Mechanisms of Skin Aging

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Aging is a progressive and multifactorial process; the pathogenesis continues to be elucidated. Multiple physiologic changes occur in various tissues, leading to impaired biologic functioning and repair mechanisms. The facial aging process involves the epidermis, dermis, and subcutaneous tissues simultaneously. Solar radiation accelerates the body's natural aging process by various mechanisms. As our knowledge of the mechanisms of the aging process increases, we are better adept at developing methods to reverse its effects.

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The mechanisms of skin aging classically have been divided into 2 groups: intrinsic aging, which is the natural or chronologic aging of skin, and extrinsic aging, which is influenced by physical and chemical factors. When discussing extrinsic facial aging in particular, solar radiation is the major contributor because of the extensive cumulative exposure to UV radiation over one's lifetime. However, intrinsic or natural mechanisms also play a role in the way an individual ages, and both intrinsic and extrinsic mechanisms share molecular pathways. In this article, we will review several different aspects of facial aging with a focus on the mechanisms of skin aging. There are multiple theories on the mechanisms of skin aging, which include oxidative stress, loss of telomeres, mutations in mitochondrial DNA (mtDNA), and hormonal changes. In addition to the epidermis and dermis, changes to the subcutaneous fat, muscle, and bone of the face also contribute to an aged appearance.

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EXTRINSIC AGING

The functional manifestations of extrinsic aging are due to epidermal damage and remodeling of the dermal collagens and extracellular matrix proteins.[1] Extrinsically aged skin is abnormally pigmented with leathery texture, laxity in the form of wrinkles and folds, and increased telangiectases. Histologically, a sun-protected epidermis becomes thin, whereas a sun-damaged epidermis often thickens as a photoprotective mechanism.[2] The rete ridges become flattened because of abnormal keratinocyte proliferation and differentiation. Photoaging results in degeneration of the dermal matrix due to breakdown of types I and III collagen and accumulation of abnormal elastic fibers.[2] There is an overall loss of glycosaminoglycans. There are numerous fibroblasts and inflammatory cells but fewer antigen-presenting Langerhans cells.[3] The skin appendages have reduced functioning, and a global reduction in lipids in the stratum corneum results in xerosis.[4]

Extrinsic aging results from the effects of external factors on the skin, mostly in the form of chronic UV light exposure. Exogenous factors such as tobacco smoke, airborne particles, infrared radiation, ozone, and malnutrition also are additive factors. Both UVA and UVB radiation produce photoaging and photocarcinogenesis. UVA is absorbed by chemical chromophores such as urocanic acid, melanin precursors, and riboflavin. UVA is thought to be more responsible for the aging process because of its high penetration depth and ability to generate reactive oxygen species (ROS), including superoxide anion, peroxide, and singlet oxygen that damage lipids, proteins,

and DNA.[5,6] UVB is absorbed by the epidermis and mainly causes DNA damage within the keratinocytes in the form of pyrimidine dimers and (6-4) photoproducts.

OXIDATIVE STRESS

The free radical theory of aging suggests that ROS, derived from oxidative cell metabolism, damage cellular components and lead to aging. The superoxide radical (O_2^-) is generated both by cellular processes in the mitochondria as well as by UV light. It is hypothesized that ROS activate a number of phosphorylase-mediated kinases, resulting in an activation of signal transduction pathways throughout the epidermis. These signal transduction pathways include mitogen-activated protein kinases, such as p38; c-jun N-terminal kinase; and extracellular signal-regulated kinases, which upregulate the nuclear transcription factor activator protein 1 (AP-1), a heterodimer composed of c-jun and c-fos proteins.[1] Activator protein 1 is responsible for activating the matrix metalloproteinase (MMP) genes for MMP-1 (collagenase), MMP-3 (stromelysin), and MMP-9 (gelatinase). The MMPs degrade types I and III collagen in the extracellular matrix and thereby weaken the structural foundation of the dermis.[7] Expression of MMPs occurs in keratinocytes and fibroblasts. Although epidermal keratinocytes are primarily affected in UV-exposed skin, the MMPs that are produced diffuse directly into the dermis.[8] Matrix metalloproteinases are upregulated in a positive dose-response relationship with UV radiation, and sustained elevations in MMP levels have been reported after exposure to suberythematous doses of UV light.[9,10] Additionally, the compensatory production of MMP inhibitors or tissue inhibitors of MMPs does not occur, causing sustained collagen breakdown.

UV radiation also downregulates gene expression of types I and III procollagen in dermal fibroblasts via 2 mechanisms. First, UV radiation–induced AP-1 inhibits transforming growth factor β (TGF-β), a profibrotic cytokine, and downregulates type II TGF-β receptors so that cells cannot respond to TGF-β and thus produce less type I procollagen.[7] New type I procollagen formation also is decreased due to reduced expression of connective tissue growth factor and reduced TGF-β/Smad signaling in dermal fibroblasts.[11] Overall, the loss of the components of the extracellular matrix produces less mechanical tension on fibroblasts, allowing fibroblasts to collapse due to the loss of binding sites to intact collagen.[12] The effect of the loss of tension is accumulation of more ROS, resulting in a positive feedback loop.

Additionally, UV radiation activates the transcription factor nuclear factor κB (NF-κB), resulting in transcription of proinflammatory cytokines such as IL-1β, tumor necrosis factor α, IL-6, and IL-8.[7] These proinflammatory cytokines then bind their respective receptors on the cell surface, resulting in further activation of AP-1 and NF-κB, which escalates the response.[7] Neutrophils containing neutrophil collagenase, or MMP-8, and neutrophil elastase are stimulated by these cytokines, leading to more damage to the extracellular matrix.[13] Activation of both MMP-1 and NF-κB are iron-dependent mechanisms, and for this reason, iron chelators such as kojic acid are used in several antiaging products.[14]

There are several intracellular defense mechanisms for handling oxidative stress, including superoxide dismutase, as well as antioxidants such as vitamins A, C, and E; ubiquinone; and glutathione to help minimize ROS-induced damage.[1] Additionally, many of the available cosmeceuticals and nutraceuticals were developed to decrease free radical production and thus improve photodamaged skin.[1] All-*trans*-retinoic acid (tretinoin), a synthetically derived antioxidant, was developed as an effective acne medication as well as a potent antiaging cream.[15] Tretinoin inhibits the accumulation of c-jun protein, thereby preventing both the formation of AP-1 and the upregulation of the MMPs that follow.[16] Tretinoin also induces TGF-β, thereby enhancing production of types I and III procollagen.[17,18] Histologically, the end result is repair of sun-damaged collagen and glycosaminoglycans.

LOSS OF TELOMERES

Telomeres form the ends of human chromosomes and defend the chromosome ends from instability. However, DNA polymerases cannot act on the final DNA bases during replication and telomeres are shortened by approximately 100 base pairs (bp) with each replication cycle.[19] Shortening of telomeres with each round of cell division initiates a DNA repair response and leads to apoptosis and premature cell cycle arrest.[20] UV radiation has been shown to enhance the disruption of telomeres.[21] Telomeres are particularly susceptible to UV damage because UV radiation targets dithymidine residues (TT), which are greater in number in the telomere region compared with the rest of the chromosome.[22] However, keratinocytes and fibroblasts have been shown to have a slow telomere loss of 25 bp per year, suggesting that telomere loss is not the predominant factor in skin aging.

MUTATIONS IN mtDNA

The main endogenous source of ROS is mitochondria, and due to its proximity to the electron transport chain, mtDNA is most susceptible to oxidative damage. Mitochondrial DNA has higher mutation rates than

nuclear DNA due to inefficient repair mechanisms.[23] Chronic UVA exposure results in the common deletion, a 4977-bp large-scale deletion of mtDNA found in fibroblasts in the dermis of photoaged skin. This deletion results from ROS produced by UVA and can be detected months after UV exposure ceases, serving as a biomarker of UV damage.[24] The theory of mtDNA damage complements the free radical theory, as it implies that the mutations in mtDNA drive more dysfunctional oxidation and therefore more ROS and more MMP production.

HORMONAL CHANGES

The reduction of lipids in aged skin is attributed to decreased levels of estrogen and testosterone and is more notable in menopausal women. Diminished sex hormones lead to dryness, wrinkling, epidermal atrophy, collagen breakdown, and loss of elasticity.[25,26] The effect of hormone replacement therapy on skin wrinkling and rigidity has been assessed with some suggestions that early estrogen therapy during menopause may diminish wrinkling and improve skin firmness.[27] Additionally, increased epidermal thickness and collagen have been reported after use of topical estradiol in postmenopausal women.[28,29] Estrogens act in the skin via 2 estrogen receptors: estrogen receptor α (ER-α) and estrogen receptor β (ER-β). Keratinocytes express ER-α, while fibroblasts express both ER-α and ER-β.[30,31] A synthetic ER-β agonist was shown to inhibit expression of MMP-1, MMP-3, IL-6, IL-8, cyclooxygenase 2, and tissue inhibitor of metalloproteinase 1 in vitro, and its effect was substantiated in a mouse model of photoaging.[31] The exact mechanism by which the ER-β induces this inhibition is unknown, but it has been hypothesized that estrogen stimulates antioxidant production within the skin.

BONY RESORPTION, FAT ATROPHY, AND MUSCULAR CHANGES

In addition to the age-related thinning of both the epidermis and dermis, aging of the face involves a combination of bony resorption and remodeling, fat atrophy and hypertrophy, and muscular changes. The facial skeleton provides the framework for the overall shape of the face. It is on this framework that the overlying soft tissues lie, following the contours of the face. As the face ages, this bony framework gets remodeled in a process of resorption and differential growth. Overall, the facial skeleton undergoes a clockwise rotation (when viewed from the right side), such that the frontal bone moves anteriorly and inferiorly while the maxilla moves posteriorly and superiorly.[32] Consequently, these bony morphologic changes alter the way the overlying soft tissues are displayed on an aged face.[32,33]

It has recently been observed that the fat of the face is composed of individual fat compartments, and cadaveric studies have demonstrated that atrophy of the superficial and deep fat compartments contributes to the process of facial aging.[34,35] Volume loss and/or ptosis of the deep fat compartments, particularly in the temporal, buccal, and suborbicularis oculi regions, have been noted.[35,36] Additionally, the junctions of thick and thin superficial fat compartments have been shown to result in the appearance of folds.[35] Overall, these changes in the fat compartments contribute to the development of an aged face.

Changes in the muscles of the face also contribute to facial aging. Repeated contractions of the muscles of facial expression may result in some of the structural changes associated with the aging face. With age, these muscles may strengthen and shorten, resulting in the displacement of the underlying fat compartments and an increase in the resting tone of the muscle.[37] The muscles of the face also may change their tension in response to modification of the underlying bone or there may be a compensatory increase in muscle tone in response to skin laxity.

COMMENT

Facial aging is an integrated process, and the changes that occur in individual tissues, including skin, muscle, fat, and bone, are interrelated. Interactions between the different components (eg, a change in one of these tissues brings about changes in the other tissues) results in an overall alteration in facial appearance as one ages.[38,39] Each of these changes in the epidermis, dermis, fat, muscle, and bone is addressed in an aesthetic practice in different ways. Over the last 25 years, we have seen the emergence of a multibillion dollar industry dedicated to improving or preventing the aging process. Some products have a sound biochemical or molecular basis; however, some have little scientific data to support their claims. Sunscreens and sunblocks attenuate the deleterious effects of UV light. Retinoids, such as tretinoin, can reverse sun damage and possibly improve the dermal extracellular matrix.[15] Targeted cosmeceuticals and botanicals address individual components in the free radical pathway, supplying antioxidants, TGF-β, or upregulators of TGF-β. Neurotoxins inhibit dynamic rhytides, while fillers and fat transfer aid in restoring volume loss due to fat atrophy and bony resorption. We can now offer patients a variety of products or techniques that will improve their appearance, and we can provide patients with the supporting data for the use of these products.

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