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REVIEW

Keloids as a Spectrum of Auto-Inflammatory Fibrotic Disorders: Beyond the Conventional Wound-Healing Paradigm

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Abstract: Keloids have traditionally been classified as fibroproliferative disorders; however, emerging evidence establishes chronic inflammation and immune dysregulation as the central pathogenic nexus, orchestrating a self-sustaining cycle of pathological healing. This review proposes a paradigm shift toward understanding keloids as a spectrum of auto-inflammatory fibrotic disorders. We synthesize recent advances to demonstrate how genetic predisposition and epigenetic modifications prime a hyperinflammatory response, which is then amplified by endocrine factors and executed through aberrant signaling pathways. Crucially, this inflammatory milieu drives the metabolic reprogramming of fibroblasts toward a Warburg-like phenotype, providing the bioenergetic and biosynthetic substrate for relentless proliferation and extracellular matrix (ECM) deposition. Infiltration and skewed polarization of immune cells further fuel this fibro-inflammatory cascade. Our integrative framework, positioning dysregulated immunity as the disease core, explains keloid persistence, recurrence, and heterogeneity, thereby providing a rationale for combination-based, mechanism-driven therapies. Ultimately, this perspective illuminates novel therapeutic strategies that target the inflammatory core (eg, biologic agents against Th2 cytokines and mast cell products) and its downstream consequences (eg, metabolic inhibitors), offering hope for more effective, mechanism-based interventions against this recalcitrant condition.

Keywords: keloids, scar, inflammation, fibroblasts, genetic

Introduction

Keloids represent a unique form of pathological wound healing, characterized by uncontrolled fibroblast proliferation and excessive extracellular matrix (ECM) deposition that arise beyond the boundaries of the original wound edges.[1] In addition to causing visible scarring, these lesions frequently provoke symptoms such as persistent pruritus and tenderness. This contributes to a significant psychological burden, which is exacerbated when they occur on exposed body parts, such as the face.[2–4] Epidemiological studies have demonstrated significant racial disparities in the prevalence of excessive scarring, with rates of 2.4% in Black, 1.1% in Asian, and 0.4% in White populations.[5] The majority of people afflicted with keloids are between the ages of 10 and 30 years.[6] Multiple pathogenic contributors have been identified, including genetics, hormone levels,[7] local skin tension,[8] trauma, folliculitis, and lifestyle.[9] Despite the widespread impact of keloids, current therapeutic options remain limited and sometimes unsatisfactory. Treatments such as surgical excision, corticosteroid injections, cryotherapy, laser therapy, and radiation are commonly employed. However, recurrence rates remain high, particularly when used alone. This clinical challenge underscores the urgent need for a deeper mechanistic understanding to guide the development of more effective and individualized treatment strategies.

Current evidence suggests that keloid pathogenesis involves a complex interplay of immune dysregulation and chronic inflammation (Figure 1). Key signaling pathways such as transforming growth factor (TGF)-β and integrin signaling have been implicated in the promotion of fibroblast activation and ECM deposition. However, their hierarchical relationships and spatiotemporal regulation remain poorly understood. Moreover, accumulating

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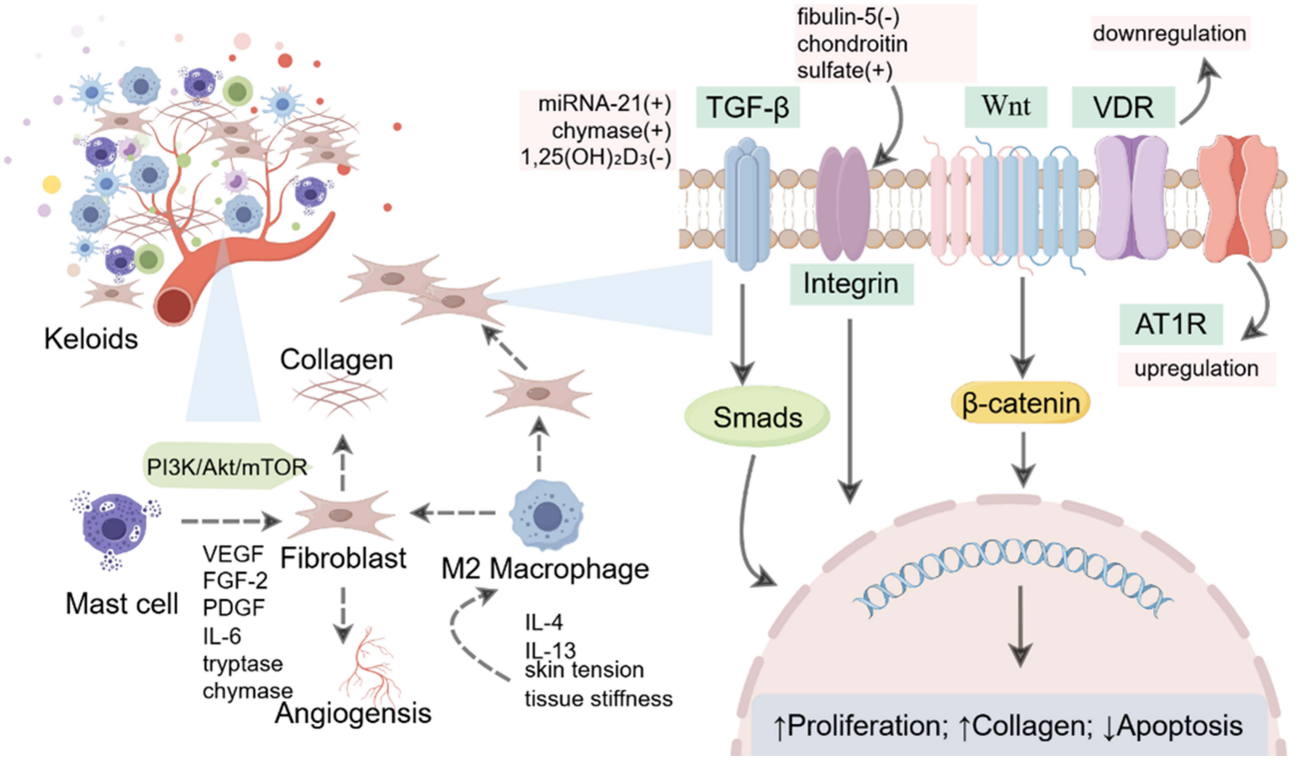

Figure 1 The immune microenvironment in keloids. This schematic illustrates the complex cellular and molecular interactions within the keloid immune microenvironment that drive pathological fibrosis. Key cellular players include mast cells, M2 macrophages, and fibroblasts. Their activation and crosstalk are mediated by a network of signaling pathways (eg, PI3K/Akt/mTOR, Wnt/β-catenin) and soluble factors (eg, IL-4, IL-13, TGF-β, VEGF, FGF-2, PDGF). The microenvironment is further modulated by endocrine factors (eg, VDR, AT1R), extracellular matrix (ECM) components (eg, fibulin-5, chondroitin sulfate), and biophysical cues (skin tension, tissue stiffness). ↑ indicates upregulation/activation; ↓ indicates downregulation/suppression. Graphics created with figdraw.com.

evidence points to important contributions from genetic predisposition, epigenetic modifications, endocrine factors, and metabolic reprogramming (Figure 2), which together sustain keloid progression. Traditional fibroproliferative models typically summarize individual mechanisms in isolation, which limits their explanatory power regarding keloid recurrence, heterogeneity, and metabolic reprogramming. In contrast, our integrative paradigm positions chronic inflammation as the central orchestrating hub, modulated by genetic predisposition, epigenetic memory, and systemic endocrine factors. This framework unifies disparate findings into a cohesive pathogenic model and highlights actionable therapeutic targets. By weaving together these strands of evidence, we aim to provide a novel perspective that not only clarifies disease persistence but also illuminates actionable targets for future therapy.

To ensure a comprehensive and contemporary synthesis of evidence supporting the proposed paradigm shift, a systematic literature search was conducted. Searches were performed in the PubMed and Web of Science databases covering the period from January 2010 to April 2025. The search strategy was designed to capture studies relevant to both the classical understanding and the emerging immune-inflammatory axis of keloid pathogenesis. Core search terms included: ("keloid" OR "keloids") combined with thematic groups of keywords such as ("inflammation" OR "immune" OR "cytokine"), ("mast cell" OR "macrophage" OR "T cell"), ("TGF-beta" OR "IL-4" OR "IL-13" OR "IL-6"), ("fibrosis" OR "extracellular matrix"), and ("metabolism" OR "Warburg" OR "epigenetic"). Boolean operators (AND, OR) were used to refine the search. The reference lists of identified articles were also screened for additional relevant publications. Inclusion criteria prioritized original research articles, systematic reviews, and meta-analyses published in English that provided mechanistic or clinical insights into keloid pathogenesis, with a focus on immune dysregulation and chronic inflammation. This approach ensured the inclusion of foundational studies and the most recent advances to construct the integrative framework presented in this review.

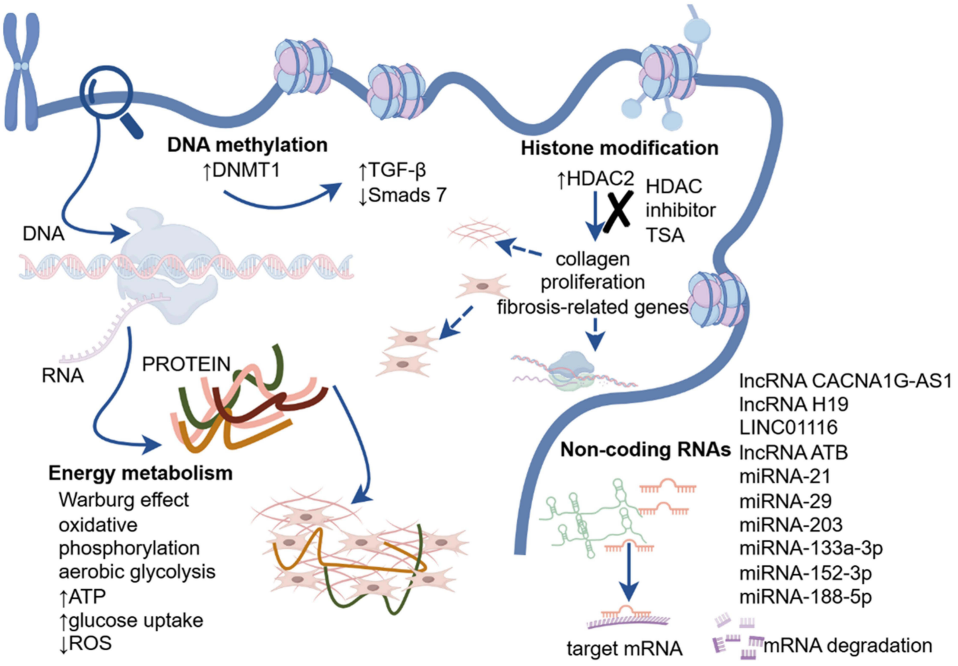

Figure 2 Key epigenetic and metabolic alterations in keloids. In This schematic integrates core regulatory layers driving fibrosis: 1) DNA methylation (DNMT1↑) silences anti-fibrotic genes; 2) Histone modification (HDAC2↑) promotes a repressive state reversible by inhibitors (eg, TSA); 3) Non-coding RNA networks (dysregulated lncRNAs and miRNAs, eg, miR-21↑, miR-29↓) post-transcriptionally regulate fibrosis; 4) Metabolic reprogramming (↑ glycolysis, ↑ glucose uptake) supporting bioenergetic demands. ↑ indicates upregulation/activation; ↓ indicates downregulation/suppression. Graphics created with figdraw.com.

Genetic Predisposition: Encoding a Hyperinflammatory Phenotype

Evidence from familial cases provides strong early indications of a genetic contribution to keloid formation. Marneros et al studied 14 pedigrees with familial keloids encompassing African American, White, Japanese, and African Caribbean populations.[10] Their findings revealed an autosomal dominant inheritance pattern with incomplete penetrance. The phenotypic expression of keloids exhibited considerable heterogeneity within the same family: some individuals presented with mild earlobe keloids, while others developed extensive and severe lesions across large body areas. Distinct anatomical predilections were observed between families. For example, one family exhibited a predominance of keloids on the extremities, while two others showed higher incidences in the axillary and groin regions. In a multicenter case-control study involving five healthcare institutions, researchers reported that individuals with a positive family history were 4.2 times more likely to develop keloids. Additionally, 43% of patients had at least one first-degree relative affected by the condition, further supporting a strong genetic contribution to keloid pathogenesis.[11] Altogether, the evidence positions keloids as a genetically predisposed fibroproliferative disorder, highlighting the need for further molecular investigations.

Guided by this clinical heredity, successive genomic and transcriptomic studies have begun to map specific susceptibility loci and functional genes. Early expression profiling across multiple ethnic groups revealed 219 genes uniquely regulated in keloids.[12] Through case-control analysis, *HLA-DRB1*15* and *HLA-DRB5* were found to be associated with keloid formation in Caucasians.[13] In a multistage genome-wide association study (GWAS) involving 4029 Japanese individuals, researchers identified four single nucleotide polymorphisms (SNPs) associated with keloid development: rs873549, rs151141, rs940187, and rs8032158. Among these, rs873549 showed the strongest statistical association with keloid formation.[14] SNPs in two myosin genes, *MYO1E* (rs747722 and rs28394564) and *MYO7A* (rs35641839), were found to be strongly correlated with keloids in African American patients.[15] *ASAH1* plays a role in tumorigenesis, cell proliferation, and inflammation. A variant in this gene was identified in a large Nigerian Yoruba family, and this alteration contributed to keloid predisposition.[16] Additionally, a positive association was identified between *HLA-DQA1* and *DQB1* alleles and genetic susceptibility to keloids in the

Chinese Han population.[17] Using an improved multiple ligase detection reaction method, Liu et al conducted a case-control study involving 651 participants, including 352 patients with keloids. Their findings revealed that polymorphisms in the *LEPR* gene were correlated with both the development and severity of keloids, particularly among individuals with a positive family history.[18] In 2015, several novel susceptibility loci, including rs181924090 (*SIRT3*, 11p15.5), rs151091483 (*MYH8*, 17p13.1), and rs183178644 (*HUS1B*, 6p25.3), were found to be strongly linked to keloid development and were particularly implicated in its tumor-like pathological characteristics. However, at rs141156594, there was no significant association with keloids, and it was involved in ECM remodeling during wound healing.[19]

A 2017 mechanistic study clarified the role of *TGFβ-inducible early gene-1*(*TIEG1*) in keloid pathogenesis and reported three key findings. First, *TIEG1* was markedly upregulated in human keloid tissue. Second, its expression was inversely correlated with Smad7 promoter activity. Finally, *TIEG1* promoted Smad2 phosphorylation by downregulating Smad7 upon TGF-β1 stimulation. Using luciferase reporter assays and chromatin immunoprecipitation, the researchers further confirmed that *TIEG1* directly targeted a GC-box/Sp1 site within the Smad7 promoter region (nucleotides −1392 to −1382), leading to the transcriptional repression of Smad7.[20] *Neural precursor cell-expressed developmentally down-regulated 4* (*NEDD4*), an E3 ubiquitin ligase, has been extensively studied for its role in keloid pathogenesis. The SNP rs8032158 in *NEDD4* was significantly associated with both keloid susceptibility and disease severity in Egyptian and Japanese populations.[14,21,22] The risk allele C of rs8032158, identified through GWAS, activated the NF-κB signaling pathway by selectively upregulating the transcriptional variant TV3. This variant interacted with the junctional protein RIP, thereby promoting chronic inflammation in keloid tissue.[23] *Neural precursor cell-expressed developmentally downregulated 4-like* (*NEDD4L*) suppressed the viability, proliferation, and migration of keloid fibroblasts (KF) by modulating Yin Yang 1 ubiquitination and glycolysis via hexokinase 2. Its expression was significantly reduced in keloid tissue compared with normal skin, whereas its downstream targets, Yin Yang 1 and hexokinase 2, were markedly upregulated. Notably, Yin Yang 1, a transcription factor, not only enhanced glucose consumption and lactate production in KFs by transcriptionally activating hexokinase 2, but also counteracted the inhibitory effects of *NEDD4L* on fibroblast growth and motility.[24] Collectively, these genetic findings extend beyond mere susceptibility loci; they encode a hyperinflammatory phenotype. Genes such as *NEDD4* and *TIEG1* directly interface with core inflammatory pathways (eg, NF-κB, TGF-β), suggesting that genetic risk is largely mediated through dysregulated immune signaling rather than autonomous fibroblast dysfunction.

The population-specific nature of genetic associations in keloids underscores the complexity of its pathogenesis but does not undermine the generalizability of key pathways. Although risk alleles in genes such as *HLA, IL-6* and *NEDD4* vary across ethnic groups, their biological functions—antigen presentation, pro-inflammatory signaling, etc.—consistently converge on immune dysregulation, indicating that genetic risk is channeled through common inflammatory mechanisms, albeit via different nodal points in the network.

Confounders such as skin phototype and local environmental factors likely interact synergistically with genetic predisposition. For example, darker skin—associated with reduced vitamin D synthesis—may couple a genetically primed hyper-inflammatory state with a vitamin-D-deficient microenvironment that impairs inflammation resolution, partly explaining racial disparities in prevalence.

Thus, the absence of a universal "keloid gene" reinforces the concept of a spectrum disorder driven by a final common pathway of immune-fibrotic dysregulation. Future genetic studies should prioritize multi-ancestral cohorts and functional validation of risk variants, shifting the focus from population-specific associations to conserved core mechanisms (eg, sustained NF-κB activation, TGF-β sensitization) that represent definitive therapeutic targets.

Epigenetic Modifications: The Molecular Memory of Inflammation

Epigenetic modifications act as a molecular memory of inflammation, stabilizing the pro-fibrotic gene expression program initiated by the inflammatory microenvironment. This persistent reprogramming of KFs is mediated mainly by three principal mechanisms: DNA methylation, histone modifications, and non-coding RNAs.

DNA Methylation

Multiple studies have reported significant differences in DNA methylation levels between KFs and normal skin-derived fibroblasts (NFs).[25–27] DNA methyltransferase 1 (DNMT1) was markedly overexpressed in keloid tissue and played a pivotal role in maintaining DNA methylation patterns. Functional experiments using the DNMT inhibitor decitabine demonstrated that DNMT1 inhibition led to a reduction in TGF-β mRNA expression, accompanied by an upregulation of Smad7, which functioned as a negative regulator of the TGF-β pathway. The increased Smad7 expression contributed to the attenuation of TGF-β pathway overactivation.[28] Thus, DNA methylation serves as a stable epigenetic marker that perpetuates the pro-fibrotic signals originally triggered by inflammation.

Histone Modifications

Histone modifications, including methylation, acetylation, and phosphorylation, regulate the chromatin structure and gene transcription. Histone deacetylase 2 (HDAC2) was found to be overexpressed in hypertrophic scars and keloids. Edmund et al proposed that the persistent elevation of HDAC2 during wound healing might contribute to keloid formation by disrupting normal epigenetic resolution.[29] The HDAC inhibitor Trichostatin A (TSA) abolished TGF-β1-induced collagen synthesis and induced apoptosis of proliferating KFs.[30] Additionally, TSA downregulated multiple fibrosis-related genes, including secreted frizzled-related protein 1, insulin-like growth factor-binding protein 5, collagen type I alpha 1 chain gene (*COL1A1*), and connective tissue growth factor.[31] CUDC-907 exerted dual inhibitory effects by targeting both HDAC2 and the PI3K/Akt/mTOR pathway, thereby reversing the pathological phenotype of KFs both in vitro and in vivo.[32] The efficacy of HDAC inhibitors further underscores the functional significance of histone modifications as a reversible "memory" of past inflammatory events.

Non-Coding RNAs

Dysregulated lncRNA expression has been closely linked to aberrant fibroblast behavior and ECM remodeling in keloid tissue.[33–35] In 2015, Liang et al first reported that lncRNA CACNA1G-AS1, which was significantly upregulated in keloids, promoted fibroblast proliferation and inhibited apoptosis by negatively regulating miRNA-205.[35] A pathway-focused lncRNA microarray analysis further identified four Wnt-associated lncRNAs (CACNA1G-AS1, LINC00312, HOXA11-AS, and RP11-91I11.1) as potential biomarkers of keloid pathogenesis.[36] Moreover, recent transcriptomic analyses have revealed 11 lncRNAs related to epithelial-mesenchymal transition that were differentially expressed in keloid tissue compared with normal skin.[33] lncRNA H19 was shown to enhance fibroblast proliferation and metabolic activity by modulating miRNA-29a and COL1A1 expression.[37] LINC01116 facilitated keloid formation by regulating the miR-203/Smad5 axis,[38] while lncRNA ATB was found to modulate TGF-β2 secretion via miRNA-200c–mediated suppression of *ZNF217*.[39] Similar to lncRNAs, multiple studies have reported differential expression patterns of miRNAs in keloid tissue compared with normal skin, with some miRNAs being significantly upregulated and others downregulated.[40,41] Inhibition of miRNA-21-5p served to increase the expression of the pro-apoptotic genes *PTEN* and *PDCD4*, thereby reducing the number of fibroblasts.[42] miRNA-21 has been extensively studied in keloids. It promoted fibroblast proliferation by suppressing Smad7.[43] Additionally, another study showed that KFs expressed elevated levels of miRNA-21, which resulted in reduced expression of FasL protein, subsequent inactivation of caspase-8, and mitochondrial-mediated apoptotic signaling pathways.[44] miRNA-29 is known to negatively regulate fibrosis, and its downregulation has been observed in various fibrotic diseases. In 2019, remlarsen, an analogue of miRNA-29, was reported to inhibit collagen and fiber expression in skin wounds and could serve as a potential preventive therapy for keloids.[45] A microarray analysis revealed nine downregulated miRNAs in keloid tissue, with miRNA-203 showing the most pronounced decrease.[41] Similarly, miRNA-133a-3p expression was also downregulated in keloids.[46] In contrast, miRNA-152-3p expression was upregulated in keloid tissue. Its direct target, FOXF1, promoted cell proliferation, invasion, and ECM production.[47] Conversely, miRNA-188-5p was downregulated in keloids and could exert its effects by modulating fibroblast proliferation and invasion via the PI3K/Akt/MMP-2/9 signaling pathway.[48] Thus, epigenetic regulation locks in the inflammatory state, creating a vicious cycle in which inflammation begets more inflammation, ultimately leading to a fixed keloid pathological phenotype.

Endocrine Modulation: Setting the Systemic Threshold for Inflammation

Endocrine factors systemically modulate the immune landscape, influencing the threshold at which physiological wound healing transitions into pathological inflammation and fibrosis. This section synthesizes predominantly observational and associative data, with mechanistic insights often derived from in vitro models. Direct interventional evidence in humans establishing causality for these endocrine factors in keloid pathogenesis remains an important area for future research.

Vitamin D

Vitamin D is synthesized in the skin from 7-dehydrocholesterol upon exposure to UVB light and is subsequently converted to its active form, 1,25-dihydroxyvitamin ($1,25(OH)_2D_3$). Cutaneous synthesis is the primary source of vitamin D in humans. Observational studies have shown a negative correlation between serum 25-hydroxyvitamin D level and keloid severity.[49] Due to the higher melanin content in darker skin, which impedes UVB penetration, individuals with darkly pigmented skin exhibit reduced vitamin D synthesis.[50] In the control group, researchers observed significantly reduced nuclear localization of the vitamin D receptor (VDR) in Black participants compared with White participants,[51] which partially explained the higher prevalence of keloids in individuals with darker skin tones.[5] Moreover, VDR protein levels were diminished in most keloid samples, and the percentage of epidermal cells exhibiting nuclear VDR localization was significantly lower in keloid tissue than that in normal skin. In a study involving a Chinese population, researchers revealed significantly reduced VDR expression in the peripheral blood lymphocytes of keloid patients compared with controls.[52]

In vitro studies suggest vitamin D may exert anti-fibrotic effects. KFs expressed functional VDRs, as evidenced by increased vitamin D response element promoter activity following stimulation with $1,25\text{-}(OH)_2D_3$. Notably, $1,25(OH)_2D_3$ suppressed TGF-β1-induced fibrotic responses in KFs, significantly reducing COL1A1 protein synthesis, fibronectin expression, and α-smooth muscle actin levels. It also regulated ECM remodeling by downregulating plasminogen activator inhibitor-1 and upregulating matrix metalloproteinase-9 (MMP).[53]

The Renin-Angiotensin System

All components of the renin-angiotensin system (RAS) are expressed in human skin.[54] Experimental data indicate that Angiotensin II type 1 receptor (AT1R) activation promoted cell proliferation and migration, enhanced collagen synthesis, and stimulated angiogenic effects that were partially mediated by the upregulation of fibrogenic and angiogenic factors, including TGF-β.[55] Furthermore, keloid-associated lymphoid tissue has been described to harbor a population of embryonic stem cell-like cells expressing key components of the RAS,[56] and the endothelium of microvessels within this tissue expressed core embryonic stem cell markers, including OCT4, SOX2, pSTAT3, and NANOG.[57]

Clinical and epidemiological observations point to a potential association between hypertension (where RAS is a key mediator) and keloid formation. For instance, a cross-sectional study of 304 patients with keloids found that individuals with severe hypertension were more likely to present with multiple or large keloid lesions.[58] Another study reported that patients with extensive keloid involvement (≥3 lesions or a large lesion area) had higher blood pressure levels than those with less severe keloid presentation.[59] It is important to note that these studies demonstrate an association but do not establish causality; the overall prevalence of hypertension in keloid patients has been similar to that in the general population. Nevertheless, the shared molecular finding of increased local RAS component expression in keloid tissue supports the hypothesis of a common dysregulated pathway beyond mere mechanical effects of elevated blood pressure.

Preliminary interventional data provide intriguing support for this link. In controlled clinical trials, topical application of 5% losartan potassium ointment significantly reduced Vancouver Scar Scale scores, indicating clinical improvement.[60] Similarly, topical captopril application led to reduction in scar thickness and pigmentation in patients with post-burn keloids.[61] While promising, these early findings require validation in larger, randomized controlled trials.

Sex Hormones

Sex hormones are considered among the systemic factors that influence keloid pathogenesis. Epidemiological data highlight sex-related differences. In 2019, a cross-sectional study was conducted in Japan involving 1659 patients with

keloids, all of Asian descent.[62] This study revealed several sex-related differences in the keloid epidemiology. First, the female sex appeared to be a significant risk factor for keloid development. Female predominance was observed across nearly all age groups at disease onset, with the number of female patients approximately double that of male patients. The female-to-male ratio was as high as 2.7:1 in patients aged <15 years. Second, sex did not influence the age of keloid onset or the age at first clinical presentation. The overrepresentation of female patients in clinical settings was not attributable to greater cosmetic concerns, as was previously assumed. Additionally, this study noted that puberty represented a peak period of keloid onset in both sexes, suggesting that hormonal fluctuations during adolescence might contribute to disease development. Pregnancy is also recognized as a high-risk period for keloid formation.[63]

At the molecular level, the expression of testosterone-binding receptor protein was found to progressively increase in both inactive and active regions of keloid tissue, with the highest expression observed in active areas, reaching levels up to fourfold higher than that in adjacent normal skin.[64] Anecdotal interventional evidence exists. For instance, intralesional injection of tamoxifen, a selective estrogen receptor modulator, resulted in a reduction in fibroblast density and collagen deposition, along with increased inflammatory cell infiltration, as observed under microscopy when compared to pre-treatment samples.[65] These observations are intriguing but remain preliminary; the precise mechanistic roles and causal contributions of sex hormones to keloid pathogenesis are not yet firmly established and warrant further investigation.

Collectively, while definitive causal proof is often lacking, the accumulated evidence positions the endocrine system as a critical modulator that likely lowers the systemic threshold for sustaining the chronic inflammatory drive characteristic of keloids.

Immune Dysregulation: A Functional Bridge from Inflammation to Fibrosis in Keloids

Cytokine-Mediated Inflammation

Among the pro-inflammatory cytokines, IL-6 has been extensively implicated in keloid pathogenesis. In 1992, McCauley et al first documented significantly elevated IL-6 production in peripheral blood mononuclear cells from Black keloid patients compared with race-matched healthy controls, with unaltered IL-1 and IL-2 levels.[66] This finding was further supported by a global gene expression analysis, which revealed that IL-6 expression was upregulated in KFs compared with NFs.[67] Furthermore, both the mRNA and protein levels of gp130 (the shared signal-transducing subunit of IL-6 receptor complexes) and its downstream effectors were significantly elevated in KFs compared with those in NFs.[68] Researchers have also investigated potential differences in IL-6 SNP between patients with keloids and healthy controls. In a Japanese cohort, researchers found a significantly higher frequency of the IL-6 promoter polymorphism rs1800796 (−572G/C) in the keloid group than in controls. In contrast, the promoter variants rs1800797 (−597G/A) and rs1800795 (−174G/C) were not detected in this population, with all individuals exhibiting the G/G genotype at both loci. Moreover, IL6R displayed comparable genotype and allele distributions between the groups.[69] Subsequent analysis in a Polish cohort failed to establish any correlation between keloid development and IL-6 polymorphisms (rs1800797, rs1800796, rs1800795) or the IL6R variant rs2228145.[70] These population-based differences suggest that IL-6 genetic contributions may vary by ethnicity.

In addition to IL-6, Th2 cytokines IL-4 and IL-13 were also implicated in keloid pathogenesis. Elevated expression levels of IL-4 and IL-13 were observed in keloid tissue and fibroblasts.[71] These cytokines primarily originated from infiltrating Th2 cells, mast cells, and M2 macrophages. Functionally, IL-4 and IL-13 induced the expression and secretion of periostin, an ECM protein that was essential for skin development and homeostasis. Secreted periostin, in turn, stimulated the RhoA/ROCK signaling pathway to promote the secretion of TGF-β1, which further enhanced periostin production, forming a positive feedback loop that drove pathological ECM accumulation and keloid formation.[72] Moreover, IL-4, IL-13, and TGF-β acted collectively to enhance collagen synthesis in KFs and the expression of matrix-remodeling enzymes such as MMP-1 and MMP-3.[73] Notably, IL-13 receptor alpha 2(IL-13Rα2), a decoy receptor that negatively regulated IL-13 signaling, was significantly downregulated in KFs compared with that in NFs. Ectopic expression of IL-13Rα2 in KFs suppressed STAT6 phosphorylation, reduced cell proliferation, migration, invasion,

ECM production, myofibroblast marker expression, and promoted apoptosis. Conversely, knockdown of IL-13Rα2 in NFs induced a keloid-like phenotype, further supporting its regulatory role in keloid pathogenesis.[74] Recent clinical findings have highlighted the therapeutic potential of targeting the Th2 cytokines. Dupilumab, a monoclonal antibody targeting IL-4 receptor alpha, could reduce keloid size and alleviate associated symptoms such as pruritus and pain in some patients.[71,75] However, a case report described a lack of therapeutic response to dupilumab in a patient with diffuse keloids,[76] suggesting that responsiveness might vary depending on disease subtype or extent. These findings underscore the need for further research to clarify the role of Th2 cytokines in keloid progression and optimize cytokine-targeted therapies.

Immune Cell Infiltration

To further understand the inflammatory milieu of keloids, attention need to be directed towards the immune cells that produce and respond to these cytokines. A significant increase in mast cell density was observed in and around keloid lesions.[77] The close contact of mast cells with nerve endings, along with elevated levels of histamine in keloid tissue, likely explained the pain and itching symptoms accompanying keloids. Clinically, the application of silicone sheets to keloid-affected skin reduced mast cell numbers within lesions and alleviated discomfort.[78] Mast cells significantly stimulated type I collagen expression in KFs via the PI3K/Akt/mTOR pathway. Researchers using green tea extract and its major catechin, (-)-epigallocatechin-3-gallate, found a reduction in the expression of *COL1A1* gene.[79] In addition to their fibrotic functions, mast cells also contributed to angiogenesis during wound healing. This pro-angiogenic activity was mediated by their secretion of various factors, including vascular endothelial growth factor, fibroblast growth factor-2 (FGF-2), platelet-derived growth factor (PDGF), IL-6, tryptase, and chymase.[80] Tryptase was strongly associated with angiogenesis in keloids.[81] Chymase activated fibroblasts and enhanced collagen synthesis via the TGF-β1 signaling pathway.[82] There are reports of the use of inhibitors to attenuate these effects. For instance, trinitostat, a trypsin-like enzyme inhibitor, alleviated pain and itching in keloid patients following transdermal iontophoretic administration.[83] Similarly, administration of the chymotrypsin inhibitor SUN-C8257 significantly decreased subcutaneous fibrotic layer thickness in a murine model of scleroderma,[84] suggesting its potential applicability in fibrotic skin conditions such as keloids.

Wound healing after skin injury is a complex, multi-phase process involving hemostasis, inflammation, proliferation, re-epithelialization, and remodeling.[85] Macrophages, as key immune regulators, exhibit functional heterogeneity depending on their polarization state. M1 macrophages dominate the early inflammatory phase, exerting antimicrobial and pro-inflammatory effects. In contrast, M2 macrophages participate in tissue remodeling and fibrogenesis, primarily through the secretion of anti-inflammatory cytokines and pro-fibrotic factors, including TGF-β.[86] A tightly regulated transition from M1 to M2 macrophages is essential for normal wound healing. However, this balance is disrupted in keloid pathology. Studies reported a skewed macrophage phenotype in keloid tissue, characterized by a disproportionate increase in M2 macrophages, which comprised a significantly larger proportion of the total macrophage population than normal skin.[87,88] This was due to the following reasons. Firstly, Th2 cytokines IL-4 and IL-13, were enriched within keloids, which favored the production of M2 macrophages.[71,72] Second, there was an increase in skin stiffness and tension in areas where keloids were present, and M2 macrophages were more sensitive to this change than M1 macrophages.[89]

While this review has focused on Th2 cells, mast cells, and M2 macrophages due to their substantial supporting evidence, a complete immunologic understanding of keloids necessitates a broader view. Evidence points to a potentially significant yet complex role for regulatory T cells (Tregs). Studies indicate their numbers are elevated within keloid tissue,[90] possibly linked to a decrease in circulating Tregs in patients with severe disease.[91] Notably, these locally abundant Tregs may not function purely as suppressors; they can produce potent fibrotic mediators like TGF-β1, suggesting a paradoxical, pro-fibrotic role in this context.[92] Dendritic cells also appear altered, with observations of increased dermal infiltration of specific subsets.[93] Neutrophils, as critical initiators of acute inflammation, have not been sufficiently studied in keloids. Elucidating the precise functions of these cells through high-resolution profiling is essential to refine the auto-inflammatory paradigm.

Signaling Pathways: The Fibro-Inflammatory Nexus

The dysregulated signaling pathways in keloids are not isolated circuits; rather, they function as an integrated network that transduces inflammatory signals into fibrotic outcomes.

TGF-β Signaling: A Central Fibrotic Pathway

In the canonical TGF-β/Smad signaling pathway, TGF-β first binds to the constitutively active type II transmembrane serine/threonine kinase receptor. This ligand-receptor complex then recruits and phosphorylates the type I receptor, activating its kinase domain. The activated type I receptor subsequently phosphorylates intracellular Smad2 and Smad3. Phosphorylated Smad2/3 then forms a complex with Smad4, which enters the nucleus to regulate target gene transcription.[94] In keloids, several upstream regulators of the TGF-β/Smad signaling pathway were upregulated, such as CR6-interacting factor 1 and nuclear receptor subfamily 3, group C, member 1.[95] Activin A of the TGF-β superfamily, which regulated fibroblast proliferation and ECM formation, was overexpressed in keloids.[96] Negative feedback regulation of this pathway was primarily mediated by Smad6 and Smad7. These molecules directly bound to activated TGF-β receptors, thereby preventing the phosphorylation of Smad2 and Smad3. However, both Smad6 and Smad7 were significantly downregulated in KFs compared with NFs, removing a critical brake in the fibrotic signaling cascade.[97] In KFs, anti-fibrotic miRNAs, such as miR-200c, miR-1224-5p, and miR-133a-3p, were markedly downregulated, while pro-fibrotic miR-21 was upregulated.[39,46,98] These alterations correlated strongly with enhanced TGF-β1/Smad activity and could explain why most keloids were stiffer than surrounding skin.

Integrin-Mediated Mechanotransduction and Fibroblast Activation

Integrins are ubiquitously expressed on the cell surface and mediate cell-cell and cell-ECM interactions. In addition to structural anchoring, integrins serve as bidirectional signaling conduits that regulate cellular processes. In response to mechanical stimuli, integrins are activated by ECM components and transmit signals to the cell, ultimately modulating fibroblast behavior.[99] KFs expressed more integrins and were more responsive to mechanical force signaling.[100,101] Importantly, integrin signaling interacted closely with the TGF-β pathway.[102–104] The integrin β1 subunit regulated the activation of latent TGF-β1. In the absence of integrin β1, TGF-β1 activation was impaired, resulting in reduced collagen production. Conversely, active TGF-β1 enhanced the binding affinity of integrins for collagen. Fibulin-5, an ECM glycoprotein, inhibited the adhesion and proliferation of keloid-derived fibroblast-like cells by interacting with integrin β1.[105] Similarly, chondroitin sulfate, a major ECM glycosaminoglycan abnormally deposited in the keloid stroma, promoted the proliferation of keloid-derived fibroblasts in an integrin α1-dependent manner. This effect was abolished by blocking integrin α1 with specific antibodies, underscoring the functional relevance of α1 integrins in keloid fibroblast activation.[106]

Other Signaling Pathways Involved in Keloid Pathogenesis

IL-17-producing cells was significantly infiltrated in the marginal region of keloids, and it induced fibroblasts to express stromal cell-derived factors and fibrotic factors through the STAT3 signaling pathway.[107] In a follow-up study, Lee et al further demonstrated that IL-17 impaired autophagic function and promoted inflammatory cell death and fibrosis in KFs through a STAT3 and HIF-1α–dependent mechanism, suggesting a multifaceted regulatory network linking inflammation and fibrosis in keloids.[108] The Wnt/β-catenin signaling pathway was also aberrantly activated in keloids. Increased levels of β-catenin during keloid formation induced fibroblast proliferation and ECM production.[109] Targeted inhibition of GSK-3β, a key upstream regulator that normally promoted β-catenin degradation, resulted in decreased Wnt/β-catenin signaling and attenuated keloid formation. When β-catenin-specific siRNA was utilized in KFs, researchers observed growth arrest at the G0/G1 phase, increased apoptosis, and reduced expression of Wnt2, cyclin D1, and phosphorylated GSK-3β, further confirming the pivotal role of this pathway in keloid progression.[110] In summary, multiple signaling pathways are aberrantly activated in keloids. The crosstalk among these pathways, especially between mechanical and inflammatory signals, highlights the complexity of keloid pathogenesis and offers promising targets for future therapeutic intervention. In essence, these pathways constitute the fibro-inflammatory nexus of keloids, translating the biological signals of immune cells (cytokines) into the fibrotic commands executed by fibroblasts (proliferation, ECM synthesis).

Metabolic Reprogramming: Fueling the Fibro-Inflammatory Engine

Alterations in cellular biological behavior are often accompanied by metabolic reprogramming, as exemplified by the Warburg effect in tumor cells. Emerging evidence suggests that keloids also exhibit abnormal energy metabolism.[111–114] Direct clinical evidence from fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET-CT) imaging *has demonstrated* a significant increase in glucose uptake in keloid tissue relative to adjacent normal skin.[113] This in vivo finding is complemented by subsequent in vitro studies indicating that KFs, unlike normal fibroblasts, may utilize both oxidative phosphorylation and aerobic glycolysis, exhibiting a metabolic phenotype that shares functional characteristics with, though is not identical to, the Warburg effect observed in cancer. Specifically, glycolysis-related gene expression is significantly elevated in keloid tissue, and the glycolytic inhibitor 2-deoxy-D-glucose has been shown to markedly reduce the proliferative capacity of KFs in culture.[111] It is hypothesized that this enhanced aerobic glycolysis could rapidly provide biosynthetic precursors and energy to support the high demands of proliferating KFs, while potentially altering the tissue redox state. However, comprehensive metabolomic profiling of human keloid tissue to directly quantify metabolic fluxes and intermediate abundances remains an important area for future investigation.

This metabolic adaptation is likely a critical response to meet the exceptionally high biosynthetic and energetic demands of keloid fibroblasts (KFs). These cells reside in a microenvironment rich in pro-growth cytokines (eg, TGF-β, FGF, PDGF) and exhibit sustained activation of proliferative signaling pathways, collectively imposing a substantial burden on cellular resources.[115] The observed enhancement of aerobic glycolysis may therefore provide the necessary fuel and biosynthetic precursors to support this pathological state of hyper-proliferation. It is crucial, however, to distinguish between a functional metabolic adaptation to a growth-factor-rich environment and a primary, driver-level metabolic switch akin to the Warburg effect in cancer. While the former is well-supported by the available evidence, the latter's role as an initiating and sustaining cause in keloid pathogenesis requires further validation in vivo.

Discussion

Integrative Mechanisms: Reconceptualizing Keloids as an Auto-Inflammatory Fibrotic Spectrum

Keloid research has been hindered by a fragmented view of pathogenesis. This review synthesizes recent advances to propose a paradigm shift: keloids are not a mere aberration of healing, but a spectrum of chronic, immune-mediated disorders whose primary expression is fibrosis. This framework positions dysregulated immunity as the central orchestrator, modulated by genetic, epigenetic, endocrine, and metabolic factors.

Evidence is compelling. Genetic predisposition (eg, in NEDD4, TIEG1, HLA) encodes a hyperinflammatory phenotype, sensitizing pathways like NF-κB and TGF-β. Epigenetic modifications act as a "molecular memory", stabilizing this state. Endocrine factors, such as vitamin D deficiency and RAS dysregulation, systemically lower the threshold for sustained inflammation.

Sustained immune dysregulation is core to this paradigm. An infiltrate of mast cells, Th2 cells, and M2 macrophages creates a self-perpetuating cytokine milieu (IL-4, IL-13, IL-6, TGF-β). These signals converge on a fibro-inflammatory signaling nexus (TGF-β/Smad, JAK/STAT, integrin), driving fibroblasts to undergo metabolic reprogramming. Enhanced aerobic glycolysis, supported by in vivo glucose uptake, supplies the energy and biosynthetic precursors for relentless proliferation and ECM deposition.

Thus, the traditional fibroproliferative view is incomplete, failing to explain chronicity, recurrence, and symptoms like pruritus. Our model reframes keloid pathology as a self-amplifying loop: predisposed immune dysfunction initiates chronic inflammation; this inflammation, via signaling pathways, activates and metabolically reprograms fibroblasts; the resulting fibrotic tissue, in turn, perpetuates immune activation. This explains why solely targeting fibrosis fails and why therapies must address the inflammatory core.

Clinical Translation: From Palliative Management to Mechanism-Informed Therapeutics

Reconceptualizing keloids as an immune-driven disorder clarifies why conventional therapies (surgery, corticosteroids, laser) often fail—they address end-stage fibrosis but not the pathogenic immune-fibrotic loop, leading to high recurrence. This underscores the need for strategies that target core drivers.

The new paradigm shifts the goal from fibrosis reduction to microenvironment reprogramming. A logical, multi-tiered strategy emerges: disrupt upstream immune drivers while silencing aberrant fibroblasts. This includes: 1) Local control (surgery/laser) for debulking; 2) Broad suppression (corticosteroids) for non-specific dampening; 3) Targeted immunomodulation (eg, anti-IL-4/IL-13 biologics, JAK inhibitors) to precisely quiet the inflammatory engine; and 4) Reversal of cellular reprogramming (eg, HDAC or metabolic inhibitors) to normalize fibroblast phenotype.

The most promising future lies in combining these tiers (eg, surgery followed by adjuvant biologic therapy) to synergistically remove lesions and prevent recurrence by resetting the microenvironment. This framework paves the way for personalized medicine, where therapy is tailored to disease endotypes (eg, "Th2-high"), moving from empiric care to pathophysiology-driven management.

Future Directions and Concluding Perspectives: Refining the Paradigm

This auto-inflammatory fibrotic paradigm offers a cohesive, testable framework that explains keloid behavior more fully than the classical model. Key priorities for its validation include: employing high-resolution spatial and single-cell analyses to map the complete immune landscape; developing advanced in vivo models to establish causal and temporal relationships within the pathogenic loop; and identifying biomarkers to define treatable endotypes (eg, "Th2-high") for personalized therapy. We must acknowledge the model's limitations, as it integrates evidence of varying depth—such as the need for in vivo metabolomic confirmation of metabolic reprogramming and more interventional data on endocrine links. This synthesis is therefore a provisional, working hypothesis designed to focus and accelerate future research. Ultimately, by shifting the focus from fibrosis to the immune-inflammatory core, this paradigm charts a clear course toward mechanism-based, effective therapies for this recalcitrant disease.

In conclusion, moving beyond the view of keloids as a disorder of faulty wound healing towards understanding them as a spectrum of immune-mediated fibrotic diseases represents a significant conceptual advance. This paradigm does not merely catalog mechanisms but weaves them into a narrative that explains disease persistence, recurrence, and heterogeneity. It shifts the therapeutic gaze upstream, from the fibrotic scar to the inflammatory fire that fuels it. While many questions remain, this reframing provides a focused direction for both basic research and clinical innovation. By embracing this immunocentric perspective, the field can accelerate the development of rational, targeted, and ultimately more effective strategies to manage this recalcitrant condition, offering renewed hope for patients.

Abbreviations

Ang II, angiotensin II; AT1R, angiotensin II type 1 receptor; COL1A1, collagen type I alpha 1 chain gene; DNMT1, DNA methyltransferase 1; ECM, extracellular matrix; FGF, fibroblast growth factor; GWAS, genome-wide association study; HDAC2, histone deacetylase 2; IL-13Rα2, IL-13 receptor alpha 2; IL6R, interleukin-6 receptor; KFs, keloid fibroblasts; MMP, matrix metalloproteinase; NEDD4, Neural precursor cell-expressed developmentally downregulated 4; NEDD4L, Neural precursor cell-expressed developmentally downregulated 4-like; NFs, normal skin-derived fibroblasts; PDGF, platelet-derived growth factor; RAS, renin-angiotensin system; SNPs, single nucleotide polymorphisms; TIEG1, TGF β-inducible early gene-1; TGF, transforming growth factor; Tregs, T cells; TSA, Trichostatin A.

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Disclosure

The authors report no conflicts of interest in this work.

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