Clinical Relevance of Elastin in the Structure and Function of Skin

Leslie Baumann, MD; Eric F. Bernstein, MD, MSE; Anthony S. Weiss, PhD; Damien Bates, MD, PhD, MBA; Shannon Humphrey, MD; Michael Silberberg, MD, MBA; and Robert Daniels, PhD

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Abstract

Elastin is the main component of elastic fibers, which provide stretch, recoil, and elasticity to the skin. Normal levels of elastic fiber production, organization, and integration with other cutaneous extracellular matrix proteins, proteoglycans, and glycosaminoglycans are integral to maintaining healthy skin structure, function, and youthful appearance. Although elastin has very low turnover, its production decreases after individuals reach maturity and it is susceptible to damage from many factors. With advancing age and exposure to environmental insults, elastic fibers degrade. This degradation contributes to the loss of the skin's structural integrity; combined with subcutaneous fat loss, this results in looser, sagging skin, causing undesirable changes in appearance. The most dramatic changes occur in chronically sun-exposed skin, which displays sharply altered amounts and arrangements of cutaneous elastic fibers, decreased fine elastic fibers in the superficial dermis connecting to the epidermis, and replacement of the normal collagen-rich superficial dermis with abnormal clumps of solar elastosis material. Disruption of elastic fiber networks also leads to undesirable characteristics in wound healing, and the worsening structure and appearance of scars and stretch marks. Identifying ways to replenish elastin and elastic fibers should improve the skin's appearance, texture, resiliency, and wound-healing capabilities. However, few therapies are capable of repairing elastic fibers or substantially reorganizing the elastin/microfibril network. This review describes the clinical relevance of elastin in the context of the structure and function of healthy and aging skin, wound healing, and scars and introduces new approaches being developed to target elastin production and elastic fiber formation.

Elastin is a critical skin protein consisting of crosslinked tropoelastin. Elastin combines with microfibrils to form elastic fibers that provide stretch and recoil to the skin.[1,2] Elastogenesis, the process of elastin formation, mainly occurs during the fetal and early neonatal development of organs such as blood vessels, lungs, and skin.[3,4] Elastin has a very low rate of turnover, so it is susceptible to damage over time from many factors. Tropoelastin, the primary building block of elastin,[1] has the highest level of expression during early development, but expression decreases during adulthood.[4,5] Age-related reduction in elastin production and damage to elastin have a substantial impact on the skin's appearance, resulting in looser, sagging, and fragile skin.[6-8]

Dr Baumann is in private practice in Miami, FL, USA. Dr Bernstein is in private practice in Ardmore, PA, USA. Dr Weiss is the McCaughey Chair in Biochemistry and Professor of Biochemistry and Molecular Biotechnology, Charles Perkins Centre, University of Sydney, Sydney, NSW, Australia. Dr Bates is the acting chief executive officer, BioCurate Pty. Ltd., Parkville, VIC, Australia. Dr Humphrey is a clinical assistant professor, Department of Dermatology and Skin Science, University of British Columbia, Vancouver, BC, Canada. Dr Silberberg is executive medical director and global strategy lead, Allergan Aesthetics, an AbbVie Company, Marlow, Buckinghamshire, UK. Dr Daniels is head of Elastagen, Allergan Aesthetics, an AbbVie Company, Gordon, NSW, Australia.

Corresponding Author:
Dr Leslie Baumann, 4500 Biscayne Blvd., Miami, FL 33137, USA.
E-mail: lbwork@derm.net

Levels of elastin, collagen, and hyaluronic acid gradually decrease in aging, sun-protected skin, thereby contributing to a loss of structural integrity and elasticity.[9-12] Wrinkles, sagging, fragility, and irregularities in skin tone and texture develop as a consequence of the aging process; these are common issues for which individuals seek aesthetic treatment.[7,8] The most severe changes in elastic fiber morphology, arrangement, and content occur in photodamaged skin.[13] There are many interventions to improve the levels of collagen and hyaluronic acid in the skin, but no established treatments that increase production of elastin. This is because elastogenesis is a complex process that involves the crosslinking of tropoelastin monomers and microfibrillar proteins to produce elastic fibers. This process is much more difficult to stimulate and regulate than collagenesis because of the multiple steps involved in the assembly process. Procedures such as injections of collagen and hyaluronic acid to rejuvenate skin have been developed, but there are currently no approved devices to introduce functional elastin into the skin. Elasticity is considered a marker of overall skin health,[12] and elastin production is fundamental to the resilience of tissues and organs.[3] Current treatments are aimed at preserving native elastin in the skin with sunscreen, antioxidants, and other topical ingredients. Treatments that could replenish or replace elastin and elastic fibers are a logical approach to maintaining healthy skin.

This review focuses on the clinical relevance of elastin to the structure and function of skin, highlighting the importance of elastin during wound healing, scarring, and aging, as well as new treatment approaches aimed at replenishing or repairing the skin elastic fiber network.

THE ROLE OF ELASTIN IN THE ANATOMY AND FUNCTION OF SKIN

Elastin in Skin

Elastic fibers are located in the skin's dermal layer and make up approximately 2% to 4% of the fat-free dry weight of the dermis in the skin of adults.[14,15] The fibers are oriented both perpendicularly and in parallel to the skin surface, thereby creating an intricate network.[14] Elastic fibers are principally composed of elastin and microfibrillar fibrillin.[16] Differences in elastic fiber composition impart variations in resilience and recoil.[2] For example, the dermal reticular and papillary layers contain elastic fibers that differ in their thickness, orientation, and relative composition of elastin, fibrillin, and other molecules. Furthermore, the high content of short-chain hydrophobic amino acids in tropoelastin, in concert with water, contributes to the capacity for elasticity and recoil in the skin.[17]
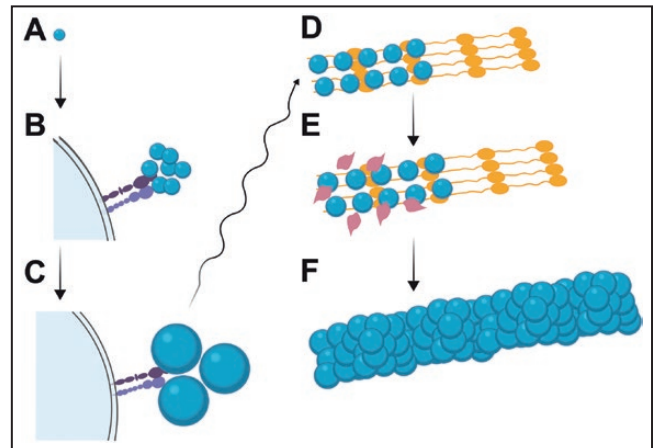

Figure 1. Role of tropoelastin in elastogenesis and the production of elastic fibers. (A) Assembling tropoelastin coalesces into 200 to 300 nm nanoparticles that remain on the elastogenic cell surface soon after secretion. (B) These nanoparticles fuse to give 1 to 2 μm spherules that (C) grow and move from the cell surface until they are (D) deposited onto microfibrillar scaffolds and the growing elastic fiber. (E) Lysyl oxidase and lysyl oxidase-like proteins oxidize lysine residues in tropoelastin before and during coacervation, allowing for (F) their covalent crosslinking into elastin. Reprinted from *Matrix Biology*, vol. 84, Vindin H, Mithieux SM, and Weiss AS, Elastin architecture, pages 4-16. Copyright 2019, with permission from Elsevier.

Elastogenesis in Skin

Elastic fibers are formed through a complex process known as elastogenesis (Figure 1). Elastogenesis hinges on the availability, assembly, and crosslinking of its dominant component, tropoelastin.[5,17,18] Elastogenic cell types, such as fibroblasts, are responsible for producing elastin. Elastogenesis begins when soluble tropoelastin monomers are secreted by fibroblasts into the extracellular environment, where they bind to the fibroblast through specific cell surface interactions. After binding, tropoelastin aggregates into microscopic globules in an initial microassembly phase[18] in which the tropoelastin monomers rapidly align and concentrate. This process, called coacervation, requires optimal physiologic conditions (ie, 37°C and a pH range of 7-8).[18] Before and during coacervation, the tropoelastin molecules are oxidized by 1 or more members of the lysyl oxidase family and then crosslinked. The crosslinked bundles of tropoelastin remain bound to the cell surface, where additional tropoelastin is added as elastin is formed and gradually deposited onto fibrillin-rich microfibrils until a nascent elastic fiber is produced and released from the cell surface.[2,18,19] Microfibrils serve as a scaffold for the formation of, and associate with, elastic fibers to aid in correct alignment.[2,17] Data also suggest that the

extracellular glycoprotein fibulin-5 can be knocked out without compromising host viability, yet may play several important roles in elastogenesis, including the aggregation of tropoelastin coacervates and deposition of tropoelastin into microfibrils.[20-23]

Elastin in Aging Skin

Skin aging, both intrinsic and extrinsic, results in wrinkled skin with decreased elasticity.[24] In the skin, the aging process is disruptive to the elastic fiber network, resulting in reduced tissue compliance and rebound, structural damage, and impaired homeostasis.[24] In addition to damage to the elastin network, aging also disrupts levels of other major skin components such as collagen, hyaluronic acid, glycosaminoglycans, integrins, and laminin.[9] Elastin is particularly vulnerable for several reasons. Elastin and elastic fibers are unique in that there is very low and slow turnover. In fact, in skin, the overall half-life of elastin is similar to the human lifespan![14,25] These long-lasting fibers suffer from years of repeated mechanical and environmental insult, and it is unlikely that these proteins and fibers will be appreciably replaced.[14,24] The inability of the skin to naturally replenish or repair elastic fibers has resulted in the majority of current therapies being aimed at protecting elastin fibers rather than replacing them.

Elastolytic enzymes called elastases, which arise from disease, sun exposure, free radical damage, inflammation, and other conditions, degrade elastin fibers.[14] Disruptions to the elastic fiber network are seen even in the absence of sun exposure in intrinsically aged skin. These disruptions occur in 2 main ways: first, the elastic fibers shorten and fragment; and second, damage accumulates to the protein through modification of aspartic acid residues, calcium and lipid accumulation, and glucose-mediated crosslinking.[24] Degradation of the elastic fiber network may also be evidenced by disrupted interactions with other components of the dermis including hyaluronan, versican, and elafin.[26,27]

Considering that production of new elastin ceases in maturity,[4] and tropoelastin synthesis does not obviously recur unless wound healing occurs, there is a need to identify treatments that can either replenish or stimulate production of tropoelastin or elastin in a structurally appropriate way in the skin, so that skin elasticity can be preserved.[18] Additionally, because elastic fibers contain >90% elastin, and elastin is composed of crosslinked tropoelastin, the replenishment of tropoelastin is an important target to consider in treatments to rejuvenate the skin.[5]

CLINICAL RELEVANCE OF ELASTIN

Genetic Conditions With Elastin Defects

Genetically acquired defects in elastin can result in diseases associated with the loss of skin elasticity.[14,28] Cutis laxa is a genetically variable disease characterized by defective elastin metabolism and abnormal elastic fibers, which contribute to inelastic, saggy skin that affects the whole body; some cases are inherited (via 3 possible modes of inheritance: autosomal dominant, autosomal recessive, or X-linked recessive) and others are acquired (ie, acquired cutis laxa).[14,29,30] To date, there are no specific treatments for cutis laxa; thus, a better understanding of the disruption of, and approaches to repairing, elastic fiber networks could potentially assist patients with this disease.

Disruption of Elastic Fiber Networks

Elastic fiber networks also degenerate during wound healing, scarring, and photoaging (ie, chronic sun exposure).[7,13,14,16,31,32] Although physiologic responses aim to repair the structure of the skin as a result of these changes, the best approach to correct the appearance of scars and sun-damaged skin by targeting reparation of elastic fiber networks is elusive and an area of active research.[1,5,18,32-34]

Wound Healing

Injury to the skin compromises the integrity and structure of the skin, resulting in a tightly regulated response near the injury to remove any foreign material, prevent infection, and heal the wound.[1] Injury can trigger rapid reinitiation of tropoelastin expression,[18] highlighting its role in wound healing. There are 4 main processes in wound healing in adults: hemostasis, inflammation, proliferation, and remodeling.[31] During the first 3 processes, there is a collective response with blood clotting and formation of a temporary extracellular matrix (ECM) as well as re-establishing the protective barrier through keratinocyte and fibroblast migration into the wounded area; various growth factors are upregulated, as are some proteins (eg, collagen type I), while other proteins undergo cell-mediated proteolysis that accompanies tissue clearing and turnover.[31,35] In the fourth process (remodeling), fibroblasts are activated and further synthesize proteases, fibronectin, a range of glycosaminoglycans, and matrix enriched for collagen type I.[35] The wound healing process progresses through each of these stages, with different extracellular matrix proteins dominating the early, middle, and later phases.[35] Initially, after the fibrin-rich matrix provides hemostasis, a hyaluronic acid-rich matrix accumulates to stimulate cell migration and tissue remodeling. Then, vascular granulation tissue, rich in chondroitin sulfate, and a mix of proteoglycans, such as decorin, associates with collagen fibers and versican, which associates with elastic fibers. This step is followed by deposition of the provisional type III collagen-rich matrix, finally followed by deposition of mature type I collagen that changes throughout the remodeling phase. Elastic fibers are the last extracellular matrix fibers that may form in small amounts. The culmination of these processes results in scar tissue with a large amount of

deposited collagen with abnormally arranged, often large, collagen bundles.[31,35] Elastin production is poor and insufficient during wound healing, which prevents the reformation of an elastic fiber network in the scar tissue, thereby reducing the elasticity compared with the original tissue.[31]

Elastin contributes to wound healing not only by providing mechanical elasticity, but also by acting on cells that gradually reduce wound contraction and improve regeneration of the dermis.[1] The production of elastin in regenerative species suggests an important role in wound healing and flexibility of newly generated skin, although the exact mechanisms for these processes remain largely descriptive.[33] Patients with wounds and scars, which can be disfiguring and psychologically traumatic, may benefit from potential treatments to improve wound healing and restore proper organization of elastic fibers.[33] Preclinical data suggest that a sufficient supply of exogenous tropoelastin can act as a substrate during tissue repair to allow for the appropriate organization of elastic fibers in wound healing and angiogenesis.[5,18,34,36,37]

Scars/Striae

Elastin production decreases as age increases.[1,5] Remodeled or scarred skin in adulthood (ie, damaged skin from severe acne, striae distensae [stretch marks], cuts, burns, sun damage, or aging) can result from the skin not being efficiently replenished with elastin and from the elastic fiber network lacking proper reorganization during the skin repair phase. Degradation and disorganization of the components that make up elastic fibers contribute to the development of atrophic (depressed), hypertrophic (raised), and keloid (overgrown) scars.[32] In fetal wound healing, elastin has been proposed to contribute to scarless recovery, the timing of which is restricted to early- to midgestation when the elastic fiber network is still undergoing development, which suggests that elastin plays an important role in healing scars.[1] Many studies have focused on characterizing the elastin content of scars compared with normal skin and, depending on the scar type and timing, most scars show decreased elastin content as well as fragmented elastic fibers and disorganization of collagen bundles.[32]

Striae distensae alba typically appear as atrophic dermal scars where gaps are filled with new, disorganized collagen and elastin.[38] Striae may develop with topical corticosteroid overuse and hormonal changes affecting elastic fiber integrity in skin.[38] Treatments for striae and scarring include topical acids and retinoids, lasers, intense pulsed light, microneedling, fractionated radiofrequency microneedles, and chemical peels, to resurface the skin and trigger extracellular matrix turnover through a controlled wound repair process.[32,38] However, scientific evidence of effective elastin repair and regeneration with these treatments is lacking compared with remodeling the collagen component of the skin.[32] In contrast, tropoelastin replenishment has been proposed as an effective and direct way to treat striae alba by acting as a substrate during the tissue repair process, subsequently improving the skin extracellular matrix structure and elastic fiber network.[34,36,38]

Aging and Photoaging/Chronic Sun Exposure

Aging skin and skin exposed to substantial sun damage presents with a changed structure to that of younger, healthier skin. In photoaged skin, these changes include coarse wrinkling, roughened texture, sallow complexion, mottled pigmentation, and marked loss of elasticity, whereas intrinsically aged skin exhibits fine wrinkling, smooth texture, clear complexion, uniform pigmentation, and gradual loss of elasticity.[13] These properties can be attributed to different physiologic changes in the elastic fiber network and skin structure.[24]

Laser scanning confocal microscopy shows the 3-dimensional arrangement of both collagen and elastic fibers in sun-protected versus photodamaged skin (Figure 2), demonstrating profound differences in the superficial dermis.[39]

Chronic sun exposure disrupts the elastic fiber architecture in substantial ways, resulting in an accumulation of elastin-containing material below the dermal-epidermal junction, known as solar elastosis, leading to the loss of skin elasticity.[7,13,14,16] With chronic photodamage the normally collagen-rich dermis, with its network of elastic fibers, degrades, resulting in solar elastosis wherein the normal dermis is replaced with abnormal clumps of large elastic fibers arranged haphazardly. In addition, the normal oxytalan fibers that extend vertically to the epidermis and contain fibrillin, but not elastin, are degraded and often absent in photodamaged skin.[13] A "grenz," or border zone of collagen-rich dermis, often separates the solar elastotic material from the epidermis; this zone can sometimes contain vertically oriented elastic fibers that are usually present in sun-protected skin (Figure 3).[16] Sun-protected skin (similar to intrinsically aged skin) shows elastin-containing elastic fibers and oxytalan fibers that are short and do not reach the epidermis; conversely, sun-exposed/-damaged skin shows that the elastic fibers are degraded and the elastic fiber network is disorganized. Microfibrillar components of elastic fibers are susceptible to damage by UV radiation, which may contribute to the demise of elastic fiber networks in photoaged skin.[24] Tropoelastin, however, is resistant to the effect of UV light.[40]

The changes seen in the elastin network are a key area of interest for scientists and clinicians aiming to develop therapies capable of treating both intrinsically and extrinsically aged skin. Of particular interest is the potential for
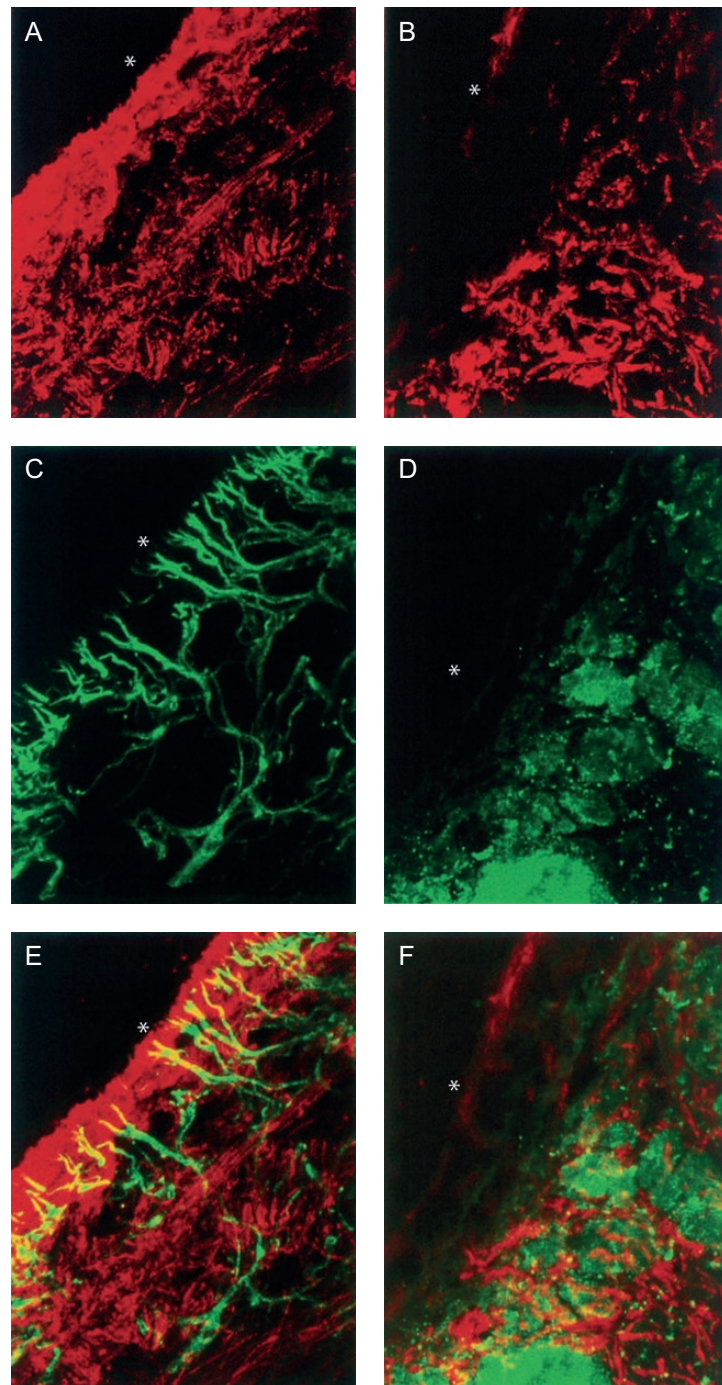
Figure 2. Confocal scanning laser microscopy is used to compare sun-protected to sun-damaged skin from the same individual. (A) Collagen immunostaining (red) reveals a dense network of collagen fibers arranged parallel to the epidermis that are brightly stained immediately beneath the unstained epidermis. (B) Photoaged skin from the same individual reveals a decrease in collagen fibers and a deteriorated architecture to the fibers that remain. (C) Elastin staining (green) of sun-protected skin reveals a rich network of elastic fibers perpendicular to the epidermis in the superficial dermis, and parallel to the epidermis in the deeper dermis. (D) Elastin staining in sun-damaged skin from the same individual reveals an absence of the vertical elastic fibers as well as large clumps of nonfunctional solar elastotic material. (E) Dual immunostaining for collagen and elastin are superimposed to demonstrate the interaction of collagen and elastic fibers in sun-protected skin. (F) The dramatic alterations of collagen and elastic fibers are seen in photoaged skin. Dermoepidermal junction is marked by.* Reprinted with permission from Elsevier, originally published in Bernstein EF, Chen YQ, Kopp JB, et al. Long-term sun exposure alters the collagen of the papillary dermis. Comparison of sun-protected and photoaged skin by northern analysis, immunohistochemical staining, and confocal laser scanning microscopy. *J Am Acad Dermatol*. 1996;34(2 Pt 1):209-218.
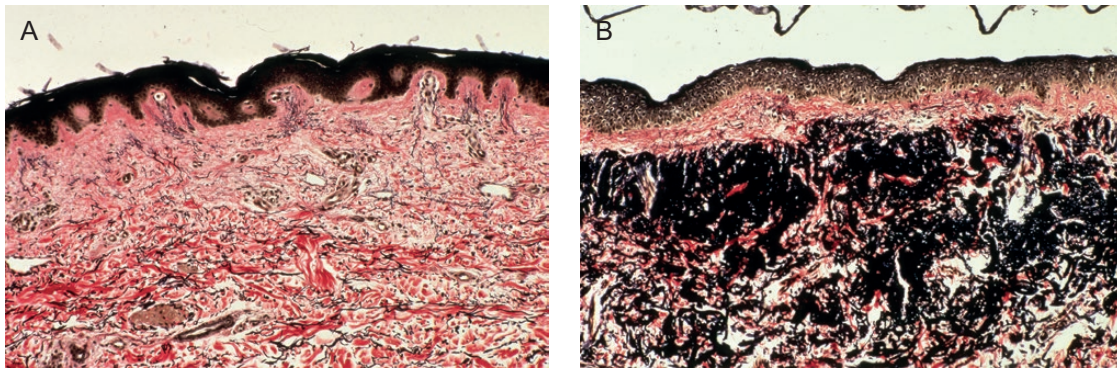
Figure 3. (A) Sun-protected buttock skin stained with Verhoeff-van Gieson stain, showing collagen fibers in red and elastic fibers in black and demonstrating a collagen-rich dermis with the fine meshwork of elastic fibers. (B) Sun-damaged neck skin from the same individual demonstrating a dense band of abnormal solar elastotic material, with large, disorganized elastic material beneath a "grenz," or border zone of normal-appearing dermis, presumably stimulated to grow by the overlying cell-rich epidermis. Magnification ×100. Images courtesy of Eric F. Bernstein, MD, MSE.

exogenous tropoelastin to act as a substrate during ECM remodeling and repair of skin elastic fiber networks.[13,24]

Treatments

There is an unmet need for improved treatments for photoaged skin, wounds, striae, and scars, with elastin production and elastic fiber structure and organization being prime potential targets for aesthetic treatments.

Current intrinsic treatment modalities, which stimulate or modulate endogenous elastin, typically involve cosmetics and topical skincare products.[41-44] Topical approaches have attempted to exploit a wide range of mechanisms, such as copper and zinc that are critical for the functioning of the elastin crosslinking enzyme lysyl oxidase, derivatives of vitamin A (eg, tretinoin) that reduce the symptoms of photoaging through the modulation of collagen and elastin fiber structure, as well as elastin matrikines (degradation products of elastin that stimulate inflammatory pathways and may help clear damaged or degraded ECM components).[41,42,45-47] However, given the complexity of tropoelastin production, assembly, and crosslinking, there is limited evidence that topical skincare products can reach the dermal layers of the skin or sufficiently stimulate elastin production.[18] Some studies have proposed that these products can stimulate elastin production or remodeling based on changes in dermal markers observed via histologic testing, biopsy, subjective patient feedback, or measurement of mechanical skin properties by probe and suction devices.[41-44] Gene expression changes can be combined with histologic stains (eg, Movat) that show regeneration of elastin fibers and increased fibrillin formation, as well as reversal of solar elastosis.[48] However, as the number of treatment approaches continues to expand, there is still a need for more validated and objective clinical assessments to measure skin elasticity and skin elastin content,

which enable histologic changes to be correlated with clinically meaningful endpoints.[32]

Efforts to pursue improved wound repair and scar prevention by stimulating elastin production have been limited, but preclinical studies demonstrate potential opportunities.[34] Successful extrinsic treatment modalities to replenish elastin may require delivery of structurally intact tropoelastin or elastin; most experimental strategies have utilized elastin fragments that are inappropriate for in vivo elastin assembly.[5,18] Proposed therapies for cutis laxa provide other potential targets for restoring elastin. For example, although no specific treatments for cutis laxa exist, it has been suggested that the disordered elastic fiber assembly in this disease might be corrected by supplementing certain carrier molecules that have a role in the secretory pathways for elastolytic enzymes involved in elastin production.[14] Other potential therapeutic strategies for increasing elastin production include stimulation of elastin gene expression.[49,50] However, because tropoelastin expression and elastin production are substantially reduced in adult tissues, even large increases in their expression are unlikely to be physiologically relevant.[4,5]

Considering tropoelastin is the main component of elastin, a more viable approach to repairing elastic fiber networks may be to use recombinant human tropoelastin-based treatments.[5,18] The recombinant human tropoelastin may act as a substrate for skin fibroblasts to promote collagen production and glycosaminoglycan deposition, contributing to tissue repair and improved hydration in skin. Tropoelastin has potential value in aesthetics, wound healing, and treatment and prevention of scars. A recent study showed that surgical delivery of exogenous tropoelastin via a collagen-based dermal substitute leads to the development of an extensive elastic fiber network in the deep dermis.[34] Recombinant human tropoelastin has demonstrated early promise for wound repair, scar prevention and treatment, cosmetic applications, and aesthetics;

it can be used by skin cells as a substrate to produce new elastic fibers.[34,36] The applied use of tropoelastin for these indications is therefore a promising area of study. Randomized clinical trials have the potential to reveal clinically relevant information on the functional role of recombinant human tropoelastin in the extracellular matrix of skin and provide an opportunity to improve wound healing, reduce scarring, and improve the structure and appearance of the skin.

CONCLUSIONS

Because elastic fibers are formed early in life and are rarely replenished in adulthood, perturbation of elastic fiber networks during wound healing, scarring, chronic sun exposure, and aging results in terminally reduced skin elasticity and altered appearance. Efforts to exogenously replenish elastin and support the structure of elastic fiber networks may provide new methods of intervention that have the capacity to improve elasticity and appearance in damaged skin, as well as reduce the appearance of scars. Elastin provides benefits to skin function beyond solely mechanical elasticity. By acting as a substrate for cell growth, elastin can support improved regeneration and remodeling of the dermis, which is critical for effective wound healing and scar repair. Tropoelastin, the dominant component of elastin and elastic fibers, serves an important role in various skin processes and is a logical component to consider when developing approaches for wound healing, scar repair, and aesthetic indications.

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