermatol. 2013;133:E2–6. https://doi.org/10.1038/skinbio.2013.176.
96. Runger TM, Farahvash B, Hatvani Z, Rees A. Comparison of DNA damage responses following equimutagenic doses of UVA and UVB: a less effective cell cycle arrest with UVA may render UVA-induced pyrimidine dimers more mutagenic than UVB-induced ones. Photochem Photobiol Sci. 2012;11:207–15.
97. Bosch R, Philips N, Suárez-Pérez J, Juarranz A, Devmurari A, Chalensouk-Khaosaat J, González S. Mechanisms of Photoaging and cutaneous photocarcinogenesis, and photoprotective strategies with phytochemicals. Antioxidants. 2015;4:248–68. https://doi.org/10.3390/antiox4020248.
98. Bhatia-Dey N, Kanherkar RR, Stair SE, Makarev EO, Csoka AB. Cellular senescence as the causal

nexus of aging. Front Genet. 2016;7:13. https://doi.org/10.3389/fgene.2016.00013.
99. Stege H, Roza L, Vink AA, Grewe M, Ruzicka T, Grether-Beck S, et al. Enzyme plus light therapy to repair DNA damage in ultraviolet-B-irradiated human skin. Proc Natl Acad Sci U S A. 2000;97:1790–5.
100. Bender K, Blattner C, Knebel A, Iordanov M, Herrlich P, Rahmsdorf HJ. UV-induced signal transduction. J Photochem Photobiol B. 1997;37:1–2):1–17.
101. Fritsche E, Schafer C, Calles C, Bernsmann T, Bernshausen T, Wurm M, Hubenthal U, Cline JE, Hajimiragha H, Schroeder P, Klotz LO, Rannug A, Furst P, Hanenberg H, Abel J, Krutmann J. Lightening up the UV response by identification of the arylhydrocarbon receptor as a cytoplasmatic target for ultraviolet B radiation. Proc Natl Acad Sci U S A. 2007;104(21):8851–6.
102. Herrmann G, Wlaschek M, Lange TS, Prenzel K, Goerz G, Scharffetter-Kochanek K. UVA irradiation stimulates the synthesis of various matrix-metalloproteinases (MMPs) in cultured human fibroblasts. Exp Dermatol. 1993;2(2):92–7.
103. Brenneisen P, Oh J, Wlaschek M, Wenk J, Briviba K, Hommel C, Herrmann G, Sies H, Scharffetter-Kochanek K. Ultraviolet B wavelength dependence for the regulation of two major matrix-metalloproteinases and their inhibitor TIMP-1 in human dermal fibroblasts. Photochem Photobiol. 1996;64(5):877–85.
104. Brenneisen P, Sies H, Scharffetter-Kochanek K. Ultraviolet-B irradiation and matrix metalloproteinases: from induction via signaling to initial events. Ann N Y Acad Sci. 2002;973:31–43.
105. Krutmann J, Morita A, Chung JH. Sun exposure: what molecular photodermatology tells us about its good and bad sides. J Invest Dermatol. 2012;132:976–84.
106. Jux B, Kadow S, Luecke S, Rannug A, Krutmann J, Esser C. The aryl hydrocarbon receptor mediates UVB radiation-induced skin tanning. J Invest Dermatol. 2011;131(1):203–10.
107. Karu TI. Mitochondrial signaling in mammalian cells activated by red and near-IR radiation. Photochem Photobiol. 2008;84(5):1091–9.
108. Schroeder P, Pohl C, Calles C, Marks C, Wild S, Krutmann J. Cellular response to infrared radiation involves retrograde mitochondrial signaling. Free Radic Biol Med. 2007;43:128–35.
109. Darvin ME, Haag S, Meinke M, Zastrow L, Sterry W, Lademann J. Radical production by infrared A irradiation in human tissue. Skin Pharmacol Physiol. 2010;23:40–6.
110. Krutmann J, Schroeder P. Role of mitochondria in photoaging of human skin: the defective powerhouse model. J Investig Dermatol Symp Proc. 2009;14(1):44–9.
111. Chung JH, Eun HC. Angiogenesis in skin aging and photoaging. J Dermatol. 2007;34:593–600.
112. Jantschitsch C, Weichenthal M, Maeda A, Proksch E, Schwarz T, Schwarz A. Infrared radiation does not enhance the frequency of ultraviolet radiation induced skin tumors, but their growth behaviour in mice. Exp Dermatol. 2011;20(4):346–50.