Skin aging

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SUMMARY

There are two main processes that induce skin aging: intrinsic and extrinsic. A stochastic process that implies random cell damage as a result of mutations during metabolic processes due to the production of free radicals is also implicated. Extrinsic aging is caused by environmental factors such as sun exposure, air pollution, smoking, alcohol abuse, and poor nutrition.

Intrinsic aging reflects the genetic background and depends on time. Various expressions of intrinsic aging include smooth, thinning skin with exaggerated expression lines. Extrinsically aged skin is characterized by photo damage as wrinkles, pigmented lesions, patchy hypopigmentations, and actinic keratoses.

Timely protection including physical and chemical sunscreens, as well as avoiding exposure to intense UV irradiation, is most important. A network of antioxidants such as vitamins E and C, coenzyme Q_{10}, alpha-lipoic acid, glutathione, and others can reduce signs of aging. Further anti-aging products are three generations of retinoids, among which the first generation is broadly accepted. A diet with lot of fruits and vegetables containing antioxidants is recommended as well as exercise two or three times a week.

KEY WORDS

skin aging, damage, extrinsic aging, intrinsic aging, stochastic damage, prevention

Skin aging

Life expectancy is continuously rising in developed countries, but the mystery of aging remains partially unresolved. The prevalence of mental and physical disability and diseases related to aging has increased. In many countries a demographic transition is occurring, involving aging of the population and reduced birthrates, as well as large-scale migrations. Advances in medical care have brought about a significant increase in life expectancy, especially throughout the 20th century. In the next 50 years, about one-third of women will be menopausal, and anti-aging medicine will gain importance.

Skin aging is particularly important because of its social impact. It is visible and also represents an ideal model organ for investigating the aging process (1). The "biological clock" affects both the skin and the internal organs in a similar way, causing irreversible degeneration (2, 3). However, Nicholas Perricone, a prominent American dermatologist, begins his book with the words "Wrinkled, sagging skin is not the inevitable result of

getting older. It's a disease, and you can fight it" (4). The five top cosmetic non-surgical procedures are botulinum toxin injection, microdermabrasion, filler injection, laser hair removal, and chemical peeling, whereas important cosmetic surgical procedures include liposuction, breast augmentation, eyelid surgery, nose reshaping, and breast reduction.

The factors that play a role in the aging process are genetic, extrinsic, and stochastic damage.

Intrinsic aging

Intrinsic aging depends on time. The changes occur partially as the result of cumulative endogenous damage due to the continuous formation of reactive oxygen species (ROS), which are generated by oxidative cellular metabolism. Despite a strong antioxidant defense system, damage generated by ROS affects cellular constituents such as membranes, enzymes, and DNA (5, 6). It has a genetic background, but is also due to decreased sex hormone levels. The telomere, a terminal portion of the eukaryotic chromosome, plays an important role. With each cell division, the length of the human telomere shortens. Even in fibroblasts of quiescent skin more than 30% of the telomere length is lost during adulthood (7). Telomeres are short sequences of bases in all mammals, and are arranged in the same mode (TTAGGG). The enzyme telomerase is responsible for its maintenance. It seems that telomeres are responsible for longevity (8). The progressive erosion of the telomere sequence (50–100 bp per mitosis) through successive cycles of replication eventually precludes protection of the ends of the chromosomes, thus preventing end-to-end fusions, which is incompatible with normal cell function. The majority of cells have the capacity for about 60 to 70 postnatal doublings during their lifecycles, and thereafter they reach senescence, remaining viable but incapable of proliferation. This event facilitates end-to-end chromosomal fusions resulting in karyotype disarray with subsequent apoptosis, thus serving as the "biological clock" (9).

Skin aging is affected by growth factor modifications and hormone activity that declines with age. The best-known decline is that of sex steroids such estrogen, testosterone, dehydroepiandrosterone (DHEA), and its sulfate ester (DHEAS) (10–12). Other hormones such as melatonin, insulin, cortisol, thyroxine, and growth hormone decline too. At the same time, induced levels of certain signaling molecules such as cytokines and chemokines decline as well, leading to the deterioration of several skin functions (13). Also, the levels of their receptors decline as well (14). At the same time, some signaling molecules increase with age. One of these is a cytokine called transforming growth factor-beta1, which induces fibroblast senescence. Cellular senescence is a result of molecular alterations in the cellular milieu as well as in DNA and proteins within the cell. All of these changes gradually lead to aberrant cellular response to environmental factors, which can decrease viability and lead to cell death (15).

Clinical manifestations of aged skin are xerosis, laxity, wrinkles, slackness, and the occurrence of benign neoplasms such as seborrheic keratoses and cherry angiomas. There are histological features that accompany these changes. In the epidermis, there is no alteration in the stratum corneum and epidermal thickness, keratinocyte shape, and their adhesion, but a decreased number of melanocytes and Langerhans cells is evident (6). The most obvious changes are at the epidermal-dermal junction: flattening of the rete ridges with reduced surface contact of the epidermis and dermis. This results in a reduced exchange of nutrients and metabolites between these two parts. In the dermis several fibroblasts may be seen, as well as a loss of dermal volume (6, 16). A decrease in blood supply due to a reduced number of blood vessels also occurs. There is also a depressed sensory and autonomic innervation of epidermis and dermis. Cutaneous appendages are affected as well. Terminal hair converts to vellus hair. As melanocytes from the bulb are lost, hairs begin to gray. Further reasons for graying are decreased tyrosinase activity, less efficient melanosomal transfer and migration, and melanocyte proliferation (17).

Factors that contribute to wrinkling include changes in muscles, the loss of subcutaneous fat tissue, gravitational forces, and the loss of substance of facial bones and cartilage. Expression lines appear as result of repeated tractions caused by facial muscles that lead to formation of deep creases over the forehead and between eyebrows, and in nasolabial folds and periorbital areas. Repeated folding of the skin during sleeping in the same position on the side of the face contributes to appearance of "sleeping lines." Histologically, thick connective tissue strands containing muscle cells are present beneath the wrinkle (18). In the muscles an accumulation of lipofuscin (the "age pigment"), a marker of cellular damage, appears. The deterioration of neuromuscular control contributes to wrinkle formation (19). The constant gravitational force also acts on the facial skin, resulting in an altered distribution of fat and sagging. Skin becomes lax and soft tissue support is diminished. Gravitational effects with advanced years play an important role and contribute to advanced sagging. This factor is particularly prominent in the upper and lower eyelids, on the cheeks, and in the neck region.

Table 1. Glogau's photoaging classification (5, 31).

Type	Characteristics
1: No wrinkles	Typical age 20s to 30s Early photoaging Mild pigmentary changes No keratosis No or minimal wrinkles
2: Wrinkles in motion	Typical ages late 30s to 40s Early to moderate photoaging Early senile lentigines Palpable but not visible keratoses Parallel smile lines beginning to appear laterally to mouth
3: Wrinkles at rest	Typical age 50 or older Advanced photoaging Obvious dyschromias, telangiectasias Visible keratoses
4: Only wrinkles	Typical age 60 or older Severe photoaging Yellow-gray skin Precancerous lesions No normal skin

Fat depletion and accumulation at unusual sites contributes to the altered appearance of the face (20). It affects the forehead, periorbital, and buccal areas, the inner line of nasolabial folds, and the temporal and perioral regions. At the same time it accumulates submentally, around the jaws, at outer lines of nasolabial folds and at lateral malar areas. In contrast to the young, in whom fat tissue is diffusely distributed, in aged skin fat tends to accumulate in pockets, which droop and sag due to the force of gravity (20, 21). The mass of facial bones and skeletal bones reduces with age. Resorption affects the mandible, maxilla, and frontal bones. This loss of bone enhances facial sagging and wrinkling with obliteration of the demarcation between the jaw and neck that is so distinct in young persons (22). Steven Hoefflin states that in the aging face the quantity and position of subcutaneous fat makes the difference. It also seems that estrogen and progesterone contribute to elastic fiber maintenance (23).

Extrinsic aging

Extrinsic aging develops due to several factors: ionizing radiation, severe physical and psychological stress, alcohol intake, poor nutrition, overeating, environmental pollution, and exposure to UV radiation. Among all these environmental factors, UV radiation contributes up to 80%. It is the most important factor in skin aging, especially in premature aging. Both UVB (290–320 nm), and UVA (320–400 nm) are responsible, and the skin alterations caused by UV radiation depend upon the phenotype of photoexposed skin (5, 24).

UVB induces alterations mainly at the epidermal level, where the bulk of UVB is absorbed. It damages the DNA in keratinocytes and melanocytes, and induces production of the soluble epidermal factor (ESF) and proteolytic enzymes, which can be found in the dermis after UV exposure. UVB is responsible for appearance of thymidine dimers, which are also called "UV fingerprints." That is, after UVB exposure, a strong covalent bond between two thymidines occurs. With aging, this bond cannot be dissolved quickly, and accumulation of mutations occurs. Affected cells appear as sunburn cells 8 to 12 hours after exposure. Reduced production of DNA can be observed during the next 12 hours. Actinic keratoses, lentigines, carcinomas, and melanomas represent delayed effects. A mnemonic for UVB is ***B*** *as in* ***b****urn* or ***b****ad.*

UVA penetrates more deeply into the dermis and damages both the epidermis and dermis. The amount of UVA in ambient light exceeds the UVB by 10 to 100 times, but UVB has biological effects 1,000 times stronger than UVA. It is accepted that UVA radiation plays an important role in the pathogenesis of photoaging, so the mnemonic for UVA is ***A*** *as in* ***a****ging* (24). The exact mechanism of how UV radiation causes skin aging is not clear. The dermal extracellular matrix consists of type I and III collagens, elastin, proteoglycans, and fibronectin, and collagen fibrils strengthen the skin. Photoaged skin is characterized by alterations in dermal connective tissue. The amount and structure of this tissue seems to be responsible for wrinkle formation. In photoaged skin, collagen fibrils are disorganized and elastin-containing material accumulates (25). Levels of precursors as well as cross-links between type I and III collagens are reduced, whereas elastin is increased (26, 27). UV radiation increases the production of collagen-degrading enzymes, matrix metalloproteinases (MMPs), and the xeroderma pigmentosum factor (XPF), which can also be found in the epidermis. XPF induces epidermal-dermal invagination, representing the beginning of wrinkle formation. At the base of wrinkles, less type IV and VII collagen is found. This instability deepens the wrinkles. Each MMP degrades a different dermal matrix protein; for example, MMP-1 cleaves collagen types I, II, and III, and MMP-9 (gelatinase) degrades type IV and V and

gelatin. Under normal conditions, MMPs are part of a coordinated network and are regulated by their endogenous inhibitors (TIMPs). The imbalance between activation and inhibition can lead to proteolysis (28). The activation of MMPs can be triggered by UVA and UVB, but molecular mechanisms differ depending upon the type of radiation. UVA radiation can generate ROS that affect lipid peroxidation and generate DNA strand breaks (29). On the other hand, within minutes after exposure UVB radiation causes MMP activity and DNA damage. These effects can be observed after exposing human skin to one-tenth of the minimal erythema dose. Topical pretreatment with tretinoin inhibits activation of MMPs in UVB-exposed skin (30). The degree of skin damage following long-lasting UV irradiation also depends on the skin phototype according to Fitzpatrick. In lighter complexes (types I and II) more serious degenerative changes are elicited than in types III and IV, in which melanosomes in the upper epidermal layer serve as relatively good UVA and UVB protection. Glogau developed a photoaging scale that is used to clinically classify the extent of photodamage (Table 1) (5, 31). It has been stated that the number of melanocytes decreases by 8 to 20% every 10 years.

Another environmental factor contributing to premature aging is smoking. "Smoker's face" or "cigarette skin" are characteristic, implying increased facial wrinkling and an ashen and gray skin appearance (32, 33). A prematurely old appearance is a symptom of long-term smokers. Yellow and irregularly thickened skin is result of elastic tissue breakdown due to smoking (34) or to UV. Premature facial wrinkling is not reduced in women on hormone replacement therapy (35). Genetic predisposition may also influence the development of facial wrinkling (36). It seems that cigarette smoking induces the activation of MMPs in the same mode as in persons with significant sun exposure (37). Smoking also reduces facial stratum corneum moisture as well as vitamin A levels, which is important in reducing the extent of collagen damage (5). The photochemical activity of smog is due to the reduction of air pollutants such as nitrogen oxides and volatile organic compounds created from fossil fuel combustion in the presence of sunlight. Emission from factories and motor vehicle exhaust are primary sources of these compounds. The major targets of ozone in the skin are the superficial epidermal layers; this results in the depletion of antioxidants such as alpha-tocopherol (vitamin E) and ascorbic acid (vitamin C) in the superficial epidermal layers (38).

As stochastic damage is explained, the damage is initiated by random cosmic radiation and triggered by free radicals during cell metabolism, which damages cell lipid compounds, especially membrane structures. The free radical theory is one of the most widely accepted theories to explain the cause of skin aging. These compounds are formed when oxygen molecules combine with other molecules, yielding an odd number of electrons. That is, an oxygen molecule with paired electrons is stable, but one with an unpaired electron is very reactive and it takes electrons from other vital components. As result, cell death or mutation appear (4, 5).

Protection of the skin

The skin is equipped with two photoprotective mechanisms: the melanin in the lower layer of epidermis, and the urocanic acid barrier of the stratum corneum, which reflects and absorbs a significant amount of UVB radiation. The thickness of the stratum corneum appears to be highly significant for photoprotection (39).

Antioxidants provide protection against UVB-induced oxidative stress, especially in stratum corneum lipids. Even systemically applied antioxidants accumulate in the stratum corneum and play an important role against UV-induced skin damage (40, 41).

The body has developed further defense mechanisms that protect against UV radiation and dangerous free radicals. Antioxidants naturally occurring in the skin are superoxide dismutase, catalase, alpha-tocopherol, ascorbic acid, ubiquinone, and glutathione. Many of them are inhibited by UV and visible light (42). The antioxidant program consists of a diet containing large amounts of vitamins A, E, and C, grape-seed extracts, coenzyme Q10, and alpha-lipoic acid (4). The most highly recommended foods include: avocados, berries, dark green leafy vegetables, orange-colored vegetables and fruits, pineapples, salmon, and tomatoes.

The mainstay in the prevention of skin aging is photoprotection. UV filters are now present in cosmetic products for daily use, such as makeup, creams, lotions, and hair sprays. The general requirements are that modern sunscreens should protect against UVA and UVB rays and be photo-stable and water resistant.

Chemical UV filters have the capacity to absorb short-wavelength UV and transform photons into heat-emitting long-wavelength (infrared) radiation. Most of them absorb a small wavelength range. They can be divided into three groups. The first group consists of molecules that primarily absorb the UVB spectrum (p-aminobenzoic acid derivatives and zincacid esters), and second of molecules that primarily absorb the UVA spectrum (butyl-methoxydibenzoylmethane). The third group consists of molecules that absorb UVA and UVB photons (benzophenone). A combination of different filters in the same product renders the whole filter system photo-unstable.

That means that UV exposure causes photochemical reactions that generate ROS with subsequent phototoxic and photoallergic reactions. Great efforts have been made to stabilize molecules in UV filters, which has improved the efficacy of photoprotection with chemical UV filters. Today there is a growing need for standardization and evaluation of UVA photoprotection, while for UVB there is already consensus on the international level (1, 43).

The use of physical filters is encouraged. The most frequently used of these are microparticles of zinc oxide and titanium dioxide with diameters in the range of 10 to 100 nm. They are capable of reflecting a broad spectrum of UVA and UVB rays. They do not penetrate into the skin and thus have low potential for developing toxic or allergic effects. Today they are increasingly being used in combination with chemical filters. One disadvantage of the inorganic micropigments is that they reflect visible light, creating a "ghost" effect. This is one reason such sunscreens are often rejected by consumers (5, 43, 44).

Conclusion

This overview shows that, during the human life cycle, the skin is exposed to a number of unavoidable as well as avoidable damaging factors. Genetics also play a highly important role. In addition to all the conditions mentioned above, further processes pertaining to oxygenation and reduction are active in skin aging.

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