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Changes in the Dermal Collagenous Matrix in Skin Aging

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Abstract:
The cumulative and superimposed negative impacts of intrinsic and extrinsic dermal aging on collagen protein occur at a cellular and molecular level. This literature report will review and summarize the cellular and molecular pathways related to changes in collagen and its types during skin aging. A literature search was conducted using MEDLINE, JSTOR, ScienceDirect, and Web of Knowledge databases. Inclusion keywords were "skin aging" AND "collagen" and filtered with "humans" and "skin". Results were further limited to English peer-reviewed journal articles from 1990 to 2020. These were then screened manually for relevance to the topic with a preference for subject review articles. Fibroblast impairment reduced collagen synthesis and increased collagen breakdown via matrix-degrading metalloproteinases (MMPs) in a self-perpetuating cycle. Ultraviolet radiation leads to additional oxidative stress and continued upregulation of MMPs via transforming growth factor-beta signaling. These pathways compounded with the natural molecular glycation of collagen over time lead to various negative effects on the dermal collagenous matrix. This literature report provides a concise summary of a vast topic for non-dermatologists. Comprehensive understanding of age-related alterations of the composition of the dermal collagenous matrix, and mechanisms underlying these alterations, can provide novel insights into the molecular basis of skin aging that helps identify novel targets for antiaging treatments.

Keywords: skin, aging, age-associated dermal microenvironment, collagen, matrix metalloproteinases.

皮肤老化过程中真皮胶原基质的变化

摘要:
内在和外在皮肤老化对胶原蛋白的累积和叠加负面影响发生在细胞和分子水平。这篇文献报告将回顾和总结与皮肤老化过程中胶原蛋白及其类型变化相关的细胞和分子途径。使用医学线、JSTOR、科学指导和知识网数据库进行文献检索。包含关键词是“皮肤老化”和“胶原蛋白”，并用“人类”和“皮肤”过滤。结果进一步仅限于1990年至2020年的英语同行评审期刊文章。然后手动筛选这些文章与主题的相关性，并优先选择主题评审文章。成纤维细胞损伤减少了胶原蛋白的合成，并通过基质降解金属蛋白酶(基质金属蛋白

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酶)在一个自我延续的循环中增加了胶原蛋白的分解。紫外线辐射通过转化生长因子-β信号传导导致额外的氧化应激和MMP的持续上调。随着时间的推移，这些途径与胶原蛋白的天然分子糖基化复合，导致对真皮胶原基质的各种负面影响。这份文献报告为非皮肤科医生提供了一个广泛主题的简明摘要。全面了解与年龄相关的真皮胶原基质组成的变化，以及这些变化背后的机制，可以为皮肤老化的分子基础提供新的见解，有助于确定抗衰老治疗的新目标。

关键词：皮肤、衰老、与年龄相关的皮肤微环境、胶原蛋白、基质金属蛋白酶。

1. Introduction

There are two types of aging, the inherent genetic process called intrinsic aging and extrinsic aging, which results from accumulated insults from the environment (Yaar & Gilchrest, 1990). The signs of the former consist of skin thinning, drying, rhytids, laxity, and loss of elasticity (Cole et al., 2019), whereas photoaging results in thickened leathery skin with coarse lines, neovascularization, and dyspigmentation secondary to ultraviolet irradiation (UVR). Both intrinsic and extrinsic aging are cumulative and superimposed on one another over time (Quan, 2016). Their combined dermatological negative impact occurs both at a cellular and molecular level (Cole et al., 2019; Quan, 2016).

Cellular damage in aging is associated with decreased cell life span, secondary to cumulative DNA damage from oxidative free radical production and replication errors. There is a loss of cell responsiveness to growth signals and increased sensitivity to growth inhibitors (Yaar & Gilchrest, 1990). This translates clinically to decreased proliferation of cells in the basal layer, reduced epidermal cell turnover, delayed wound healing, predisposition to skin cancer, and cutaneous diseases (Quan, 2016; Yaar & Gilchrest, 1990). Cellular senescence means the prolonged cessation of the proliferation of keratinocytes, fibroblasts, and melanocytes (Gorgoulis et al., 2019). The dermis is largely composed of a dense collagen-rich extracellular matrix (ECM). Impaired dermal fibroblast function significantly impacts the properties of connective skin tissue. With intrinsic aging, there is atrophy of the epidermis and thinning of the dermis with loss of definition of the dermal-epidermal junction. Comparatively, photoaging leads to a large accumulation of disorganized elastic fibers throughout the dermal connective tissue (Quan, 2016; Naylor et al., 2011).

Molecular manifestations of skin aging are altered composition of the ECM (Yaar & Gilchrest, 1990; Fisher et al., 2002). There is an imbalance in the formation and degradation of ECM structural elements in terms of collagens, elastin, and proteoglycans that provide tensile strength, elasticity, and hydration to the skin (Quan, 2016). In young skin, fibroblasts produce and adhere to the dermal ECM, composed primarily of type I collagen fibrils (Cole et al., 2019). In young photoprotected skin, the collagen fibrils are intact, numerous, and densely organized (Quan, 2016). With aging skin, collagen proteins become increasingly fragmented, disordered, and glycated with resultant loss of ECM support and impaired fibroblast function (Cole et al., 2019; Quan, 2016; Quan & Fisher, 2019). Fibroblasts, therefore, synthesize fewer ECM proteins and more matrix metalloproteinases (MMPs), perpetuating further dysfunction. These events compounded with the natural molecular glycation of collagen over time lead to the various negative effects seen on the dermal collagenous matrix as a consequence of aging. However, such pathways have complicated cross involvement which is not always apparent in literature reports on independent pathways. Understanding the molecular mechanisms of dermal aging offers opportunities for intervention using appropriate antiaging technology and identification of novel targets for dermal rejuvenation, which prompted the authors to review and summarize the cellular and molecular pathways related to changes in collagen and its types during skin aging. Dermal aging is a vast topic for which this literature report aims to provide a concise summary for non-dermatologists.

2. Method

A literature search was conducted using MEDLINE, JSTOR, ScienceDirect, and Web of Knowledge databases. Inclusion keywords were "skin aging" AND "collagen" and filtered with "humans" and "skin". Results were further limited to peer-reviewed English journal articles from 1990 to 2020 and were available in full text online. These were then screened manually for relevance to the topic with a preference for subject review articles. These were more comprehensive, and any gaps in their coverage will be covered by this literature review.

3. Collagen and Normal Fibroblast Function

The skin is the largest bodily organ and acts as a physical barrier against environmental insults. Histologically it is divided into the epidermis and dermis, each with a specific structure and function (Quan & Fisher, 2019; Zhang & Duan, 2018). The epidermis is relatively cellular but avascularized and prevents unwanted water loss or absorption (Harris & Korolchuk, 2018). This layer consists mainly of cornified keratinocytes, which have undergone terminal differentiation to produce keratin filaments that aid skin mechanical stability (Quan & Fisher, 2019). The dermis is vascularized but acellular and supports the epidermis with papillary and reticular extensions (Naylor et al.,

2011). Sparsely located dermal fibroblasts within the dermis synthesize the dense connective tissue ECM network comprised of elastin, proteoglycans, oligosaccharides, and a high concentration of collagen (Quan & Fisher, 2019; Naylor et al., 2011; Harris & Korolchuk, 2018).

Collagen and its numerous types are the main components of the ECM and comprise 90% of the dry weight of skin (Quan & Fisher, 2019; Harris & Korolchuk, 2018). Collagen proteins consist of a repeating triplet sequence of amino acids with glycine every third residue often attached subsequently to proline or hydroxyproline. The repeating sequence creates polypeptide chains that embrace a triple helical structure with further covalent crosslinking between other collagen molecules residues (Harris & Korolchuk, 2018; Ricard-Blum, 2011). The dermis contains 85-90% and 10-15% of collagen type I and III, respectively (Fisher et al., 2009; Chung et al., 2001). Within the papillary and deep reticular dermis, types I and III fibril-forming collagens copolymerize to provide tensile mechanical strength via bundles aligned parallel to the dermal-epidermal junction (DEJ) or in a basket-weave configuration (Naylor et al., 2011; Harris & Korolchuk, 2018; Kaur et al., 2019). Through a mechanism of perpendicularly oriented anchoring fibrils, collagen VII secures the dermis to the DEJ and the network, forming a collagen IV-rich basement membrane. Collagen VI microfibrils are found in skin and connective tissue and are proposed to mediate cell-matrix signaling. Produced by fibroblasts via a procollagen precursor, collagen fibrils are bound to the cell's transmembrane surface adhesion integrin receptors (Harris & Korolchuk, 2018).

Like many other cell types, dermal fibroblasts sense the mechanical load of their environment via mechanotransduction (Rittié & Fisher, 2015). The normal function of fibroblasts in the dermis requires appropriate interactions with collagen fibrils (Quan & Fisher, 2019). Mechanical forces from cytoskeletal contractile forces against the pull of intact fibrils result in collagen organization and flattened spreading of the fibroblast cell shape, which is critical to cellular function (Cole et al., 2019). Fibroblasts able to stretch under this relatively high tension will exhibit normal collagen homeostasis (Rittié & Fisher, 2015).

4. Cellular Mechanisms of Skin Aging

The phenotypical skin changes seen during intrinsic and extrinsic aging are due to unfavorable changes in collagen synthesis. Age-related dermal collagen changes include lower levels of procollagen production and reduced collagen density, fiber area, and thickness. Increased collagen fragmentation adversely affects fibroblast connectivity (Cole et al., 2019). Damaged collagen fibrils are more pliable than native fibrils and provide less resistance to interacting fibroblasts (Fisher et al., 2002). The cells appear collapsed with little cytoplasm due to reduced mechanical stretch and dissociation with collagen fibrils. In-vivo quantitative morphometric analysis of aged skin reveals that fibroblast contact with collagen fibrils is reduced 80%, and cross-sectional fibroblast surface area is reduced 75% (Varani et al., 2006). Fibroblast function is impaired, and reduced secretory proteins result in additional degradation of the ECM network compounded with further fibroblast apoptosis in a self-perpetuating cycle (Harris & Korolchuk, 2018). Regardless of fibroblast age, within this deleterious environment, there are higher levels of oxidative stress, pro-inflammatory mediators, and MMPs, leading to dysfunction of fibroblast migration, proliferation, cell-matrix interactions, and cell adhesion (Fisher et al., 2009). MMPs are an important family of zinc-containing proteinases produced by fibroblasts that regulate collagen turnover (Cole et al., 2019; Quan & Fisher, 2019; Fisher et al., 2009).

4.1. MMP Proteases and Collagen Degradation

Although several specific MMPs can break down native fibrillar collagen types I and III in human skin, mature collagen fibers are highly crosslinked and relatively resistant to proteolytic cleavage (Cole et al., 2019). The gradual accumulation of collagen fragments is due to the action of elevated MMPs over time and progressively impairs the structure and function of the dermal ECM. However, the exact molecular mechanisms of how this occurs are unclear. MMPs can be divided into the following groups: MMP-1 (collagenases), MMP-2 and MMP-9 (gelatinases), MMP-3 and MMP-11 (stromelysins), MMP-17 (membrane-associated), and newly discovered MMP-27 (Quan & Fisher, 2019). UVR elevates the synthesis of MMP-1, MMP-3 & MMP-9 by fibroblasts and keratinocytes in-vivo. Up-regulation of these proteases plays a strong role in the connective tissue damage seen in intrinsic and extrinsic aging characterized by loss of normal collagen structure and fragmentation (Figure 1) (Quan, 2016; Quan & Fisher, 2019). MMP-1 cleaves dermal fibrillar collagen types I and III at a single site within its central triple helix (Fisher et al., 2002). Once cleaved by MMP-1, further collagen proteolysis by MMP-3 and MMP-9 can occur (Quan & Fisher, 2019). Depending on the extent of degradation, partially degraded collagen can remain crosslinked within the insoluble collagen matrix (Fisher et al., 2002). Experiments on sun-protected human skin added to purified human MMP-1 in culture media result in similar collagen fragmentation and disordered fibril architectural changes within the dermis as aged skin (Quan & Fisher, 2019).

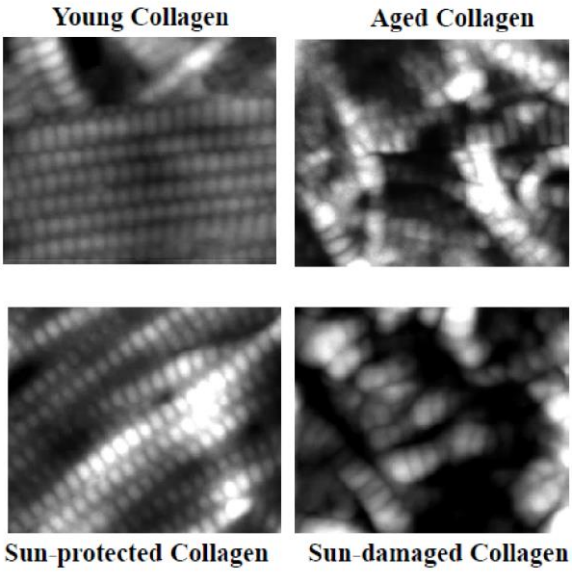

Figure 1. Nanoscale human collagen fibers analyzed by atomic force microscopy showing alteration of chronological and photoaged skin
Note: Representative images of dermal collagen fibrils in 21-years-old vs. 83-years-old individuals (top panel) and 54-years-old photoprotected underarm vs. sun-damaged forearm skin (lower panel). In young and sun-protected skin, collagen is abundant and well organized. In contrast, aged and sun-damaged skin has reduced and fragmented collagen in disarray (Adapted from Quan (2016))

In addition to direct collagen degradation, UVR induced MMPs also indirectly inhibit collagen synthesis by MMP generated collagen degradation products (Quan, 2016). This would explain the sustained reduction in procollagen synthesis following UVR exposure. Studies show that fibroblast numbers and type I procollagen synthetic function are comparable in-vitro for photodamaged and photoprotected skin. Exposure of these two types of cultured fibroblasts to partially degraded type 1 collagen with a mixture of MMPs inhibited collagen synthesis. It is postulated that elevated levels of degraded collagen in photodamaged skin act to downregulate type I procollagen synthesis. However, this finding applied only to high molecular weight collagen breakdown fragments, and further breakdown of MMP-1 cleaved collagen by MMP-9 lessened this inhibition (Cole et al., 2019). The skin also expresses natural tissue inhibitors of MMPs (TIMPs) and proteoglycan decorin, which slow collagen breakdown. Studies confirm that elevated MMP levels in UVR skin aging are not due to a reduction of endogenous TIMP (Quan & Fisher, 2019). Elevated MMP levels with each subsequent extrinsic UVR exposure compounded with intrinsic reduction of fibroblast numbers and collagen production over time leads to negative effects on the dermal collagenous matrix as a consequence of aging.

4.2. Oxidative Stress in Skin Aging

The exogenous generation of reactive oxygen species (ROS) by UVR is another mechanism that can damage the structure and function of the skin collagen (Cole et al., 2019; Varani et al., 2006). In cells, UVR can induce ROS creation by reducing the production of detoxifying enzymes catalase and protein kinase C and up-regulating nitric oxide synthase in human keratinocytes. UVR is also able to modify DNA and other chromophores, also leading to the creation of ROS. Other sources for ROS development related to extrinsic aging include environmental toxins and pollutants, cigarette and alcohol use. Endogenous ROS are principally produced as a by-product of ATP production during mitochondrial aerobic respiration (De Jager et al., 2017). Oxidative stress is proposed to be a significant contributor to natural aging due to damage of cellular components such as proteins, nucleic acids, and lipids (Rittié & Fisher, 2015).

Whether endogenously or exogenously produced, ROS in the skin results in collagen degradation and downregulation of neocollagenesis via up-regulation of MMPs as well as several signaling cascades (Figure 2) (Quan, 2016; Rittié & Fisher, 2015; Kohl et al., 2011). Through interaction with cell surface receptors, ROS results in stimulation of MAP-kinases p38, JNK (c-Jun amino-terminal kinase), ERK (extracellular signal-regulated kinases), and transcription nuclear factor-kappa B (Cole et al., 2019). These factors stimulate the expression of MMPs and lead to increased transcription of activator protein-1 (AP-1) and Smad proteins (see sections below), which interferes with collagen gene expression in human dermal fibroblasts by inhibiting the effects of transforming growth factor beta (TGF-β) (Quan, 2016).

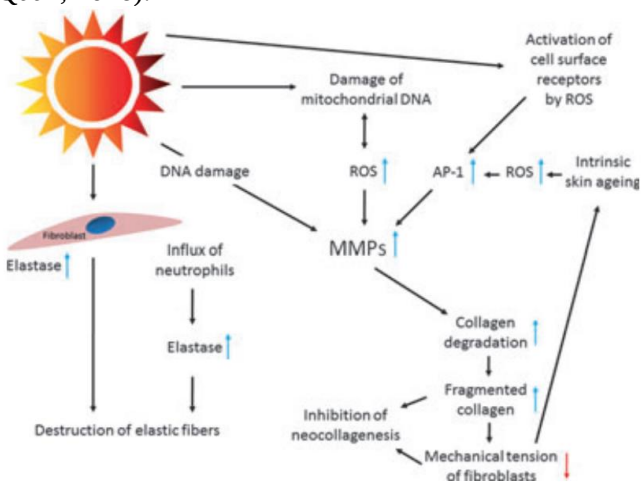

Figure 2. Schematic depiction of pathogenic factors of skin aging
Note: UV-induced ROS and DNA damage induce MMPs as well as proteases which degrade collagen and other ECM components. Partially degraded collagen and reduced mechanical tension further inhibit fibroblast neocollagenesis and a vicious cycle of further ROS and MMP production (From Kohl et al. (2011))

4.3. Transforming Growth Factor-Beta Signalling and Procollagen Gene Expression in Aged Skin

Photoaged skin is characterized by disorganized collagen fibrils and disrupted type I and type III procollagen gene expression and biosynthesis (Yaar & Gilchrest, 1990). Two interrelated mechanisms related to the induction of transcription factor AP-1 are proposed to contribute. Transcription factor AP-1 binds factors that are important for the procollagen transcription pathway. It also decreases collagen

synthesis by blocking the effects of the profibrotic cytokine TGF-β and sequestering one of the signaling proteins it activates directly and indirectly (Quan & Fisher, 2019). AP-1 induces collagen degradation and inhibition of procollagen synthesis by up-regulation of MMP-1, MMP-3, and MMP-9 (Fisher et al., 2002).

TGF-β signaling is important in ECM biosynthesis and structural maintenance (Quan & Fisher, 2019). In-vivo studies propose that expression of connective tissue growth factor and reduced TGF-β/Smad signaling are responsible for the loss of collagen type I expression in intrinsically aged skin (Kohl et al., 2011). In human dermal fibroblasts, TGF-β signaling controls collagen homeostasis, and its downregulation in aged skin results in diminished collagen production (Yaar & Gilchrest, 1990). Binding of TGF-β to its TGF-β type I (TβRI) and TGF-β type II (TβRII) receptor complex results in phosphorylation of intracellular Smad transcription factors. Activated Smad transcription factor complexes within the nucleus bind to elements in the promoter regions of TGF-β target genes, enhance collagen gene expression, and downregulate MMPs. The TGF-β/Smad signaling pathway also up-regulates TIMPs and plasminogen activator inhibitor-1, both of which inhibit MMP activation (Quan & Fisher, 2019). UVR exposure disrupts type I procollagen gene transcription by downregulating TβRII and causing cell insensitivity to TGF-β (Quan, 2016). Figure 3 illustrates the pathway which impaired TGF-β in aged fibroblasts contributes to the reduction of collagen in aging skin connective tissue.

4.4. Advanced Glycation End-Products

The longevity of ECM proteins, in general, predisposes them to the risk of molecular aging in the form of advanced glycation end-products (AGEs). The formation of AGEs from circulating sugars is slow and affects only proteins with long half-lives and exposed lysine residues (Gautieri et al., 2017). Compared to other intracellular proteins, which have half-lives measured in hours or days, collagen types I and II in humans have respective half-lives of 15 and 95 years (Cole et al., 2019; Gautieri et al., 2017). Collagen crosslink age-associated glycation occurs when a sugar molecule (glucose or ribose) is inserted between collagen molecules in place of amino acid side chains. Two lysine-arginine crosslinks, pentosidine (a fluorescent product formed from ribose), and glucosepane (a nonfluorescent product formed from glucose) have been identified in collagens (Gautieri et al., 2017).

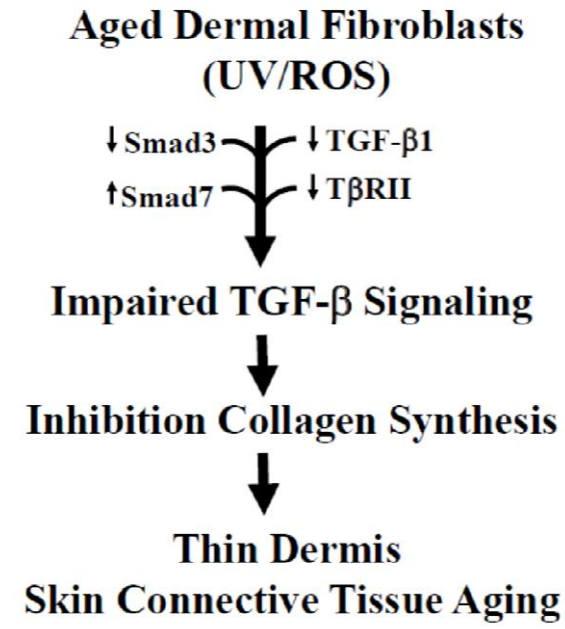

Figure 3. Impaired TGF-β pathway in dermal fibroblasts contributes to reduced collagen biosynthesis in human skin aging

The most abundant AGEs in human tissues is glucosepane, a lysine-arginine crosslinking product. Glucosepane and other collagen AGEs result in molecular deformation, adversely affecting mechanical tissue compliance and reducing collagen's capacity for binding hyaluronic acid and glycosaminoglycans (Reiser, 1998). The molecular or functional importance for AGE-mediated macroscopic collagen changes is yet to be clarified. Due to dense collagen packing, these glycated crosslinks primarily affect fibrils at their surface and result in progressive insolubility and increased stiffness of collagen in aged tissue.

5. Conclusion

Intrinsic and extrinsic aging results in several negative effects on the dermal collagenous matrix. Aged skin has increased collagen fragmentation with subsequent impairment of fibroblast function due to dissociation with collagen fibrils and reduced mechanical stretch. Resultant fibroblast dysfunction and upregulation of MMPs lead to increased collagen degradation as well as reduced procollagen production. Accumulation of further collagen degradation products and cumulative UVR exposure results in a self-perpetuating cycle of further MMP production with degeneration of the ECM due to cascades related to TGF-β signaling, transcription factor AP-1 and ROS generation. The above factors compounded with inherent chronological aging and natural glycation of tissue collagen types lead to the disorganized and fragmented collagen fibril architecture. These pathways should be considered as a complex integrated dermal collagen ecosystem during dermal aging.

This literature report summarizes the current understanding of age-related alterations of the composition of the dermal collagenous matrix and mechanisms underlying these alterations to provide

insight into the molecular basis of skin aging to help identify novel targets for antiaging treatments.

6. Limitations and Further Study

Further research is required on the exact molecular mechanisms of how MMPs are up-regulated in impaired fibroblasts which may potentially provide the key to unlock the mysteries in delaying skin aging. In addition, there is a need for further investigation into the molecular mechanisms involved in dermal collagenous ECM homeostasis in the aging dermis and how age-related changes in dermal ECM collagen influence skin diseases, such as impaired wound healing and skin cancer in the elderly.

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