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Biology of Skin Aging: A Review

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ABSTRACT

The skin is the interface between man and his environment. It is involved in water regulation, protection against micro-organisms, thermoregulation, excretion, vitamin D synthesis, and the reception of various stimuli. Wrinkles are a major topic in dermocosmetics as it is fundamental to understand modifications associated with cutaneous damage. Aging is a multistep, multifaceted, time-dependent phenomenon characterized by the decreased ability of a system to respond to exogenous and endogenous stress from either physical, chemical or biologic agents. It is only in the last 30 years researchers have become aware of the distinction between intrinsic , chronologic aging and extrinsic aging due to habitual sun exposure. In Skin, the principle extrinsic factor is ultraviolet light(UV) which is responsible for the constellation of changes termed photoaging. This review provides an overview on mechanisms of skin aging.

Keywords: Photaging, Elastin, Collagen, Ultraviolet light

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INTRODUCTION

The Skin is a complex tissue which consists of two layers; a superficial epidermis which is an epithelium derived from the ectoderm, while the thicker, deeper layer is comprised of connective tissues of mesodermal origin. Together they form a cohesive integument covering the whole body , which varies in thickness depending on location and is anchored to the underlying subcutaneous tissue by irregularly spaced bundles of collagen.

The Epidermis is composed of a non viable stratum corneum composed of enucleated squames and keratin and a viable cellular layer composed of keratinocytes, Langerhans cells, and melanocytes.

Dermis is divided into two components: a superficial, immediately subepidermal papillary dermis and the deeper reticular dermis.The principal cells within the dermis are fibroblasts although endothelial cells and mast cells are also affected by age..

Major age-related changes in the skin's appearance include "dryness" (roughness), wrinkling,laxity and a variety of benign neoplasms. Histological features and functional decrements [1] associated with cutaneous aging are listed in tables 1 and 2

Table 1: Histological Features of Aging Human Skin

S.No	Epidermis	Dermis	Appendages
1	Flattened dermal-epidermal junction	Atropy(Loss of dermal Volume)	Depigmented hair
2	Variable Thickness	Fewer Fibroblasts	Loss of hair
3	Variable cell size and shape	Fewer mast cells	Conversion of terminal to vellus hair
4	Occasional Nuclear atypia	Fewer blood vessels	Abnormal nailplates
5	Fewer Melanocytes	Shortened capillary loops	Fewer glands
6	Fewer Langerhans Cells	Abnormal Nerve endings	

Table 2:Function of Human skin that Decline with Age.

Cell Replacement	Immune Responsiveness
Injury Response	Vascular Responsiveness
Barrier Function	Themoregulation
Chemical Clearance	Sweat production
Sensory Perception	Sebum Production
Mechanical Protection	Vitamin D Production

The most striking and consistent histologic change is flattening of the dermal-epidermal junction with effacement of both the dermal papillae and epidermal rete pegs [2, 3].

Aging is associated with a reduction in cell turnover which will influence wound repair and the ability of the skin to withstand wear and tear. Thus, we may anticipate that the effectiveness of the integument will be compromised and it may be less of a barrier to water

loss, or the entry of bacteria. Furthermore it is possible that aging is a predisposing factor in the various proliferative disorders that affect the skin. There are age-related changes in the connective tissue molecules, collagen and elastin which may influence the elastic properties of the skin and contribute to the phenotypic wrinkling and laxity of its appearance later in life. Alterations in the blood supply could alter the transport of metabolites from the blood vascular system to the cells of the epidermal and dermal layers, and age-related changes in the nervous system may alter the ability of the skin to perform its role of frontier message reception. Finally we must consider a variety of central effects which may influence the organization, structure and function of the skin including age-related alterations in endocrine function. It is impossible to cover all these topics in the space available and it will be appreciated that many of the changes would overlap with age-related disease states. The remainder of this section concentrates on aging in the fibroblast and keratinocyte cell populations, and on some of the connective tissue changes which occur in the aging skin [4].

Age-related changes in skin cells:

There are various age-related changes in the process of epidermal renewal. The thymidine-labelling index invivo is reduced by about 50 % [5]. Keratin replacement takes approximately 20 days in young subjects and increase to about 30 days in the elderly, although the changes is not linear because the most marked increase occurs after 50 years of age [6]. Aging is a predisposing factor in neoplasia and various elements may be involved such as cumulative exposure to carcinogens, decreased DNA repair capacity, a decline in immuno surveillance, reduced pigementation compromising the UV barrier, alterations in the regulation of keratinocyte proliferation and changes in the dermal matrix.

The role of telomeres in cellular aging:

The ends of the chromosomes are capped by specialized structures, the telomers. The telomers are made out of thousands of hexameric nucleoid sequences which forms a well-defined three dimensional structure, the t-loop [7]. The telomers are required for protecting chromosomes against illegitimate fusion events, mediating chromosome location in the nucleus and protecting the outermost end from being recognized as defective DNA. Thus, telomers are important bufferes to guarantee the stability and functionality of the chromosomes.Research on cell replication in vitro has often been aimed at trying to identify the way that cultured cells count the number of cell division they undergo. It is now known that the telomeres, which are 'tails' of nucleotide repeats at the ends of chromosomes, progressively shorten during aging of HDF. Immortalized tumor cells have stable telomeres that retain a constant length. In addition, the telomere length in stem cells is greater than that found in somatic cells, and the length of the telomeres in germ-line cells is constant,despite the age of the donor. Out of these observations came the telomere hypothesis of aging and immortalization [8, 9]. This hypothesis suggests a way in which the dividing cell may count its number of divisions, and may partiallly explain the loss of division potential in vitro. However, it probably has nothing to do with aging in cells that do not undergo cell division in the adult.

Proteins in aging skin:

Lavker et al [10] using a method more definitive than scanning electron microscopy, made separate studies of the changes in collagen and elastin fibers. In neonatal skin, collagen exists in small bundles aligned parallel to the skin surface. This collagen undergoes gradual changes. In the elderly, the bundles of collagen fibers have become tighter and denser, with less space between them.

Elastin structures:

The three-dimensional distribution of elastin is mesh-like. In young adult skin, it has relatively large voids. As age advances, this mesh tightens, and the voids becomes smaller. In the papillary dermis of normal adult skin, elastin fibers are less abundant than are collagen fibers.

Cross-links:

Both elastin and collagen may form cross-links, which increase fiber stiffness and reduce their water solubility. Covalent cross-links evidently result from oxidative changes in lysine residues among adjacent protein chains. The cross-links then react with each other to form pyridinium nuclei.

Aging and Collagen synthesis:

Collagenase is primarily a fibroblast product, but collagenase activity has been observed in epidermal keratinocytes upon stimulation by inflammogens. Collagen synthesis is a complicated process that starts with polypeptide synthesis. Proline and lysine hydroxylation is followed by glycosylation, which leads to intracellular triple-helix formation. After secretion, via the Golgi complex into the extra cellular space, pro peptides are cleaved to from collagen monomers. They in turn spontaneously aggregate to form fibrils, which are then further cross-linked. Based on currently available evidence, skin aging appears to parallel a decrease in collagen synthesis and/or an increase in proteolysis. An increase in collagens activity seems a more likely rationale, since procollagen synthesis does not decrease past the ages of 30 to 40.

Physical participation of collagen:

For years, scientists have known about the pronounced flattening of the dermo-epidermal junction during skin aging. Unfortunately, no explanations of this strange phenomenon have been proposed. The loss of interdigitation in the epidermis and papillary dermis causes many adverse effects. The junctional surface area decreases by about 30 to 40 %. The number of stem cells residing in the basal layer declines, reducing the number of keratinocytes that differentiate into corneal cells. In addition, adhesion between the papillary dermis and the viable epidermis decreases.

Collagen building blocks:

Chemists have been studying the fibrillar proteins at the dermo-epidermal junction for sometime. The papillary dermis, which lies just below the dermo-epidermal junction, consists primarily of collagen, 75 %, by weight of dry, fat-free skin. The predominant component is collagen I, which probably accounts for the dermis network's tensile strength. The significance of up regulation of collagen I formation after dermabrasion of photo-aged skin is apparent from a recent invivo study by Nelson et al [11]. This team investigated the clinical benefits of dermabrasion when accompanied by increased collagen formation in the papillary dermis. The authors suggest that the clinical improvements in photo-aged skin from superficial dermabrasion are, to a large degree, the result of increased fibroblast synthesis of collagen I.

Types III and V collagen contribute to the skin's elastic behavior. Attachment of the epidermal cells occurs via the lamina densa and two additional collagens, types IV and VII. This brief summary is based on studies by Burgeson [11] and Uittoet al [12]. Evidently, synthesis of these collegians occurs in the fibroblasts [13].

Photo aging

Photoaging refers to premature skin aging caused by repeated exposure to UV radiation from the sun for many years. Fine and coarse wrinkles, dyspigmentations, sallow color, dry texture, and loss of tone in habitually sun-exposed skin characterize the photoaged phenotype [14]. Because many of these clinical characteristics of photoaged skin are also those associated with advanced age, distinguishing photo aging from chronologic aging is sometimes problematic. However, even to untrained eyes, the markedly more youthful and healthy appearing skin of the sun-shielded areas (i.e., upper inner arm and buttocks) in individuals with prominent photoaging clearly demonstrates the significant contribution repeated sun exposure makes to the ultimate skin appearance.

Photoaging is most frequently progressive, yet modified by both environmental exposure and genetics

1 .Uneven tanning
2. Skin easily distends
3. Slow return to normal contour
4. Thinned skin easily traumatized
5. Sensory decrease
6. Decrease in immune competence

Above table-II shows the functional abnormalities of photoaging. The clinical presentation of Photo damage is therefore highly polymorphic but with many characteristic signs and symptoms [15].

Experimental studies

Photoaging in human is a slowly evolving process, taking decades to become clinically apparent and many more years to develop all of the manifestations, whether microscopic or biochemical. Furthermore, the UV dosimetry of human sun exposure is impossible to quantify with any degree of accuracy. Systematic studies require animal models for practical, as well as ethical, reasons. The hairless mouse has proved to be a relevant model for human photo aging [16]. The UV-induced changes, ranging from immediate responses [17] to those associated with prolonged exposure, such as tumorigenesis18 and connective tissue damage [19, 20] are comparable with those in human skin.

Ultraviolet B and Photo aging

The Ultraviolet B (UVB : 290-320 Nm) waveband is responsible for erythema, DNA damage, and skin cancer. Some evidence was provided by Samset etal [21] that it was also effective in damaging connective tissue. Ultra structural changes in the elastic fibers bear a remarkable similarity to those seen in photo damaged human skin [22]. In irradiated animals, fibroblasts become more numerous. Ultra structurally, they appeared to be metabolically active, producing increased quantities of collagen that contributed to a thickening of the dermis. Reticulin fibers, normally limited to the basement membrane zones, were prominent throughout the upper dermis, an indication of new collagen synthesis . Schwartz et al [23] also reported no change in the ratio in UVB-irradiated mouse skin, as did Oikarinen and Kallioinen [24] in photodamaged human skin. These results suggest that both types I and III collagen increase proportionally until end-stage photodamage,when there may be reduced synthesis of type I collagen. On examining explants of UV-irradiated hairless mouse skin

Invitro synthesis of heparin and heparan sulfate was increased, whereas that of dermatan sulfate and hyaluronic acid was not. By contrast, histochemical observations indicated large increases in hyaluronic acid [25].

Ultraviolet A and Photoaging

Brief exposure to UVA (320-400 Nm) can, similar to UVB, produce erythema [26] and damage blood vessels [27]. Because such effects require doses that may be hundreds of times greater than UVB, the role of UVA in photo aging was thought to be negligible. However, UVA is present in sunlight in amounts that can be 100-500 times that of 300 nm UVB . Furthermore, its longer wavelengths allow more of it to reach the dermis than does UVB. These considerations make it important to examine the effects of UVA and to compare it with those of UVB. Studies have shown elastic fiber hyperplasia and increased GAGs with high, but not unrealistic doses [28] . In contrast with UVB, neither full spectrum UVA or UVA1 had a histological effect on collagen. Supporting the hypothesis that it is the proteolytic enzymes of the inflammatory infiltrate that degrade collagen, prolonged UVA, at the doses used, did not induce inflammation. Biochemically, however, UVA has a profound effect on collagen. Recent ultra structural studies in the hairless mouse have shown that chronic exposure to UVA is

exceedingly damaging to skin and in ways that differ from UVB. Notably, vascular endothelial cells are severely damaged, and the surrounding basement membrane is highly reduplicated, whereas that of the dermal-epidermal junction is not. With prolonged UVB radiation, endothelial cells show little or no damage and no membrane duplication, but the basal lamina of the dermal-epidermal junction is reduplicated [29].

Interestingly, UVA appears to be more effective in inducing elastosis than erythema. A recently constructed action spectrum for elastosis, although resembling the erythema action spectrum, has shown that a 50 % increase in elastic fiber hyperplasia requires only 20 times more UVA than UVB, whereas for erythema, 500-1000 times more is required [30].

Solar-simulating radiation and photo aging:

Solar-simulated radiation appears to induce UVB type wrinkles, with a decrease in the micro topography of skin markings. Skin-fold thickness increases as does trans epidermal water loss. Clearly, more research is needed in this vital area.

Matrix metalloproteinases (MMP's) and Photo aging:

The matrix metalloproteinase (MMP's) are a family of enzymes responsible for degrading connective tissue [31]. They are structurally related endopeptidases that mediate degradation of different macromolecular components of the extra cellular matrix and the basement membrane [32, 33]. The human family of MMP's is composed of at least 16 members, which can be classified in to 4 different sub families; the collagenases, the gelatinases, the stromelysins, and the membrane MMP's [34, 35].

UV irradation induces MMP-1 but not MMP-13, in human in vivo. In addition, UV irradiation induces MMP-9 and MMP-3 in human skin invivo [36]. Together, these 3 MMP's can fully degrade skin collagen [37, 38]. Initially, MMP-1 cleaves the triple helical collagen molecule in to 3 quarter and one quarter length fragments. Collagen is then further degraded into smaller fragments by MMP-3 and MMP-9 [39-41]. MMP's are likely to be their primary mediators of connective tissue damage in skin exposed to UV irradiation [42].

Elastase and photo aging:

Studies have shown an elevated elastase activity in skin with actinic elastosis elicited by long-term UVB irradiation [43]. Among the types of elastase that are found in the skin, neutrophil elastase and skin fibroblast elastase have generally been reported [44], and the activity of skin fibroblast elastase increased after repeated fibroblast subculture [45]. Such evidence suggests a close involvement of skin fibroblast elastase in photoaging and chronologic aging. Elevated levels of 1L-1β expression in aging human fibroblasts [46] stimulation of human fibroblast elastase activity by 1L-1β [47], and inhibition of elastin synthesis by 1L-1β [47], have been reported. In mid-dermal elastolysis, which is characterized by the appearance of fine wrinkles in non sun exposed areas, fibroblast elastase activity in affected was up regulated in

the absence of UVB irradiation, and elastic tissue in the dermal middle layer completely disappear [48]. This evidence allows us to speculate that the secretion and activation of fibroblasts responding to UVB irradiation and or to cytokines related by UV-B exposed keratinocytes are responsible for the degeneration of the three dimensional structure of elastic fibers during the formation of wrinkles. In considering the relationship between the degeneration of elastic fibers and wrinkle formation due to decreases in skin elasticity, it would be interesting to determine inhibiting elastases during long-term UVB irradiation could prevent wrinkle formation in the skin by preventing the degeneration of the elastic fiber network.

CONCLUSION

The literature on aging has expanded dramatically during the past 30 years.Cell and molecular biologic studies are increasing our knowledge of the steps in cellular regulation. Progress in understanding the pathogenesis of age-related changes in skin has been unusually slow. This is due in part to the fact that age-related changes in skin and related connective tissues. Aging of skin is, as with other organs a highly complex process and intrinsic aging must be separated from the effects of environmental factors. The study of aging skin particularly as a consequence of the ready accessibility of cutaneous tissue is one that presents a paradigm for aging of other organs.

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