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Clinical and Molecular Insights into Hypertrophic Scars and Keloids: A Literature Review

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ABSTRACT

Background: Hypertrophic scars and keloids represent two distinct forms of abnormal wound healing, characterized by excessive fibrous tissue formation. Despite their prevalence, the pathophysiological mechanisms underlying their development and persistence remain incompletely understood. This literature review synthesizes current clinical and molecular insights into hypertrophic scars and keloids, aiming to highlight differences in their etiology, pathogenesis, and therapeutic responses.

Methods: A comprehensive review of the literature was conducted, focusing on articles that provided significant insights into the clinical manifestations, genetic predispositions, molecular pathways, and treatment strategies related to hypertrophic scars and keloids. Experimental studies and clinical trials were included to encompass a wide range of data sources.

Results: Hypertrophic scars are confined to the original wound boundary and may regress over time, whereas keloids extend beyond the wound margins and do not regress. Clinically, hypertrophic scars and keloids differ in their appearance, texture, and predilection sites. At the molecular level, these differences are underscored by distinct profiles of cytokine expression, growth factor activity, and extracellular matrix composition. Genetic studies have identified several predisposing factors, including specific gene mutations and polymorphisms. Treatment strategies vary; however, intralesional corticosteroids remain the first-line treatment for both conditions. Emerging therapies targeting specific molecular pathways offer potential for improved outcomes.

Conclusion: Hypertrophic scars and keloids are complex conditions with distinct clinical and molecular characteristics. Understanding these differences is crucial for developing targeted and effective therapies. Future research should focus on unraveling the genetic basis of these conditions and exploring novel therapeutic targets. Enhanced knowledge of the pathogenic mechanisms will facilitate the advancement of personalized medicine approaches in the management of hypertrophic scars and keloids.

KEYWORDS: Hypertrophic scars, keloids, wound healing, pathophysiological mechanisms, genetic predispositions, molecular pathways, cytokine expression, intralesional corticosteroids, extracellular matrix, personalized medicine

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INTRODUCTION

Wound healing is a complex physiological process essential for skin regeneration, involving stages of hemostasis, inflammation, proliferation, and remodeling. However, deviations in this process can lead to the formation of excessive scars, notably hypertrophic scars and keloids, which arise from deep dermal insults.[1] Hypertrophic scars are characterized by raised, red formations confined within the

original wound, with disorganized collagen deposition leading to functional and aesthetic challenges.[2] Keloids, on the other hand, extend beyond the wound boundaries, manifesting as aggressive growths with irregular topography due to aberrant wound healing marked by fibroproliferation and neovascularization. These distinct clinical presentations prompt an investigation into the underlying molecular mechanisms driving their development and progression.[3-6]

The prevalence and incidence of hypertrophic scars and keloids vary across demographics, influenced by genetic predisposition and environmental factors. While hypertrophic scars commonly arise from trauma, surgery, or burns, keloids exhibit a notable propensity for certain populations, especially those with pigmented skin. These pathological scars extend beyond physical discomfort, impacting patients' quality of life and self-esteem. They can restrict joint mobility, cause discomfort, and induce psychological distress, highlighting the importance of comprehensive management strategies addressing both physical and emotional aspects.[1,7,8]

The psychological toll on patients affected by hypertrophic scars and keloids cannot be overstated, with heightened self-consciousness and anxiety prevalent due to the visible nature of these scars. Emotional concerns include fear of permanent scarring and a decline in quality of life, indicating the need for tailored therapeutic interventions. As we explore the molecular pathways underlying these pathological scars, understanding their clinical impact becomes imperative for advancing therapeutic modalities and enhancing patient outcomes.[9-11]

CLINICAL CHARACTERISTICS

Hypertrophic scars

Hypertrophic scars, representing thickened, elevated fibrotic areas at the site of previous wounds, exhibit growth confined within the boundaries of the original injuries, often posing challenges in histopathological differentiation.[12,13] These scars display specific collagen fiber structures characterized by systematic, parallel organization with fine, thin wavy patterns, reaching a growth peak several months post-injury before partially regressing. Emerging within 4-8 weeks post-wound closure, hypertrophic scars typically peak within 6-8 months, stabilizing thereafter and undergoing variable degrees of maturation similar to normotrophic scars. Notably, hypertrophic scars are associated with scar contractures, leading to reduced joint mobility due to tissue shortening.[14]

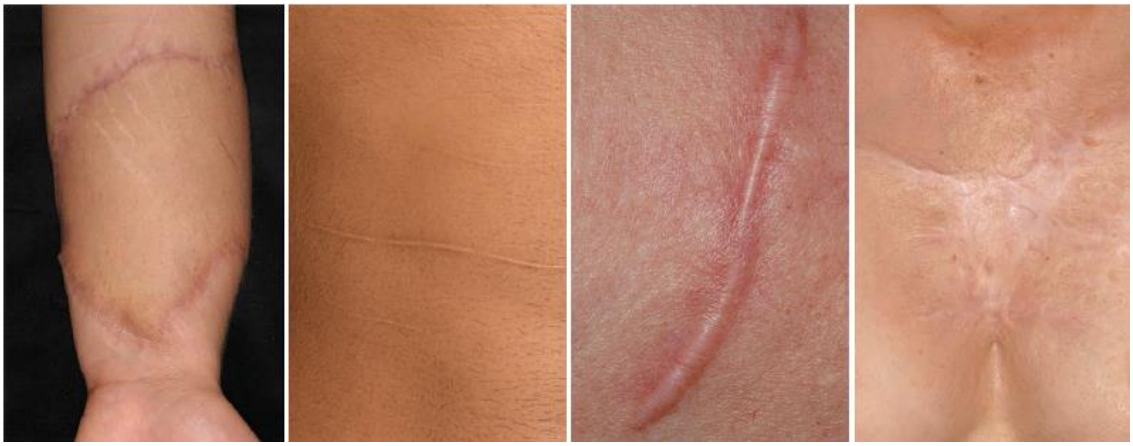

Figure 1. Appearance of scars. From left to right: Immature, mature, linear hypertrophic, and extensive hypertrophic.[1]

Anatomically, hypertrophic scarring commonly occurs in regions subject to high tension and mobility, including the perioral areas, neck, shoulders, upper arms, elbows, wrists, dorsal hands, presternal/intermammary areas, knees, and ankles.[14] While scars intersecting joints or skin creases perpendicularly are predisposed to hypertrophic scar formation, consistent overall anatomical associations remain unclear.[14,15] Importantly, scar contracture, uniquely associated with hypertrophic scars, is not observed in keloids.[14]

Despite their frequent occurrence following dermal injuries, scars can induce aesthetic concerns and significant discomfort, with patients reporting pain, tenderness, anxiety, and depression, leading to sleep disturbances. Scar formation adversely affects various aspects of psychological, social, physical, and sexual well-being, with reports indicating scar hyperesthesia and functional interference in half of patients undergoing hand surgeries, persisting up to two years post-surgery. Clinicians often observe adverse scar events such as pain and hypersensitivity, yet the lack of established diagnostic criteria and standardized evaluation techniques impedes a comprehensive understanding of scar morphology and its associated symptoms. While prolonged or persistent scar pain is assumed to relate to the extent of local tissue trauma and psychological factors, the underlying mechanisms remain incompletely understood and likely involve multiple factors.[16,17]

Keloids

Keloids manifest as firm, rubbery nodules with a tendency to protrude above the surrounding skin. They commonly exhibit a broad-based plaque or pedunculated lesion morphology,

extending beyond the area of original trauma. Keloids may present with varying colors, including erythematous, flesh-colored, or hyperpigmented, and their appearance may evolve over time. These lesions typically develop following non-severe trauma such as folliculitis, acne, vaccination, ear piercing, or cesarean section incisions,[18] with onset occurring within months to a year post-injury. Predominantly affecting areas subjected to tension and movement, keloids frequently emerge on the deltoids/shoulders, upper back, presternal/intermammary regions, and ears, particularly the earlobes and posterior sides, due to passive mobility and repeated minor trauma.

Clinical observations delineate two major morphological types of keloids: superficially spreading and exophytic (see **Figure 2** and **3**).

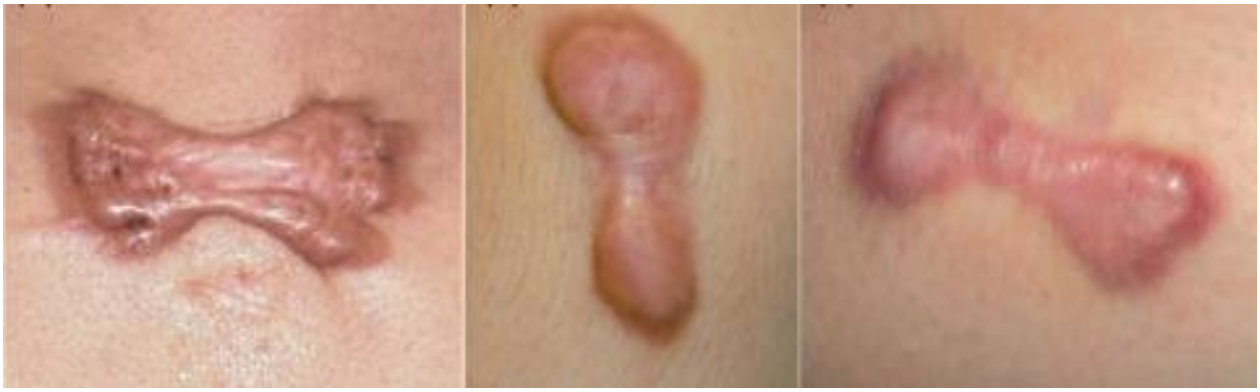

Figure 2. Superficially spreading keloids commonly grow into butterfly, crab's claw or dumbbell shapes.[5]

Superficially spreading keloids initially appear as small nodules or flat plaques, evolving into elongated forms resembling diplococci, dumbbells, or comets. Moreover, the active extremities via which a keloid extends it growth can split longitudinally to form characteristic pseudopods, from which the word ''keloid" is derived (the term *cheloid* was originally described in 1800s from the Greek word *chele* means "crab claw"). Superficially spreading keloids may also exhibit centrifugal spreading, often surrounded by areas of regression or bumpy relief.

In contrast, exophytic keloids commence in a bulbous shape, with less distinct central regression compared to superficially spreading types. Some exophytic keloids may appear smooth, while others exhibit furrows or botryoidal formations (from the Ancient Greek bótrus, meaning "a bunch of grapes").[19]

Despite their benign nature, keloids commonly present with symptoms such as bulkiness, erythema, itch, and pain.[18,20-22] Itch and pain can be intense and debilitating, often triggered by minimal contact (alloknesis, allodynia) or changes in ambient temperature.

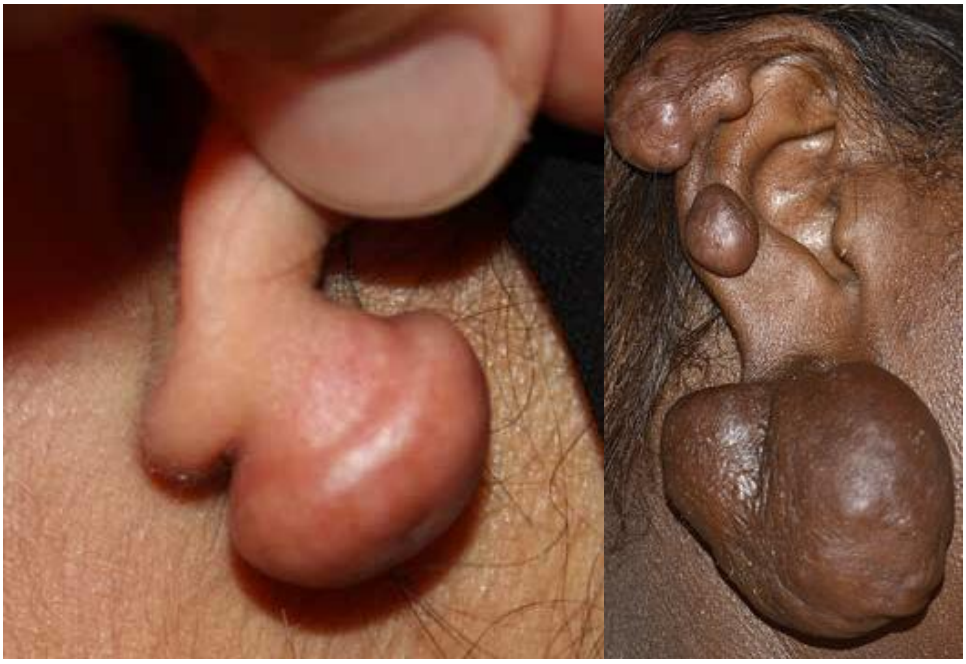

Figure 3. Keloids arising from earlobes usually grow as the exophytic/pedunculated type, and sometimes they grow into the more complex botryoidal forms.

Histopathological and Immunohistochemical Differences

Hypertrophic Scars

Hypertrophic scars and keloids represent dynamic processes in wound healing, undergoing transformation from granulation tissue to scar tissue over several months, known as scar maturation. This maturation involves changes in appearance, texture, and functional activity, reflecting alterations in cellular and extracellular matrix components within the epidermal and dermal layers. Both hypertrophic scars and keloids are characterized by the presence of alpha-smooth muscle actin (α-SMA) producing myofibroblasts and distinctive arrangements of collagen fibers, with hypertrophic scars exhibiting elevated cyclooxygenase-1 (COX-1) expression and keloids showing increased cyclooxygenase-2 (COX-2) expression relative to normal skin. Epidermal Langerhans cells (LCs) and keratinocytes play active roles in scar formation, with hypertrophic scars demonstrating aberrant regulation of dermal remodeling compared to normal scars.[23]

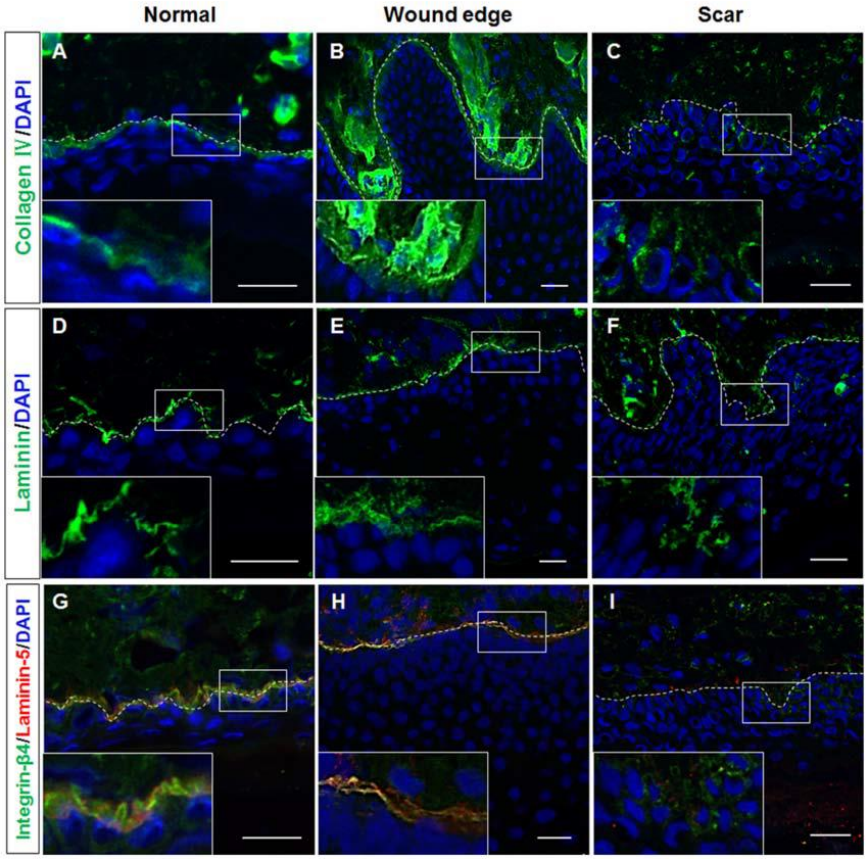

Figure 4. Different distribution patterns of basal membrane components in normal, wound edge and hypertrophic scar tissue. Representative fluorescence images show collagen type IV expression was detectable in the basal membrane area in both normal (section A) and wound edge tissues (section B), but collagen type IV staining was absent in the epidermis of hypertrophic scar tissues (section C). Representative fluorescence images also reveal the localization of laminin-5 and integrin-β4 in normal (section D and G), wound edge (section E and H) and hypertrophic scar tissues (section F and I). Negative staining of both laminin-5 and integrin-β4 was observed in the hypertrophic scar tissues (section I) as compared with the normal (section G) and wound edge tissues (section H). White dotted lines denote the basal membrane, which separated the epidermis and dermis. Insets show a close-up view of area within the white markings.[24]

The presence of smooth muscle actin alpha (α-SMA) expression and the formation of whorl-like or nodular arrangements of collagen fibers defines the hypertrophic scars and keloids, reflecting significant alterations in cellular and extracellular matrix (ECM) components within the epidermal and dermal layers. In a more specific term, the epidermis of hypertrophic scars exhibits elevated cyclooxygenase-1 (COX-1) expression, whereas keloids show increased cyclooxygenase-2 (COX-2) expression relative to normal skin and to one another. These findings underscore the crucial role of epithelial-mesenchymal interactions in the development of cutaneous scarring. Recent studies indicate active involvement of epidermal Langerhans cells (LCs) and keratinocytes in scar formation, with hypertrophic scars showing higher numbers of epidermal Langerhans cells, increased interleukin-4 (IL-4) expression, and reduced interleukin-1α (IL-1α) expression compared to normal scars, indicating aberrant regulation of dermal

remodeling. Additionally, activated keratinocytes in hypertrophic scar tissue show enhanced expression of keratins K6 and K16, which may contribute to delayed re-epithelialization, prolonged epidermal inflammation, and disrupted epidermal-mesenchymal interactions. These observations suggest that wounds such as severe thermal injuries tend to develop hypertrophic scarring due to inadequate regulation of collagen production by fibroblasts in response to keratinocytes and their products, ultimately leading to excessive collagen deposition.[25]

Fibroblasts and myofibroblasts are responsible in fibrotic diseases by producing excessive collagen during abnormal wound healing processes. Communication from epidermal keratinocytes trigger dermal fibroblast proliferation, although this communication may also reduce collagen production. Hypertrophic scars are characterized by an abundance of alpha-smooth muscle actin (α-SMA) producing myofibroblasts and a higher ratio of type III collagen to type I collagen.[26]

Some experts subdivide the inflammatory phase of wound healing into early and late stages. In the early phase, endothelial cells up-regulate the expression of adhesion molecules, leading to the recruitment and migration of inflammatory cells including neutrophils, monocytes, lymphocytes, and mast cells. In the late phase, macrophages transition into the anti-inflammatory M2 phenotype, which is crucial for resolving inflammatory reactions and initiating the proliferation phase by secreting various angiogenic and growth factors such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and fibroblast growth factor 2 (FGF2).[27] Excessive inflammation is a primary pathological mechanism underlying both hypertrophic scar and keloid formation, with dysregulated modulation of fibrogenesis by type 1 T-helper cells (TH1) and TH2 cytokines secreted by CD4+ T cells contributing significantly to abnormal scar development.[27] Immune responses involving infiltration of inflammatory cells such as CD3+, CD45RO+, and HLA-antigen D–related CD4+ T cells, as well as CD1a+/CD36+/intercellular adhesion molecule positive dendritic cells, into the dermis further exacerbate pathogenic scar formation, with various factors released by these cells activating fibroblasts and influencing scar formation.[27] Studies have shown reduced expression of certain pro-inflammatory factors such as interleukins-6 and -8 (IL-6, IL-8), and the chemokines (C-C motif) ligand 2 (CCL2) during the early phase of hypertrophic scar healing, suggesting an inadequate pro-inflammatory response that may render certain wounds vulnerable to impaired healing. Notably, studies showed cytokines such as interleukins-6 and -10 (IL-6, IL-10) play significant roles in scar formation and clinicians now consider them potential therapeutic targets for hypertrophic scar treatment. Alterations in fatty acid metabolism also contribute to inflammation and excessive scarring, highlighting potential therapeutic targets for scar prevention and treatment.[28] Further research is needed to elucidate the intricate interactions between immune responses, cellular components, and extracellular matrix dynamics in scar formation, paving the way for novel treatment strategies and improved patient outcomes.[27,28]

Keloids

Keloids exemplify dermal fibrosis, characterized by a substantial increase in fibroblasts primarily within the reticular dermis. However, the mechanisms underlying keloid formation extend beyond fibroblast proliferation. The dermis of keloids is highly expanded by multiple packed collagen bundles that exhibit a larger distance between collagen bundle centers than in normal skin and normal scars. This feature reflects an imbalance in collagen synthesis and degradation. Specifically, there is up-regulation of type I pro collagen alongside unaltered type III pro-collagen expression, leading to an elevated ratio of type I : III pro-collagen mRNA compared to normal skin. Moreover, keloids demonstrate reduced degradation of newly synthesized collagen, contributing to excessive collagen accumulation and the presence of large, hyalinized, eosinophilic fibers of various lengths with random orientation. Additionally, keloids may display distinct morphological features such as non-fibrotic papillary dermis, horizontal cellular fibrous bands, and fascia-like bands within the scar tissue. Some keloids present with dermal nodules that are composed of focal aggregates of fibroblasts and randomly oriented collagen fibers, and these have less distinct borders than the nodules in hypertrophic scars. Chronic inflammation, involving lymphocytes, macrophages, and mast cells, further contributes to keloid pathogenesis.[18]

At the morphological level, keloid blood vessels often appear partially occluded due to endothelial hypertrophy or perivascular matrix deposition. At the quantitative level, keloid patients exhibit elevated numbers of circulating endothelial progenitor cells (i.e. CD45-/CD34+/C D133+/VEGFR2+ cells) and altered endothelial function indices, indicating potential endothelial dysfunction implicated in keloid growth. At the functional level, keloids differ in two endothelial function indices: keloids have greater baseline brachial artery diameters and smaller endothelium-dependent vasodilatory responses. This endothelial dysfunction may interact with genetic mutations, systemic conditions, or local inflammatory stimuli to exacerbate keloid pathogenesis.[18]

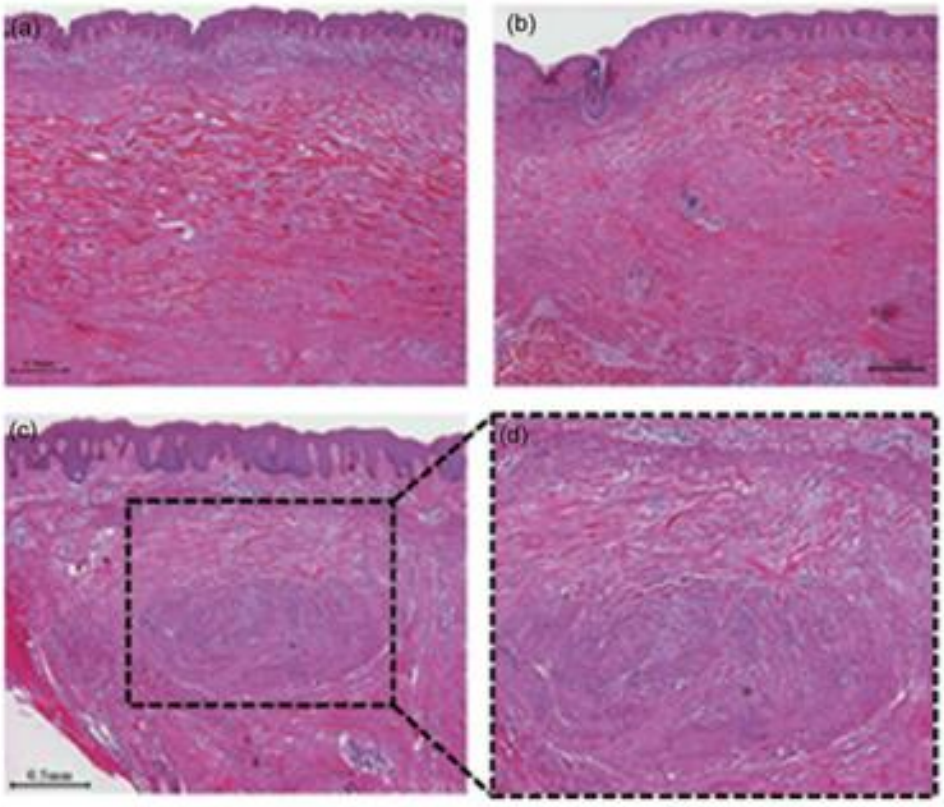

Figure 5. H&E-stained keloid sample showing keloidal collagen coexist with dermal nodules of classical hypertrophic scars. (a) central area (40×); (b) peripheral area (40×); (c) coexistence of keloidal collagen and dermal nodules (40× magnification). The area indicated by dashed lines is enlarged (d) (100× magnification).[5]

Genetic and Molecular Basis

Hypertrophic Scars

The regulation of skin tissue regeneration is intricately linked to complex gene networks, where abnormalities in gene expression can predispose individuals to cutaneous scarring or directly contribute to abnormal wound healing and scar formation. Genetic variations, which refer to differences in DNA sequence among individuals, play a critical role in determining susceptibility to specific diseases, including skin scarring. Notably, variations in major histocompatibility complex (MHC) genes and single base-pair substitutions are significant genetic factors that increase the risk of skin scarring. In humans, MHC genes, also known as human leukocyte antigen (HLA) genes, influence cutaneous fibrosis by modulating antigen presentation and regulating the immune system. Human leukocyte antigen (HLA) molecules serve as co-inducers of inflammation and cytokine expression, impacting lesions by promoting fibroblast proliferation and collagen deposition. Certain alleles of the human leukocyte antigen (HLA) system exhibit a heightened ability to bind antigens, leading to more robust immune responses in predisposed individuals. Studies have identified increased levels of specific human leukocyte antigen (HLA) alleles, such as HLA-DR, HLA-B14, and HLA-Bw16, in individuals with hypertrophic and keloid scars compared to normal tissue.[29]

Recent investigations have explored the correlation between genes related to skin pigmentation, such as the melanocortin 1 receptor (MC1R) gene, and hypertrophic scar formation. Researchers have identified R163Q single-nucleotide polymorphism (SNP) in the melanocortin 1 receptor (MC1R) gene, rs56234898 single-nucleotide polymorphism (SNP) in protein tyrosine phosphatase non-receptor type 5 (PTPN5) gene, and rs11136645 single-nucleotide polymorphism (SNP) in the CUB and Sushi multiple domains 1 (CSMD1) gene among many. The R163Q SNP in MC1R is responsible to an elevated likelihood of post-burn hypertrophic scarring. MC1R acts as a G-protein-coupled receptor that binds to α-melanocyte-stimulating hormone (α-MSH), a product of pro-opio-melanocortin (POMC) which is mainly produced by the hypothalamus and pituitary gland but also locally generated by keratinocytes ad melanocytes, initiating the synthesis of dark eumelanin by melanocytes. The α-melanocyte-stimulating hormone (α-MSH) suppresses the expression of pro-inflammatory cytokines in leukocytes while increasing the production of anti-inflammatory interleukin-10 (IL-10) in human monocytes and keratinocytes. [29,30]

Growth factors, particularly transforming growth factor-beta (TGF-β) isoforms, are pivotal in the pathogenesis of hypertrophic scars. The over-expression of TGF-β1 and TGF-β2 are responsible in hypertrophic scar tissue, whereas scarless healing is associated with elevated TGF-β3 levels. The TGF-β/Smad signaling pathway plays a central role in

scar formation by regulating collagen synthesis and fibroblast activity. Animal studies have shown that overexpression of TGF-β1 receptors induces skin fibrosis, highlighting its significance in scar pathogenesis.[31]

In keloid pathology, studies have found various pro-inflammatory products of cyclooxygenase-1 (COX-1) such as interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-18 (IL-18), chemokine-like factor-1 (CKLF-1), and prostaglandin significantly elevated. These molecules contribute to the inflammatory milieu in keloid tissue, although their precise role in keloid formation remains elusive. Animal models have demonstrated that manipulation of specific cytokine expression can influence scar formation, indicating their potential as therapeutic targets Chemokine CXCL12 could promote scar formation in mice, where induction of CXCL12 led to larger scar size, while abrogation of CXCL12 resulted in downregulated scar formation. A similar effect was observed for the monocyte chemoattractant protein-1 (MCP-1), as mice with MCP-1 deficiency exhibited milder inflammation and a normal skin architecture compared to wild-type mice, which showed robust inflammation and abnormal collagen bundle thickening after bleomycin injection. Studies also showed interleukin-17 (IL-17), a cytokine associated with T-helper 17 (Th17) cells, elevated in hypertrophic scar tissues. Injection of recombinant IL-17 into the wound area during the inflammatory stage exacerbated fibrogenesis and inflammation, accompanied by increased levels of the monocyte chemoattractant protein-1, -2, and -3 (MCP-1, MCP-2, MCP-3). However, this pro-fibrotic effect of IL-17 could be counteracted by depleting macrophages with clodronate liposomes, indicating that macrophages mediate the pro-fibrotic effect of IL-17.[32]

Clinicians associate platelet-derived growth factor (PDGF) with hypertrophic scar formation through its actions on fibroblast proliferation and collagen synthesis. Scar-derived fibroblasts exhibit heightened responses to PDGF, suggesting its role in promoting scar pathogenesis.[33] It transmitting its signal through tyrosine kinase receptors, PDGF-α receptors (PDGF-aR) and PDGF-BB receptors (PDGF-BBR), and the downstream extracellular signal-regulated kinase (ERK) cascade. Platelet-derived growth factor (PDGF) acts as a potent chemoattractant for monocytes and fibroblasts, stimulating fibroblast proliferation and regulating collagen synthesis, thereby contributing to hypertrophic scar formation. Scar-derived fibroblasts have shown heightened responses to the chemotaxis and mitogenic effects of PDGF compared to normal skin cells, with increased extracellular signal-regulated kinase (ERK) phosphorylation observed in scar-derived fibroblasts.[33]

The dynamic interplay between synthesis, accumulation, and degradation processes determines the equilibrium of extracellular matrix (ECM) levels in a wound. Matrix metalloproteinases (MMPs) are crucial enzymes in wound healing, as they degrade the extracellular matrix (ECM) and regulate bioactive substances. MMPs, categorized into collagenases, gelatinases, stromelysins, and membrane type MMPs, play roles in all phases of wound healing. MMP-1, MMP-8, and MMP-13 target collagens I and III in scar tissue. Conversely, tissue inhibitors of metalloproteinases (TIMPs), like TIMP-1, modulate MMP activity.

Specific MMPs have been implicated in keloids and hypertrophic scars. MMP-1, a zinc-dependent neutral endopeptidase, is crucial in ECM degradation. In wound healing, MMP-1 typically appears later, but in one animal study with axolotls shows MMP-1 appear early, possibly indicating its role in scarless healing. MMP-1 may promote scar-free wound healing by modulating fibroblast proliferation and apoptosis. This proteinase enzyme, responsible for initiating the degradation of type I collagen, shows decreased expression and activity in keloids and hypertrophic scars, possibly due to elevated levels of TIMP-1 in hypertrophic scars. Conversely, MMP-2 levels increase in keloids and hypertrophic scars compared to normal skin, despite its traditional association with tissue remodeling involving gelatin degradation. This increase in MMP-2 in abnormal scars appears paradoxical considering typical role of MMPs in collagen degradation.[34,35]

While experts agreed that MMP-1 suppresses fibroblast proliferation, studies observed that microRNA-222 (miR-222) down-regulates MMP-1 expression. This supports the idea that miR-222 is the factor behind MMP-1 expression that modulates fibroblast proliferation and apoptosis. Later, researchers identified a potential feedback loop between miR-222 and MMP-1, suggesting that MMP-1 could counteract the effects of miR-222 on fibrogenesis. Overexpression of miR-222 in hypertrophic scar fibroblasts led to a significant increase in apoptosis rates, followed by decreased expression of proliferating cell nuclear antigen (PCNA) and cyclin D1, and increased levels of cleaved caspase-3.[36]

Keloids

Individuals with a family history of keloids are at a heightened risk of developing multiple keloids of greater severity, indicating a strong genetic predisposition. Evidence supporting genetic susceptibility includes familial heritability, increased prevalence in certain ethnicities, occurrence in twins, and findings from linkage studies, case-control association studies, and gene expression studies. Most evidence suggests an autosomal dominant inheritance pattern with incomplete penetration and variable expression, explaining why carriers may not express the keloid phenotype and why not all keloid patients respond to trauma with keloid scarring. Several gene polymorphisms associated with keloids have been identified, including the neural precursor cell expressed developmentally down-regulated protein 4 (NEDD4), forkhead box protein L2 (FOXL2), myosin 1e (MYO1E), myosin 7a (MYO7A), and human leukocyte antigen (HLA), although the precise underlying mechanism remains unclear. Additionally, epigenetic modifications may

contribute to keloid pathogenesis, further complicating the understanding of its genetic basis. However, the specific genetic variations responsible for keloid scarring have yet to be fully elucidated, likely involving multiple genes and polymorphisms, leading to variations in phenotype among keloid patients.[37-39]

Keloid formation is attributed to an imbalance between increased synthesis of collagen and extracellular matrix (ECM) and decreased degradation of these products. Over-activation of keloid fibroblasts, driven by the overexpression of inflammatory mediators like transforming growth factor beta 1 (TGF-β1), leads to excessive collagen production. Differential production of transforming growth factor beta (TGF-β)isoforms, with overexpression of transforming growth factor beta 1 (TGF-β1) and transforming growth factor beta 2 (TGF-β2) and decreased expression of transforming growth factor beta 3 (TGF-β3), results in increased fibroblast activity and ECM collagen formation. Keloid fibroblasts exhibit increased sensitivity to TGF-β1 due to receptor upregulation, leading to reduced collagen degradation mediated by matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs). Other inflammatory proteins such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) may also contribute to collagen overproduction, possibly through mechano-transduction pathways activated by mechanical stress. Understanding the cellular processes underlying keloid formation remains an active area of research, although various therapies are available to mitigate keloid formation, progression, recurrence, and symptoms.[5]

ENVIRONMENTAL AND EXTERNAL FACTORS

Hypertrophic Scars

The skin responds to mechanical pressures at tissue and cellular levels, along with external tensile strain in form of tension, profoundly influences wound healing and scarring outcomes. Tension, considered beneficial, exhibits anisotropic characteristics due to the nonlinear viscoelastic properties of the skin. Various factors contribute to tension, including underlying skeletal structures like the sternum and external elements like jewelry. Managing these forces is crucial for maintaining the skin's biomechanical and mechanobiological balance throughout the body.[40]

Early observations in anatomy and surgery underscore the significance of mechanical tension in wound healing. Langer lines, reflecting natural tension bands in human skin, influence scarring outcomes. Wounds located in areas subjected to greater mechanical force tend to exhibit increased scar formation. Conversely, techniques reducing mechanical tension, such as tension shielding, can mitigate scarring. Fibroblasts subjected to stretching exhibit enhanced migration and orientation perpendicular to the applied force, mediated by integrin and mechano-transduction pathways. Additionally, mechanical stretching activates protein kinase B (Akt) in keratinocytes, highlighting cellular responsiveness to mechanical stimuli.[41]

In hypertrophic scar development, mechanical tension transmitted from the extracellular matrix activates Piezo1, a mechanically activated cation channel expressed in dermal fibroblasts. This activation leads to increased proliferation, migration, and differentiation of dermal fibroblasts, contributing to hypertrophic scar formation. Piezo proteins, including Piezo1 and Piezo2, regulate various physiological functions, with Piezo2 implicated in neurosensory functions like proprioception and touch sensation.[42]

The wound healing process is influenced by various physiological factors, including proper nutrition, tissue oxygenation, immune response, and absence of pathogens. Acute wound infections, initiated by local microorganisms, may lead to colonization, localized infection, and systemic complications. Staphylococcus aureus commonly causes wound infections, although the reasons for its prevalence remain unclear. Normal wound healing involves hemostasis, inflammation, proliferation, and maturation; however, infected wounds disrupt these processes, leading to suboptimal healing and potential chronicity. Bacterial toxins can trigger vascular injury, affecting hemostasis, and anaerobic bacteria activity impedes endothelial tubule formation. Platelets play a role in antimicrobial defense but may contribute to local thrombosis, creating a hypoxic environment favoring bacterial proliferation.[43]

Pro-inflammatory mediators identified in fetal wound healing, such as interleukins-6 and -33 (IL-6, IL-33), prostaglandin E2 (PGE2), and high mobility group box 1 (HMGB-1) protein, also promote scar formation in adults. Inhibition of PGE2 production reduces scar formation in adult wounds. Interleukin 17 (IL-17), monocyte chemoattractant protein-1, and osteopontin (OPN) are associated with scar formation and inflammation. Osteopontin knockdown in a mouse model resulted in reduced inflammation and scar formation compared to control wounds.[44]

Scar formation progresses through phases that include extracellular matrix reorganization, reduced inflammation, decreased vascularity, and fibroblast to myofibroblast transition, facilitating contraction. Matrix maturation involves a balance between degradation and replacement of ECM components, with early remodeling involving breakdown of collagen III, fibronectin, and hyaluronic acid by matrix metalloproteinases (MMPs), regulated by tissue inhibitors (TIMPs). Myofibroblasts produce collagen I to replace collagen III, enhancing wound strength, yet scars remain acellular and avascular, with less organized collagen, prone to dehiscence. Wound contraction, influenced by epithelialization delay, contraction intensity, and wound size, leads to less therapy-responsive mature scars, challenging clinical management and increasing surgical revision risks,

especially in young scars at risk of hypertrophic scarring and keloids.[23, 27]

Keloids

Environmental factors are crucial prerequisites for keloid scar formation, as they often precede the onset of keloid scar formation. These factors encompass a spectrum of insults to the skin, ranging from minor to major trauma, as well as processes leading to skin inflammation. Examples of minor insults include insect bites or vaccinations, while major trauma typically arises from surgical or non-surgical wounds such as lacerations, abrasions, piercings, tattooing, or blunt trauma. Inflammatory skin conditions like acne, (peri)folliculitis, chickenpox, herpes zoster, and hidradenitis suppurativa may also contribute to keloid development. Isotretinoin, commonly used to treat acne, has been proposed as a potential predisposing factor, although conclusive evidence is lacking. Although burns are often cited as potential keloid-inducing events, they typically result in widespread hypertrophic scars rather than keloids. Fortunately, venipuncture has not been implicated in keloid scarring. Regardless of the nature of the injury, keloid scar formation tends to exhibit a disproportionate response compared to the original inciting injury.[37]

CLINICAL MANAGEMENT STRATEGIES

Hypertrophic Scars

The development of effective treatments for hypertrophic scars requires efficient carrier systems like ethosome and transethosomes, known for their superior spreading ability and capacity to concentrate drugs at scar sites. Ethosomal systems are particularly effective due to their deformability and penetration capabilities, delivering drugs 5–10 times smaller than their own size into the skin. This efficiency is attributed to two main factors: the inclusion of ethanol, which enhances skin penetration by increasing lipid fluidity and reducing epidermal density, and their flexible nature, allowing deep skin penetration. A study using a rabbit ear model to test a 5-fluorouracyl (5-FU) ethosomal gel on hypertrophic scars showed significant reductions in scar thickness when combined with CO_2 fractional laser treatment, highlighting its potential efficacy.[13]

Conversely, the use of onion extract gel has shown improvements in scar softness, redness, texture, and appearance in a randomized controlled trial following superficial skin lesion removal. Despite its effectiveness on superficial scars, its benefits appear limited for deeper scar tissues. An open-label study reported that twice-daily application of a gel containing onion extract for 24 weeks led to significant improvements in scar appearance, including reduced redness and new blood vessel formation. Additionally, combining onion extract with a topical triamcinolone acetonide was found to be more effective than triamcinolone alone in reducing pain, itching, and scar thickness. However, some studies argue that onion extract's benefits do not surpass those of petrolatum emollients, and the evidence quality supporting its use remains limited.[45]

Intralesional corticosteroids, often combined with 5-fluorouracil (5-FU) and lidocaine, represent the cornerstone of pathological scar treatment, delivering targeted therapy with proven effectiveness in scar improvement and symptom relief, as evidenced by numerous randomized controlled trials and meta-analyses. An international expert panel in 2014 endorsed monthly corticosteroid injections as the primary keloid treatment due to their 50–100% efficacy and manageable recurrence rates of 9–50%. These injections not only reduce scar volume and enhance elasticity, as demonstrated in studies with hypertrophic scars and keloids, but also show promise in combination treatments. For example, a study highlighted a remarkable 96.92% effectiveness and a low recurrence rate in treating auricular keloids with surgery and corticosteroid injections, while another approach combining surgery, intraoperative triamcinolone acetonide injections, and postoperative radiotherapy reported a recurrence rate of just 6.7% over an average follow-up of 24.1 months, underscoring the potential of multimodal strategies.[46]

Fractional ablative CO_2 (10,600 nm) and Er:YAG (2940 nm) lasers have been shown to significantly improve erythema, height, and pliability of hypertrophic scars and keloids, outperforming the pulsed dye laser (PDL) at 585 nm. The 1470 nm fiber laser emerges as a promising, safe, and effective treatment, enhancing the minimally invasive options for scar management. Surgical excision, often a last resort for refractory cases, has high recurrence rates for keloids (50%-80%), but combining surgery with corticosteroids can reduce recurrence to below 50%. Studies demonstrate that adjunct use of both intralesional and topical corticosteroids post-excision significantly lowers recurrence rates to 14.3% for keloids and 16.7% for hypertrophic scars. Additionally, postoperative radiation therapy further reduces recurrence to under 10%, especially when 30 Gray is administered within 48 hours of surgery. However, radiation's effectiveness varies, with monotherapy showing a 37% recurrence rate, which decreases to 22% when combined with surgical excision. The choice of radiation technique also affects outcomes, with x-ray showing the highest recurrence (35%), followed by brachytherapy (21%) and electron beam therapy (17%). Radiotherapy is generally considered for scars unresponsive to other treatments, highlighting the need for a tailored approach given the variable efficacy across different modalities.[34,45,47]

Keloids

Intralesional steroids, particularly triamcinolone, are a cornerstone in keloid treatment, with doses varying based on the keloid's location. Typically, triamcinolone is injected at a concentration of either 2.5 milligrams to 20 milligrams for facial keloids or 20 milligrams to 40 milligrams for non-facial keloids. They mitigate keloid formation by suppressing

inflammation and fibroblast activity and promoting collagen breakdown. Mechanisms by which triamcinolone alters fibroblast growth include inducing fibroblast hypoactivity by decreasing transforming growth factor beta (TGF-β) expression and reducing fibroblast density by increasing fibroblast apoptosis. Side effects may include injection pain, skin atrophy, pigment changes, and telangiectasias.[5]

Silicone gel sheeting (SGS) is widely used for keloid prevention,[48,49] creating a moisture-rich environment that curbs fibroblast activation and collagen production, although it requires diligent application and can raise infection risks in humid climates.[5] It can be used on healing skin to help soften and flatten a keloid scar,[49] and is more effective as preventive method rather than treatment. However, it needs restrict application for at least 12 hours a day for 12 months.[48]

Cryotherapy, more effective when combined with intraleional steroids, employs freeze-thaw cycles to necrotize keloid tissue, with potential side effects like hypopigmentation and pain. Clinicians apply 1, 2, or 3 freeze thaw cycles, each lasting 10-30 seconds to obtain satisfying results. Sessions may be needed every 3 weeks to a month interval. Studies reported success rates are 30- 75% either by spray or contact with liquid nitrogen. Novel methods of cryotherapy can even improve outcomes with fewer sessions.[48] Its main side effects are permanent hypopigmentation and pain.[48]

Radiotherapy, used post-surgery, aims to prevent keloid recurrence by inhibiting angiogenesis and fibroblast activity, albeit with a slight risk of carcinogenesis and a reported recurrence rate of 9.59%.[50] The radiation dose used is 40 Gray which is divided into several therapy sessions to minimize unwanted side effects of carcinogenesis. In one study, keloid recurrence with radiotherapy was reported to be 9.59%.[50]

FUTURE DIRECTIONS AND EMERGING THERAPIES

Genetic investigations into hypertrophic scars have revealed significant variances in gene expression, particularly within fibroblasts, compared to healthy skin, indicating a unique fibrotic profile. Dysregulated genes and genetic alterations have been linked to abnormal wound healing and scar development, emphasizing the importance of understanding the genetic and epigenetic contexts in hypertrophic scar genesis.[30,51] Therapeutic interventions targeting distinct molecular pathways, including transforming growth factor beta (TGF-β)signaling, fibroblast activity, collagen regulation, and inflammatory responses, hold promise for addressing hypertrophic scars.[51,52] Recent scientific inquiry underscores the necessity of tailored methodologies in scar management, with the precision scar medicine paradigm offering a potential avenue for more personalized and efficacious treatment strategies.[54,55]

Emerging therapy modalities for keloids include interferons, bleomycin, verapamil, Imiquimod, tamoxifen, type-A botulinum toxin, and captopril. Interferon, administered via intralesional injection, exhibits anti-proliferative and anti-fibrotic effects, reducing collagen synthesis and fibroblast proliferation.[50,56] Bleomycin, a cytotoxic agent, can reduce collagen synthesis and induce apoptosis, often resulting in significant keloid reduction with minimal systemic side effects.[50] Verapamil, a calcium channel blocker, decreases collagen production and fibrotic tissue production, showing promise as an intralesional therapy for keloids without significant systemic side effects.[50,56] Imiquimod, tamoxifen, botulinum toxin type A, and captopril also offer potential therapeutic benefits for keloids, targeting various pathways involved in keloid formation and progression.[50,56,57] These emerging therapies represent promising avenues for improving the management of keloids and enhancing patient outcomes.

CONCLUSION

Recent research has elucidated various molecular pathways involved in hypertrophic scar formation, including transforming growth factor beta (TGF-β) signaling, fibroblast function, inflammation, and collagen modulation. Personalized approaches to scar management, tailored to individual patient characteristics and biomarkers, have been emphasized, offering potential for more effective treatment strategies. Implementing precision scar medicine, which involves subclassifying patients based on biomarkers, holds promise for improving clinical outcomes in scar management.

Future research in hypertrophic scar management should focus on further elucidating the molecular mechanisms involved in scar formation and investigating novel therapeutic targets within key pathways, such as tsignaling and fibroblast function. Additionally, studying the efficacy and feasibility of implementing precision scar medicine in clinical practice will be essential for advancing personalized approaches to scar management.

Keloids remain a condition causing significant morbidity, especially in patients of skin of color. Recent research has identified associations with other medical conditions and emphasized the inflammatory component to the disease. Future studies aim to identify more causal genes linked to keloids and explore therapeutic options targeting the upregulated inflammatory and fibroproliferative genes. As understanding of keloids deepens, it is hoped that future treatments will be able to prevent or reverse what has been thought to be an irreversible scarring process.

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