Clinical, Cosmetic and Investigational Dermatology

Dovepress
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REVIEW

Langerin$^+$ Dendritic Cells in Cutaneous Fibrosis: The TGF-β1 Signaling Axis

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Abstract: Cutaneous fibrosis – including hypertrophic scars and keloids – arises when immune, epithelial, and stromal signals fail to re-equilibrate after injury. Langerin$^+$ dendritic cells (DCs) – epidermal Langerhans cells and dermal cDC1 – sit at the center of this process. These DC subsets generate latent transforming growth factor-β1 (TGF-β1) that keratinocyte integrins αvβ6/αvβ8 locally activate, creating an epidermal "cytokine gate" that restrains immunity in homeostasis yet seeds fibrosis when overdriven. Downstream, active TGF-β1 cooperates with mechanosensitive YAP/TAZ to drive fibroblast activation and matrix stiffening, while immune skewing (Th2/Th17/Treg and M2 macrophages) sustains a pro-fibrotic milieu. We synthesize how epithelial integrins, DC programs, and fibroblast mechanotransduction converge on TGF-β1; compare normal wound resolution with hypertrophic scar and keloid; highlight insights from single-cell and spatial omics; and outline therapeutic strategies targeting the αv integrin–TGF-β1 axis, YAP/TAZ, and immune cues. Framing cutaneous fibrosis through a DC-centric lens clarifies testable hypotheses and points toward mechanism-guided, combinatorial therapies.

Keywords: cutaneous fibrosis, Langerin$^+$ dendritic cells, TGF-β1 activation, hypertrophic scar, keloid, extracellular matrix remodeling

Introduction

Cutaneous fibrosis, characterized by excessive scar formation and dermal extracellular matrix (ECM) deposition, arises when wound healing processes become dysregulated.[1–3] Conditions like hypertrophic scars and keloids represent pathological fibrosis, leading to functional and cosmetic morbidity. A central mediator of fibrosis is transforming growth factor-β1 (TGF-β1), a pleiotropic cytokine that drives fibroblast proliferation, myofibroblast differentiation, and collagen production.[4] However, fibrosis is not solely a fibroblast-autonomous process; it is profoundly influenced by the immune system and the tissue microenvironment. Skin-resident immune cells – in particular, dendritic cells (DCs) – are emerging as key regulators of the repair-versus-fibrosis outcome.[1] Among these, Langerin$^+$ dendritic cells in the skin (which include Langerhans cells in the epidermis and Langerin-expressing dermal DCs) are strategically positioned at the interface of immunity and tissue remodeling. These cells can shape local immune responses and secrete or respond to TGF-β1, linking them to fibrogenic pathways.[5–7]

First, we outline the biology of epidermal Langerin$^+$ Langerhans cells and dermal Langerin$^+$ cDC1 in skin. Next, we connect keratinocyte αvβ6/αvβ8-mediated activation of latent TGF-β1 to fibroblast Smad2/3–YAP/TAZ programs and immune polarization, and we examine mechanobiology (matrix stiffness, integrin signaling, mechanotransduction) that shapes pro-fibrotic niches. Finally, we summarize DC-centric single-cell/spatial insights and assess mechanism-based therapeutic strategies that target this LC/DC–epithelial–stromal circuit.

Here, we narrow the lens to Langerin$^+$ dendritic cells in cutaneous fibrosis and ask three questions: (i) how keratinocyte αvβ6/αvβ8–dependent activation of latent TGF-β1 gates LC residency and sets immune tone; (ii) how LC/cDC1-driven immune polarization interfaces with fibroblast Smad2/3–YAP/TAZ programs and tissue mechanics; and (iii) what single-cell/spatial evidence exists for human DC heterogeneity in scars, and where the critical gaps remain. We

Received: 25 June 2025
Accepted: 11 October 2025
Published: 27 October 2025

also note species-specific differences between murine and human Langerin$^+$ DC subsets and caution against uncritical extrapolation.

Langerin$^+$ Dendritic Cell Subsets in Skin

Langerin (CD207) is a C-type lectin receptor that defines specialized DC subsets in the skin. The epidermal Langerhans cells (LCs) are the prototypical Langerin$^+$ cells: they reside in the epidermis, form a self-renewing network, and contain characteristic Birbeck granules.[8–12] Phenotypically, LCs express Langerin, E-cadherin, and CD1a, distinguishing them from other skin DCs.[8,12–14] Although historically classified as dendritic cells, LCs share developmental features with tissue-resident macrophages – arising from embryonic progenitors and maintaining themselves independently of blood monocytes in steady state.[10–12] Indeed, modern lineage-tracing and transcriptional studies have "reclassified" LCs as macrophage-like cells that nonetheless perform antigen-presenting functions. In contrast, the dermis harbors conventional dendritic cells (cDCs) derived from bone marrow precursors. Among these, a subset of dermal cDC1 (CD141$^+$ in humans, CD103$^+$IRF8$^+$ in mice) also expresses Langerin. These dermal Langerin$^+$ cDC1 are distinct from LCs in ontogeny and turnover: they depend on the FLT3 ligand for development, derive from circulating DC precursors, and are short-lived, continually replaced from bone marrow.[5,12–15] Notably, fate-mapping in mice demonstrates that epidermal LCs and dermal langerin$^+$ DCs are separate lineages – embryonically seeded LCs vs hematopoietic cDC1 – with different functional roles.[9,10]

Functional Roles

Langerin$^+$ LCs serve as immune sentinels in the epidermis, sampling antigens and migrating to lymph nodes to prime T cells. They can promote immunogenic responses against pathogens and tumors yet also maintain tolerance to self and innocuous antigens.[8,9] For example, LCs have been shown to expand antigen-specific regulatory T cells to prevent autoimmunity. Dermal Langerin$^+$ cDC1, on the other hand, excel at cross-presenting antigens to CD8$^+$ T cells and biasing Th1-type responses, owing to their high expression of XCR1 and BATF3/IRF8 dependence.[8,16] In steady state, LCs form a "tolerogenic" firewall in the epidermis – supported by local TGF-β1 and IL-34 – to quell aberrant inflammation.[5] But upon skin injury or infection, LCs become activated and migrate out, while dermal DCs influx to orchestrate immunity. This balance of LCs and dermal DCs is thought to influence wound healing outcomes. If LCs tilt toward regulatory functions (eg inducing T_regs or producing IL-10), they might limit inflammation and potentially fibrosis. Conversely, if LCs or other DCs produce pro-fibrotic mediators, they could encourage scar formation.

Interestingly, recent research identified a novel Langerin$^+$ migratory DC in murine dermis that behaves like an "LC-like" population during inflammation.[17–19] Using fate-mapping, Zhao et al showed a wave of monocyte-derived Langerin$^+$ cells can temporarily enter the epidermis after LC depletion, but these cells are short-lived and require inflammation (they do not persist long-term).[5,20] Their role is not fully clear, but they may participate in inflammatory cytokine circuits in diseases such as psoriasis.[5] In fibrosis contexts, one could speculate that monocyte-derived inflammatory DCs might infiltrate and either exacerbate or resolve scarring depending on signals encountered.

In summary, the skin's Langerin$^+$ DC network comprises: (1) Epidermal LCs – self-renewing cells with immunoregulatory capacity, dependent on local TGF-β1 and cytokines for homeostasis; and (2) Dermal Langerin$^+$ cDC1 – bone-marrow-derived migratory DCs specialized for antigen presentation.[5] Outlines key differences are shown in Table 1.

Both subsets express the Langerin receptor and thus can capture glycosylated antigens, but they likely have distinct contributions during wound healing and fibrosis. LCs, by virtue of their epidermal position and longevity, might regulate keratinocyte–fibroblast crosstalk and control chronic inflammation in scars. Dermal Langerin$^+$ cDC1, through their cytokine production and T cell activation, might modulate the type of immune response (Th1 vs Th2 vs Th17) in healing wounds and thereby indirectly influence fibrotic outcomes. The following sections will explore how these cells interact with the TGF-β1 axis and other pathways relevant to fibrosis.

Table 1 Key Phenotypic Signatures of Murine Skin Antigen-Presenting Cell Subsets

APC Subset	Anatomical Location	Key Transcription Factors (TFs)	Representative Surface Markers	Common Aliases
Langerhans cells (LCs)	Epidermis	ID2$^+$, Runx3$^+$, IRF8$^+$	CD207 (Langerin)$^+$, CD11b$^+$	–
Dermal cDC1	Dermis	ID2$^+$, Batf3$^+$, IRF8$^+$	CD103$^+$, XCR1$^+$, CD207$^+$	XCR1$^+$ dDCs (CD103$^+$ dDCs)
Dermal cDC2	Dermis	IRF4$^+$	CD11b$^+$, CD172a$^+$, CD301b$^+$	CD11b$^+$ dDCs (IRF4 dDCs)

Keratinocyte-Derived TGF-β1: Production and Integrin-Mediated Activation

TGF-β1 in Skin: TGF-β1 is abundant in the skin microenvironment, produced by multiple cell types including keratinocytes, Langerhans cells, fibroblasts, and immune cells.[21–24] However, TGF-β1 is secreted as a latent complex – a dimer of TGF-β1 bound to latency-associated peptide (LAP), often tethered to the matrix via latent TGF-β binding protein (LTBP).[25] Activation of latent TGF-β1 (release of the bioactive cytokine) is a critical control point. In the epidermis, keratinocytes play a dominant role in activating latent TGF-β1 via specific integrins on their surface.[6,7,24] Integrins are cell-surface receptors that, in addition to binding ECM components, can bind the RGD motif present in LAP of TGF-β1 (and TGF-β3).[26–28] Notably, keratinocytes upregulate the integrins αvβ6 and αvβ8 in the context of wound healing and inflammation.[29] These integrins are uniquely suited to activate TGF-β1: αvβ6 and αvβ8 both bind LAP and effect TGF-β release – αvβ6 primarily via mechanical force and αvβ8 via proteolytic cleavage in concert with metalloproteinase MT1-MMP.[30–32]

In unwounded skin, αvβ6 is minimally expressed; but during re-epithelialization of wounds, keratinocyte αvβ6 is strongly induced.[29] αvβ8 is constitutively expressed by specific keratinocytes (for instance, around hair follicles).[5] These two integrins have non-overlapping localization – αvβ6 mainly in interfollicular epidermis, αvβ8 near follicles – collectively ensuring that latent TGF-β1 can be activated across the epidermis. Critically, studies have shown that loss of integrin-mediated TGF-β1 activation phenocopies the loss of TGF-β1 itself.[5] Mice lacking αvβ6 (or with mutations preventing TGF-β activation) develop skin and immune abnormalities akin to TGF-β1 knockout, including the absence of epidermal LCs and excessive inflammation.[5] Yang et al demonstrated that mice unable to activate latent TGF-β1 (due to integrin β6/β8 double deficiency) show unchecked inflammation and failure to maintain immune homeostasis, underlining the physiological importance of this mechanism.[5]

In steady-state epidermis, keratinocyte integrin activation of TGF-β1 provides "tonic" TGF-β signaling that is required for LC residency and immune quiescence. Langerhans cells themselves produce TGF-β1 and depend on it in an autocrine manner, but keratinocyte integrins must activate LC-derived latent TGF-β1 to make it bioavailable.[5] This fascinating LC–keratinocyte crosstalk was shown by Kaplan et al: epidermal LCs leave the skin if TGF-β1 activation is impaired, and conversely, constitutively active TGF-β receptor in LCs locks them in the epidermis.[5] Thus, keratinocyte αvβ6/αvβ8 integrins are gatekeepers of TGF-β1 activity in the skin. They ensure a baseline level of active TGF-β1 that enforces immune tolerance (eg via LCs expressing the inhibitory receptor Axl) and prevents spontaneous DC migration or activation. This homeostatic role has direct implications for fibrosis: TGF-β1 availability influences not only immune cells but also fibroblasts in the dermis. For instance, if keratinocytes in a wounded area highly express αvβ6, they can activate large amounts of latent TGF-β1 in the wound milieu.[29] This active TGF-β1 could then act on dermal fibroblasts to drive scar formation. Conversely, tissue contexts that reduce αvβ6/β8 expression – such as scarless healing environments (fetal skin or oral mucosa) – show attenuated TGF-β1 activity and bias toward regeneration over fibrosis.[29] Indeed, gingival (oral) wound epithelium has high αvβ6 along with elevated TGF-β3, which is thought to counterbalance TGF-β1 and promote scarless repair.[29] This suggests that modulating keratinocyte integrin expression or the ratio of TGF-β isoforms (β3 vs β1) could influence scarring outcomes.

In pathologic scars, evidence indicates persistent activation of TGF-β1 by integrins. Hypertrophic scar tissue and keloids often show prolonged epithelial expression of αvβ6 beyond the acute wound phase.[29] A feed-forward loop may ensue: TGF-β1 itself can induce more integrin expression on keratinocytes and fibroblasts,[25,33] thereby amplifying its own activation. Additionally, high mechanical tension in skin (common in keloid-prone areas) can increase integrin-mediated TGF-β activation, as integrins like αvβ6 require a resistant force to pull against to activate latent TGF-β (the latent complex is like a spring that must be stretched).[25] Fibrotic tissue, being stiff, provides such resistance, thus mechanically reinforcing TGF-β activation (discussed more in mechanobiology section). In summary, keratinocyte-derived TGF-β1 and its activation via αv integrins represent a crucial initiating event in cutaneous fibrosis. By regulating how much active TGF-β1 is available in the wound microenvironment, keratinocytes indirectly govern downstream events: DC activation, immune polarization, and fibroblast behavior. Therapeutically, this axis is attractive – for example, blocking αvβ6 integrin has shown efficacy in reducing fibrosis in preclinical models.[34,35] An αvβ6/β1 inhibitor (bexotegrast, PLN-74809) is in trials for idiopathic pulmonary fibrosis and could potentially be repurposed for skin fibrosis.[36] Local strategies to inhibit keratinocyte integrins or enhance TGF-β3 (a TGF-β1 antagonist in scarring) are being explored to reduce scar formation.[29] Before delving into therapies, we must understand how TGF-β1 influences the fibrogenic machinery of fibroblasts and how Langerin$^+$ cells intersect with these pathways.

Fibroblast Activation: Crosstalk of TGF-β/SMad and YAP/TAZ Pathways

Why this matters for DCs. The keratinocyte αvβ6/αvβ8 TGF-β1 gate that tunes LC residency also sets the baseline ligand availability sensed by dermal fibroblasts. In DC-permissive contexts (eg, IL-10/IDO-skewed), the fibroblast Smad2/3–YAP/TAZ axis is preferentially engaged and sustained; conversely, Th1-biased DC programs can transiently antagonize Smad-dependent collagen transcription. We, therefore, view fibroblast activation here as a downstream readout of DC- and epithelium-controlled TGF-β dynamics.

Fibroblasts are the effectors of fibrosis, producing and remodeling the ECM that constitutes scar tissue.[37] Under the stimulus of active TGF-β1, quiescent dermal fibroblasts are stimulated to proliferate and differentiate into myofibroblasts – a contractile, ECM-secreting phenotype marked by α-smooth muscle actin (α-SMA) stress fibre.[1] TGF-β1 signals through Smad proteins (the canonical pathway) as well as non-canonical pathways (eg MAPK, Rho/ROCK) to drive transcriptional programs of fibrosis. In the canonical pathway, TGF-β1 binding to TGF-β receptors activates receptor SMAD2/3, which complex with SMAD4 and translocate to the nucleus to induce target genes such as COL1A1 (collagen I), fibronectin, and connective tissue growth factor (CTGF).[1,38] In keloid fibroblasts, TGF-β/Smad signaling is often hyperactive – studies have found higher expression of TGF-β receptors or prolonged Smad phosphorylation in keloid-derived cells. This may explain why keloid fibroblasts are **e**xceptionally sensitive to TGF-β1, producing abundant collagen and resisting apoptosis signals compared to fibroblasts from normal scars.[1] For example, keloid fibroblasts show elevated TGF-β type I receptor (TβRI) levels and can overcome growth-arrest cues, leading to a persistent fibrotic state.[1]

YAP/TAZ in Fibrosis: In parallel to Smad pathways, fibroblasts integrate mechanical and other cues via the Hippo-YAP/TAZ pathway. Yes-associated protein (YAP) and WWTR1/TAZ are transcriptional co-activators that shuttle to the nucleus when the Hippo pathway is inactive (often in response to cell shape changes or matrix stiffness). In fibrotic conditions, YAP/TAZ are typically activated in fibroblasts due to the stiff ECM and ongoing mechanotranduction.[39,40] YAP/TAZ are now recognized as major drivers of fibroblast activation: they can induce profibrotic genes and reinforce TGF-β signaling. Crosstalk between YAP/TAZ and TGF-β/Smad is bidirectional. On one hand, TGF-β1 can promote YAP/TAZ nuclear localization by altering cytoskeletal dynamics and through downstream effectors (eg via Rho GTPases).[40,41] On the other hand, YAP/TAZ can enhance TGF-β/Smad signaling in fibroblasts by various mechanisms. Recent work in human dermal fibroblasts showed that YAP/TAZ activity sustains Smad2/3 activation by suppressing the inhibitory SMAD7.[37] Specifically, YAP/TAZ limit SMAD7 expression via AP-1 – when YAP/TAZ are knocked down, AP-1 drives up SMAD7, which then blocks TGF-β/Smad signaling and collagen production. Conversely, active YAP/TAZ keep SMAD7 low, allowing Smad3 to remain phosphorylated and fibrogenic genes to be expressed. In essence, YAP/TAZ act as amplifiers of TGF-β signals in fibroblasts. Additionally, YAP/TAZ can directly co-activate transcription of pro-fibrotic genes (like CTGF and CNN1) and repress anti-fibrotic genes (like certain MMPs). The outcome is a feed-

forward loop: stiff matrix → YAP/TAZ activation → more matrix and TGF-β signaling → even stiffer matrix, etc.[37] This loop helps explain why once a keloid scar is established, it can become autonomous and progressive.

Importantly, mechanical forces and TGF-β signals converge on fibroblasts in wound healing. During normal wound healing, as the provisional matrix is laid down, fibroblasts exert traction forces to contract the wound. If the wound mechanically offloads (eg by splinting), fibroblasts gradually undergo apoptosis and scar resolution ensues.[42] But, if mechanical load persists or is excessive early in healing, fibroblast apoptosis is inhibited, leading to hypercellularity and hypertrophic scarring.[42] Aarabi et al demonstrated in a mouse model that applying mechanical stress to wounds led to 20-fold increased cellular density in scars, due in part to an Akt-dependent survival signal in fibroblasts. TGF-β1 was implicated in this response, as mechanical strain can activate latent TGF-β and because downstream of integrins, the Akt pathway can be engaged.[42] In turn, TGF-β1 induces α-SMA and cytoskeletal remodeling, which increases cellular force generation and YAP activation – a vicious cycle. Indeed, keloid fibroblasts often display nuclear YAP and high CTGF levels, indicating active mechanotransduction, whereas normal scar fibroblasts (in a less stiff matrix) have lower YAP activity.[43] Recent single-cell analyses found that mechanosensitive fibroblast subpopulations are dominant in keloids, characterized by upregulation of YAP/TAZ target genes and contractile machinery.[43] These "mechano-responsive" fibroblasts are likely sustained by the dense collagen network and elevated TGF-β1 in keloid tissue, highlighting how biochemical and biomechanical signaling entwine in fibrosis.

Fibroblast–Immune Crosstalk: TGF-β1 and YAP/TAZ signaling in fibroblasts does not occur in isolation – fibroblasts both influence and are influenced by immune cells. Fibroblasts secrete chemokines (eg CCL2/MCP-1, CXCL12) that recruit monocytes and other leukocytes, and they can present antigens or express co-stimulatory molecules under certain conditions, thereby interacting with DCs and T cells in the tissue.[37] In fibrosis, fibroblasts often adopt an inflammatory phenotype (sometimes termed fibro-inflammatory phenotype) where they produce IL-6, IL-8 and other cytokines that sustain immune cell infiltration.[1] TGF-β1 can enhance this: for instance, TGF-β1 in concert with IL-17A (from Th17 cells) was shown to strongly induce IL-6 and CCL2 production by keloid fibroblasts.[38] The IL-6 can feedback to amplify Th17 differentiation, and CCL2 attracts macrophages, which then produce more TGF-β1 – a positive feedback loop driving fibrosis.[38] Moreover, fibroblasts respond to immune cell-derived signals: eg IL-13 and IL-4 from Th2 cells or ILC2 can directly stimulate collagen gene expression and myofibroblast differentiation. Fibroblasts express IL-4Rα/IL-13Rα and these cytokines activate STAT6, which has pro-fibrotic effects in parallel to TGF-β/Smad (IL-4/13 can induce periostin, a matricellular protein that stiffens ECM).[1] Thus, crosstalk between fibroblasts and immune cells creates an amplification network: TGF-β1-activated fibroblasts produce chemokines and growth factors that modulate immune cells; activated immune cells (T cells, macrophages, mast cells) in turn produce mediators (cytokines, enzymes) that further activate fibroblasts or free more TGF-β1. This sets the stage for understanding how normal wound healing resolves versus how fibrotic healing persists.

Wound Healing Versus Pathological Fibrosis

Table 2 contrasts the molecular, cellular, mechanical, and clinical features of normal wound healing, hypertrophic scars, and keloids.

Under ideal conditions, cutaneous wound repair is self-limited (listed in Table 2). After an initial inflammatory phase and a proliferative phase of tissue formation, a remodeling phase leads to scar maturation and contraction, often resulting in a flat, flexible scar with refined collagen architecture. In normal wound healing, pro-fibrotic signals like TGF-β1 are elevated transiently: they spur granulation tissue formation and re-epithelialization, then subside as matrix remodeling and apoptosis of excess cells occur.[42] Hypertrophic scars and keloids deviate from this trajectory. Both involve excessive collagen deposition, but they differ clinically and at the molecular level. Hypertrophic scars remain confined to the wound boundaries and often partially regress over time, whereas keloids grow beyond the original wound edges and tend to continually expand without spontaneous regression.[44,45] In keloids, the scar tissue can form tumor-like mounds with a chronic course.

Several key differences have been identified: (1) Persistent Inflammation: Chronic inflammation is a feature of pathological scars. Keloids, for example, show prolonged presence of inflammatory cells and mediators long after the inciting injury. Histologically, keloids have perivascular lymphocytes and mast cell clusters deep in the lesion, and

Table 2 Comparative Features of Normal Wound Healing, Hypertrophic Scar, and Keloid in Human Skin

Parameter	Normal Healing	Hypertrophic Scar(HTS)	Keloid
Inflammation windows	3-7 days	≥ 2 weeks	≥ 4 weeks (often chronic)
Dominant cytokines	IL-10↓ TGF-β1 IL-6	TGF-β1↑↑↑ IL-6 CC L2	TGF-β1↑↑↑ IL-4 IL-13
Fibroblast phenotype	Transient myo-fibroblast	α-SMA+ myofibroblast persists but wanes	Variable α-SMA^{+} myofibroblast clusters; enriched mesenchymal fibroblast subsets (eg, COL11A1^{+} / POSTN^{+})
ECM architecture	Basket-weave collagen	Parallel thick collagen bundles	Nodular/ whorled hyalinized collagen
Mechanical tension	Baseline dermal strain	↑ (edge of wound)	Nodular/whorled keloidal collagen; altered HA distribution (dermal HA ↓, epidermal HA ↑)
Clinical course	Flattens < 6 mo	Regresses ± therapy	Progressive; rare spontaneous regression; high recurrence after excision (45–100%)

Notes: Key molecular, cellular, mechanical, and clinical characteristics are contrasted across the three healing outcomes. *Footnote*: ↑ increase; ↑↑ substantial increase; ↑↑↑ marked increase (≥5-fold). Abbreviations are listed in the table header; only symbols used in this table are defined here.

a "keloid margin" zone rich in proliferating fibroblasts and immune cells at the interface with normal skin.[1,46] Transcriptomic analyses reveal that lesional and even non-lesional skin of keloid patients exhibit a heightened immune activation state, particularly a Th2-skewed cytokine milieu (high IL-4, IL-13) along with Th17 and Th1 signals.[1] This contrasts with normal scars where immune activity subsides in the remodeling phase. (2) TGF-β Signaling Intensity and Duration: Both hypertrophic scars and keloids have increased TGF-β1 levels relative to normal skin, but keloids may have a more sustained or amplified TGF-β/Smad signaling. Keloid fibroblasts display higher Smad2/3 phosphorylation and less sensitivity to the negative feedback by SMAD7. Additionally, keloid tissues often overexpress TGF-β1 and TGF-β2 (profibrotic isoforms) while having relatively lower TGF-β3 (an isoform associated with regenerative healing). Hypertrophic scars also have elevated TGF-β activity but to a lesser degree, and their fibroblasts can eventually re-enter quiescence as the scar matures. (3) Fibroblast Phenotypes: Fibroblasts in hypertrophic scars versus keloids are not identical. Keloid fibroblasts have been noted to proliferate more, migrate more, and resist apoptosis compared to those from hypertrophic scars.[42] They also produce different ratios of collagen types (keloids often have thick hyalinized collagen bundles, abundant type I collagen, and unique nodules of hyaline ECM in the dermis). A study found that keloid fibroblasts have a higher TβRI: TβRII ratio and can maintain activation with lower exogenous stimulus than hypertrophic scar fibroblasts.[47] Single-cell sequencing directly comparing keloid and hypertrophic scar from the same patient showed that mechano-responsive (YAP-activated) fibroblasts predominated in keloid, whereas hypertrophic scar had more fibroblasts in a resting or inflammatory state.[43] This suggests keloid fibroblasts are locked in an activated state by the stiff ECM and ongoing signals. (4) Role of Immune Cells: In hypertrophic scars, once the acute injury phase passes, immune cell numbers (eg macrophages, T cells) decrease significantly. But keloids show ongoing immune cell involvement. Notably, keloids have an increased infiltration of regulatory T cells (Tregs) and M2-polarized macrophages even in established lesions. Tregs and M2 macrophages are known to secrete TGF-β1 and IL-10, creating an immunosuppressive yet pro-fibrotic environment. By contrast, a normal resolving wound would see a balance between pro-inflammatory (M1) and anti-inflammatory signals that tips toward resolution. (5) Mechanical Tension: Hypertrophic scars typically form in areas of high skin tension (shoulders, neck, extensor surfaces) and may flatten if tension is relieved (for instance, via surgical excision and proper wound support).[42,48] Keloids are also promoted by tension, but even low-tension areas can suffer if other factors (genetic predisposition, chronic inflammation) exist. In keloids, the tissue stiffness becomes intrinsically high, which perpetuates mechanotransductive signaling (YAP/TAZ, FAK) driving further collagen

deposition. Pressure therapy can help hypertrophic scars presumably by reducing tensile forces, whereas keloids often require more aggressive therapy (surgery, radiation, etc) and still recur, indicating an internal drive beyond external tension.[42,49]

Immune Environment Differences: Normal wound healing involves a well-orchestrated handoff between innate and adaptive immune responses. Neutrophils and M1 macrophages dominate early, clearing debris and fighting infection, then M2 macrophages and specialized T cells (like Tregs) come in to resolve inflammation and aid in tissue repair.[1] In pathological fibrosis, this transition is altered. Keloids demonstrate a persistent Th2 bias (high IL-4, IL-13) and chronic activation of innate immune pathways even in unaffected skin of keloid patients.[1] There is simultaneous upregulation of Th17/IL-17 pathways and an increase in immunosuppressive elements (Tregs, IL-10).[1] This paradoxical mix suggests that keloid scars exist in a state of "smoldering" inflammation coupled with pro-fibrotic immune suppression – meaning, the immune system in keloids is actively producing fibrogenic cytokines but not effectively mounting a wound termination response. Hypertrophic scars, on the other hand, might have a more transient immune response – for instance, they may feature a strong early IL-6 and IL-8 burst that contributes to fibroblast activation, but over months, immune activity and vascularity wane, leaving a collagenous scar that can gradually soften. Clinically, hypertrophic scars often improve within 1–2 years (collagen becomes more organized and scar flattens), whereas keloids often do not without intervention.[1]

Mast Cells and Others: Mast cells are noteworthy in fibrosis differences. They are present in normal wound healing to some degree, releasing histamine and proteases that help remodel tissue and attract cells. However, keloids harbor an increased density of mast cells, and these mast cells release pro-fibrotic mediators such as tryptase and chymase in abundance.[1] Mast cell chymase in keloids can drive a local angiotensin II production (by converting angiotensin I), which in turn activates the renin–angiotensin system in fibroblasts leading to upregulation of TGF-β1, platelet-derived growth factor (PDGF), and other growth factors. This is not a typical feature of a normal resolving wound. In hypertrophic scars, mast cells are present and contribute to early angiogenesis and fibroblast recruitment, but their profibrotic influence is less pronounced than in keloids.

In summary, normal wound healing is self-limited and balanced by pro- and anti-fibrotic signals that eventually lead to scar resolution, whereas pathological fibrosis (hypertrophic scars, keloids) is marked by sustained TGF-β1 signaling, aberrant mechanotransduction, and a dysregulated immune milieu that fails to shut down the fibrotic program. Keloids represent the extreme of this spectrum, often requiring therapeutic intervention. Understanding these differences provides rationale for targeting specific pathways (eg TGF-β, IL-13, mechanotransduction, etc) to prevent or treat pathological scars.

Immune Modulation of Fibrosis: Cytokines and Cells

Fibrosis is increasingly recognized as an immunologically active process, where the interplay of cytokines and immune cells determines the fibrotic outcome.[1] Key immune contributors in cutaneous fibrosis include T helper cell subsets (Th1/Th2/Th17), regulatory T cells, macrophages of different polarization states, and mast cells. These cells communicate via cytokines such as interleukins (ILs) and growth factors, orchestrating the balance between regenerative healing and scarring. A concise overview of immune-cell contributions to cutaneous fibrosis – highlighting mediators, net effects, and coupling to the TGF-β1 axis – is provided in Table 3.

Th1 vs Th2 vs Th17 Responses

Th1 cells (characterized by IFN-γ production) generally counteract fibrosis. IFN-γ can directly inhibit collagen synthesis by fibroblasts and oppose TGF-β signaling. A shift away from Th1 towards Th2 has been correlated with fibrosis. In keloid patients, there is a notable Th2 predominance both in lesions and systemically.[1] Th2 cytokines IL-4 and IL-13 are elevated in keloid tissue and blood.[1] These cytokines promote alternative macrophage activation (M2) and directly stimulate fibroblast ECM production. IL-13 is a potent fibrogenic cytokine: it upregulates collagen I and III in fibroblasts and reduces matrix metalloproteinases, leading to matrix accumulation. Increased IL-4/IL-13 levels in keloids support the observation of M2 macrophage skewing and excessive collagen deposition. Therapies that tilt the balance back toward

Table 3 Immune-Cell Roles in Cutaneous Fibrosis

Immune Cell Subset	Key Mediators (Selected)	Net Effect on Fibrosis	Link to the TGF-β1 axis	Representative Human Evidence / Notes	Potential Therapeutic Levers (Examples)
Th1 (IFN-γ)	IFN-γ	Generally anti-fibrotic; antagonizes collagen synthesis and myofibroblast persistence	Inhibits TGF-β signaling; favors M1 polarization	Reduced IFN-γ responsiveness reported in keloids; historical intralesional IFN trials noted	Boost Th1 tone (eg, TLR7 agonist imiquimod post-excision; mixed results); monitor inflammation
Th2 (IL-4, IL-13)	IL-4, IL-13, periostin	Pro-fibrotic; drives fibroblast ECM production and M2 macrophage skewing	Amplifies TGF-β effects; converges on STAT6 programs	Elevated IL-4/IL-13 signatures in keloids; clinical responses to Th2-targeting reported	IL-4Rα blockade (dupilumab) in selected patients; combine with tension control
Th17 (IL-17A)	IL-17A, IL-6 (induced), CCL2 (induced)	Pro-inflammatory/ pro-fibrotic synergy with TGF-β1	Cooperates with TGF-β1 to induce IL-6/CCL2 in fibroblasts	Elevated IL-17A with active fibro-inflammatory loops in keloids	Target IL-17A or IL-6 signaling (context dependent; investigational for scars)
Regulatory T cells (Treg)	IL-10, TGF-β1	Context dependent: acute pro-healing; chronic pro-fibrotic via tolerance and fibroblast support	Provide TGF-β1/IL-10 that sustains a permissive milieu	Increased Tregs in keloids; co-culture shows TGF-β-dependent collagen upregulation	Modulate local TGF-β axis; avoid global Treg depletion; consider site-restricted approaches
Macrophage (M1)	IL-1β, TNF, ROS, MMPs	Acute inflammation; may limit fibrosis via matrix turnover if timely	Opposes sustained TGF-β signaling when transient	Lower proportion vs M2 in established keloids	Re-polarization strategies; time-limited pro-inflammatory cues
Macrophage (M2)	TGF-β1, IL-10, PDGF, VEGF	Pro-fibrotic; promotes myofibroblast activation and angiogenesis	Direct source of TGF-β1; reinforces fibroblast activation	Dominant in keloids; "keloid-associated macrophage" states described	CCR2 axis inhibition; Th2 dampening; macrophage re-programming
Mast cells	Tryptase, chymase, histamine	Pro-fibrotic; promotes fibroblast activation and ECM remodeling	Chymase can activate latent TGF-β; augments local RAAS→TGF-β	Increased density/activity in keloids; enzymatic links to TGF-β activation	Stabilizers (tranilast); chymase inhibitors; adjunct antihistamines
Langerhans cells (LC; Langerin$^+$)	TGF-β1, IL-10, IDO; keratinocyte αvβ6/β8 gate	Immune-tone setter; miswiring may favor tolerance-biased fibrosis	Require tonic TGF-β1; keratinocyte αvβ6/β8 activate LC-derived latent TGF-β1	LC residency and migration tightly tied to epidermal TGF-β gate; DC clusters at scar margins noted	Modulate αvβ6/β8 activity; UVA1 to reset LC dynamics; DC-centric sampling in human scars
Dermal cDC1 (Langerin$^+$)	XCR1, IL-12 (context)	Potential Th1-bias; human fibrosis roles emerging	Spatial proximity to profibrotic niches; may intersect with TGF-β-permissive states	Human single-cell/spatial hints of DC modules; heterogeneity unresolved	DC-targeted immune modulation; prioritize DC-enriched, spatially resolved studies
Natural killer (NK) cells	Perforin, granzymes	Anti-fibrotic via cytotoxic clearance of activated fibroblasts	TGF-β suppresses NK cytotoxicity	Reduced cytotoxic signatures reported in keloids	Enhance NK activity; relieve TGF-β-mediated suppression locally

Abbreviations: ECM, extracellular matrix; IDO, indoleamine 2,3-dioxygenase; LC, Langerhans cell; MMP, matrix metalloproteinase; NK, natural killer; RAAS, renin–angiotensin–aldosterone system; STAT6, signal transducer and activator of transcription 6; TLR7, Toll-like receptor 7; Treg, regulatory T cell. Evidence lines are synthesized from the manuscript's cited studies and DC-centric framing in the revision plan.

Th1 (for instance, interferon γ injections were historically tried in keloids with some success in flattening scars) aim to counter this Th2 dominance.

Th17 cells, defined by IL-17A production, have a more nuanced role in fibrosis. IL-17 can be pro-fibrotic by inducing fibroblast proliferation and cytokine secretion (such as IL-6 and TGF-β) but can also sustain inflammation that might lead to scar breakdown in some contexts. In keloids, IL-17 levels are elevated alongside IL-6, suggesting an active Th17 axis. IL-17A synergizes with TGF-β1 in driving fibrosis: as noted earlier, in keloid fibroblasts IL-17A + TGF-β greatly increases IL-6 and CCL2 output.[38] This results in recruitment of monocytes/macrophages and further TGF-β release, fueling fibrosis. Meanwhile, IL-6 can reinforce Th17 differentiation in a feed-forward loop. Therefore, Th17 contributes to the chronic inflammation+ fibrosis cycle in keloids. Blocking IL-17A has shown antifibrotic effects in some models (eg pulmonary fibrosis), and it might mitigate the inflammatory component of keloids, though this strategy remains experimental for skin scars. Notably, Th22 cells (which produce IL-22, often alongside Th17) have also been implicated in keloids, but their role is less clear; IL-22 can be pro-wound healing but also pro-inflammatory. Keloid transcriptomes indicate some Th17/Th22 upregulation,[1] meriting further research.

Th1 responses, in contrast, may protect against excessive fibrosis. IFN-γ downregulates TGF-β and collagen gene transcription. Patients with intrinsically higher Th1 activity might scar less. However, in pathological scars, Th1 signals like IFN-γ and IL-12 are relatively reduced or present at the wrong time. For example, keloid T cells produce less IFN-γ (and more IL-10) upon stimulation than normal skin T cells.[50] Augmenting Th1 or suppressing Th2/Th17 is, therefore, a considered approach (eg, topical imiquimod, a TLR7 agonist that induces IFN, has been used post-excision to prevent keloid recurrence, with mixed results).

Regulatory T Cells (Tregs)

Tregs ($FoxP3^+$ $CD25^+$ regulatory T cells) accumulate in skin wounds within days after injury and play a beneficial role in normal healing by resolving inflammation and aiding tissue regeneration.[50] They secrete anti-inflammatory cytokines like IL-10 and can produce amphiregulin (AREG) to stimulate keratinocyte growth and wound re-epithelialization.[50] In normal wounds, Treg depletion delays healing and increases scarring due to unchecked inflammation.[50] Thus, Tregs are generally seen as fibrosis-limiting in the acute phase – they tamp down pro-inflammatory macrophages and IFN-γ production, preventing excessive tissue damage.[50] Paradoxically, in chronic fibrosis, Tregs can contribute to the fibrotic milieu. Keloid lesions have significantly higher Treg counts than normal scars. These Tregs in keloids are highly activated ($CTLA\text{-}4^+$, $ICOS^+$) and produce TGF-β1 and IL-10 abundantly. Their presence is associated with enhanced collagen synthesis: co-culture experiments show Tregs can directly stimulate collagen production by keloid fibroblasts, an effect dependent on TGF-β1.[38] Moreover, IL-10 from Tregs, while anti-inflammatory, may reduce antifibrotic M1 macrophage activity and thereby skew towards fibrosis-promoting M2 macrophages. In muscle injury models, Tregs promote regeneration by converting M1 to M2 macrophages; in scars, a similar conversion might inadvertently support fibrosis (since M2 drive fibrogenesis).

Thus, Tregs have a "dual role": early on they prevent exuberant inflammation and limit scar size, but if they remain elevated chronically, they can create an immunosuppressive environment that allows fibrosis to proceed unchecked. In hypertrophic scars, Treg numbers eventually recede as inflammation resolves, whereas keloids show persistently high Treg signatures. Some have suggested keloids may represent an over-exuberant wound healing response where Tregs and others halt the inflammatory phase but then fail to transition to a regenerative remodeling phase, instead continuously stimulating fibroblasts via TGF-β1. Therapeutically, modulating Tregs is tricky – completely removing them can worsen inflammation, but tempering their profibrotic actions (eg blocking TGF-β1 or IL-10 signaling specifically in the scar) could be beneficial.

Macrophage Phenotypes (M1 vs M2)

Macrophages are central coordinators of wound healing. Classically activated M1 macrophages (induced by IFN-γ, TNF, LPS) dominate in early wounds to clear bacteria and secrete inflammatory cytokines (IL-1β, IL-6, TNF-α) that also activate fibroblasts and endothelial cells. Alternatively, activated M2 macrophages (induced by IL-4, IL-13, IL-10) take over later to promote tissue repair – they secrete growth factors like TGF-β1, VEGF, PDGF, and enzymatically remodel

the matrix.[51,52] In normal wound healing, a timely switch from M1 to M2 is observed once debris is cleared.[51] Dysregulation of this transition is implicated in fibrosis. Keloids and hypertrophic scars are heavily infiltrated by macrophages, predominantly of the M2 phenotype in established lesions.[53–57] M2 macrophages are "protogenetic" in fibrosis: they encourage fibroblast proliferation and myofibroblast differentiation via TGF-β1 and other mediators.[51,58] In keloids, studies have found M2 markers (CD163, CD206) to be significantly elevated, with M2 cells outnumbering M1 cells in tissue.[53–57] This correlates with local Th2 cytokines that drive M2 polarization. M2 macrophages, in turn, produce high levels of TGF-β1 – enough that depleting or re-polarizing macrophages can markedly reduce fibrosis in models. M2 macrophages also crosstalk with Tregs: they can induce $FOXP3^+$ Tregs from conventional T cells, and Tregs secrete IL-10 that favors M2 maintenance. Thus, a positive feedback loop between Tregs and M2 macs can establish a pro-fibrotic, anti-inflammatory niche within scars.[59–71]

By contrast, M1 macrophages produce pro-inflammatory cytokines and reactive oxygen species that, if persistent, could cause tissue damage but also help limit fibrosis by upregulating collagen-degrading enzymes and antagonizing TGF-β effects. Some evidence suggests that therapies which maintain a longer presence of M1-like activity (for example, topical diphenylcyclopropenone in keloids causing an immunostimulatory reaction) can reduce scar bulk, presumably by breaking down collagen. However, chronic M1 inflammation can also cause repetitive injury and perpetuate repair cycles – a double-edged sword. The key seems to be a properly timed M1→M2 transition and then resolution. In hypertrophic scars, this transition might occur but then slowly resolve, whereas in keloids, an M2 dominance persists pathologically.[53–57] Interestingly, recent single-cell analysis identified a unique "keloid-associated macrophage" phenotype with a gene expression profile suggesting interactions with fibroblasts and promotion of their proliferation.[72] These macrophages express high levels of fibronectin and galectin-3, which can activate fibroblasts, and they likely represent the M2-skewed population in keloids.

Targeting macrophages in fibrosis is a promising angle: strategies include inhibiting their recruitment (eg blocking CCL2–CCR2 signaling, which has reduced fibrosis in some trials), or repolarizing them from M2 to a more inflammatory but fibrosis-resolving state. For instance, CD40 agonists can push macrophages toward a pro-inflammatory phenotype that might digest scar tissue. Conversely, overly abundant M1 signals might need tempering to prevent chronic wounds. A nuanced approach is needed, and ongoing research aims to identify surface markers (like folate receptor-β, CD301b on M2 macs) to specifically target pro-fibrotic macrophages for depletion or modulation in scars.[53–57]

Mast Cells and Other Innate Cells

Mast cells are long-lived resident granulocytes loaded with pro-inflammatory and pro-fibrotic compounds (histamine, heparin, proteases such as tryptase and chymase). They are normally involved in wound healing by increasing vascular permeability, recruiting other leukocytes, and even assisting re-epithelialization and angiogenesis.[59,62–64,67,73–79] However, their role in fibrosis is significant: mast cell numbers correlate with scar severity, and they are particularly numerous in keloids.[2,3,58,60–66,68,70,71,80–114] Mast cells produce TGF-β1, basic fibroblast growth factor (bFGF), IL-4, and IL-13, all of which can directly stimulate fibroblasts. Moreover, mast cell chymase can cleave latent TGF-β, activating it similarly to integrins do.[115] Chymase also cleaves angiotensin I to angiotensin II, triggering local renin–angiotensin system signaling that upregulates TGF-β1 and other growth factors in fibroblasts. In keloids, chymase and tryptase activity are elevated; in fact, one study found that topical tranilast (a mast cell stabilizer) and a transdermal chymase inhibitor reduced hypertrophic scar formation, highlighting mast cells as a therapeutic target.[116] Clinically, intralesional antihistamines or cromolyn to stabilize mast cells have shown modest improvements in scar pliability, supporting their involvement.

Other innate immune cells like γδ T cells in the epidermis produce IL-17 and IL-22 early after injury and might influence fibrosis (though their role is less studied in humans). Neutrophils are acute responders that typically leave after a few days; prolonged neutrophil presence (seen in chronic non-healing wounds) can exacerbate tissue damage and indirectly fibrosis via neutrophil extracellular traps and ROS, but in normal scars neutrophils are not a major component beyond the first week. Natural killer (NK) cells can limit fibrosis by targeting activated fibroblasts for apoptosis (NK cells become more active when fibroblasts downregulate MHC in a TGF-β-rich environment). Some keloid studies noted

reduced NK cell cytotoxic gene signatures, suggesting keloid fibroblasts might escape NK surveillance.[117] This is an emerging area – boosting NK activity might help clear fibrotic cells.

Finally, dendritic cells themselves (beyond LCs) shape the immune context of fibrosis. In keloids, increased DC markers (eg CD11c, CD209) have been observed. These could include inflammatory monocyte-derived DCs that present debris from tissue damage to T cells, potentially skewing the T cell responses. DCs also produce cytokines: for instance, DC-derived IL-10 in the skin can increase TGF-β1 and collagen expression via induction of Tregs.[4,59,62–64,73–79,118] It has been postulated that Langerhans cells or dermal DCs in keloids may produce tolerogenic signals (like IL-10, IDO) that favor fibrotic healing. Moreover, DCs interact with mast cells and macrophages; an intricate interplay exists where DCs can spur mast cell degranulation and vice versa. Overall, immune cells create a cytokine soup in fibrotic skin that includes high TGF-β1, IL-6, IL-10, IL-13, IL-17, TNF-α, and low antifibrotic mediators (eg IFN-γ, IL-34). Therapeutic strategies are being developed to modulate these immune inputs – for example, IL-6 blockade (using tocilizumab) has shown some success in systemic sclerosis and could be tried in keloids to break the IL-6/Th17 feedback loop, or IL-13/IL-4 blockade (dupilumab) might reduce type 2 skewing in scars.

In the next two sections, we first outline DC–ECM/Mechanosensing/YAP-TAZ interfaces and then review core mechanobiology, framing how DC-tuned TGF-β1 availability couples to fibroblast Smad2/3–YAP/TAZ programs in stiff, inflamed dermis.

Langerin$^+$ DC and ECM/Mechanosensing/YAP-TAZ: Evidence and Testable Hypotheses

Direct demonstrations of YAP/TAZ control in Langerin$^+$ DCs within human scars are limited; however, several converging observations motivate testable models. First, LC residency depends on tonic TGF-β1 that is activated by keratinocyte αvβ6/αvβ8 and perturbing this axis triggers LC migration – linking DC behavior to epithelial-ECM mechanics and integrin signaling. Second, DCs express integrins and operate on actin-dependent motility programs, suggesting potential sensitivity to FAK–RhoA inputs that also gate YAP/TAZ in stromal cells. We, therefore, hypothesize a two-node coupling: (1) epithelial stiffness and αvβ6-mediated force release of TGF-β1 tune LC activation/migration; (2) in stiff, inflamed dermis, DCs experience cytoskeletal tension that may bias antigen presentation and cytokine output toward IL-10/TGF-β-skewed programs that reinforce fibrosis. We outline experimental handles – substrate stiffness titration for LC-like cells, integrin/FAK blockade, and single-cell multiome readouts – to resolve if YAP/TAZ-target gene sets track DC functional states in scars. This section explicitly delineates what is known versus hypothesized, preventing over-claims while focusing the field on measurable endpoints.

Mechanobiology of Fibrosis: ECM Stiffness, Integrins, and YAP/TAZ

Interface to DCs. LC residency and activation depend on tonic, epithelial integrin-activated TGF-β1, linking DC behavior to epidermal mechanics. In stiff dermis, integrin/FAK–RhoA cues likely bias DC cytokine programs toward TGF-β1-permissive or tolerogenic states. Framed by this DC interface, the following mechanobiology section distills the stiffness–integrin–YAP/TAZ circuit that couples epithelial control of TGF-β1 to fibroblast persistence. As illustrated in Figure 1, tissue mechanics are integral to fibrosis. As a scar forms, the ECM becomes enriched in collagens and cross-linking enzymes, increasing tissue stiffness. This stiffness not only is a result of fibrosis but also a driver of further fibrotic signaling. Fibroblasts, as mechanosensitive cells, sense the rigidity of their surroundings through integrin receptors and the actin cytoskeleton. In stiff environments, fibroblasts exhibit enhanced focal adhesion formation and activate downstream mechano-transducers like focal adhesion kinase (FAK) and talin/vinculin complexes.[119–124] These signals lead to nuclear localization of YAP/TAZ (as discussed) and increased resistance to apoptosis. Indeed, a hallmark of pathological scars is a feedback loop where increased matrix stiffness leads to increased myofibroblast activation, which produces more matrix and further increases stiffness.[125–128]

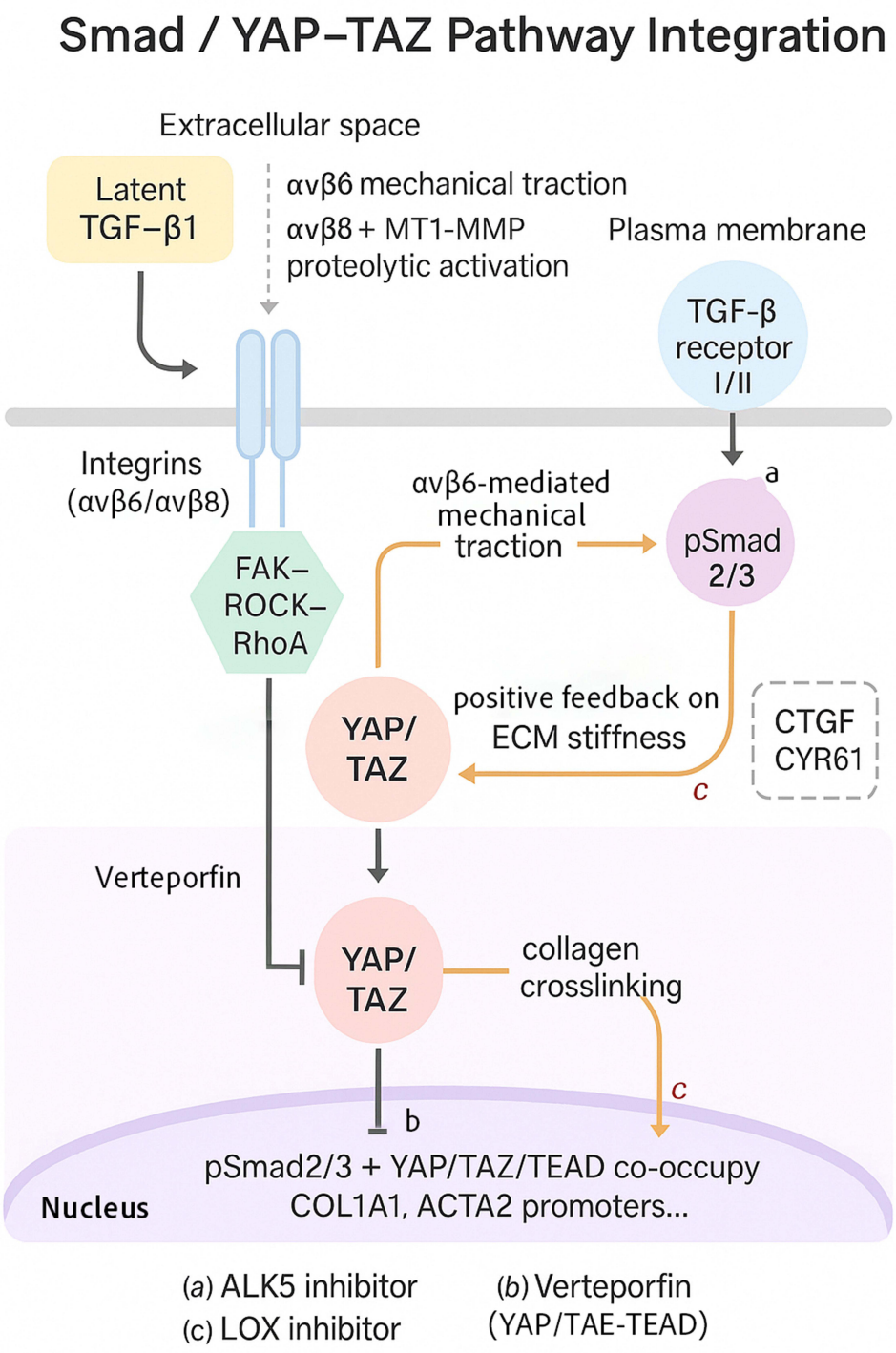

Figure 1 Integrated schematic of canonical TGF-β/Smad and mechanotransduction-driven YAP/TAZ signaling in dermal fibroblasts under the control of an epithelial αvβ6/αvβ8–TGF-β1 gate active TGF-β1 engages TβRI/II to phosphorylate Smad2/3 (purple pathway), while extracellular matrix (ECM) stiffness and integrin ligation activate FAK–RhoA–ROCK, resulting in dephosphorylated YAP/TAZ nuclear translocation (pink pathway). Nuclear Smad2/3 and YAP/TAZ cooperate with TEAD to up-regulate profibrotic genes (eg, COL1A1, ACTA2, CTGF) and suppress SMAD7, establishing a positive feedback loop that further stiffens the ECM. Pharmacologic inhibitors targeting critical nodes – ALK5 inhibitor (**a**), verteporfin (**b**), and LOX inhibitor (**c**) – are indicated in red italics. Dashed grey lines represent mechanotransductive links; the Orange circular arrow depicts the feed-forward loop to ECM stiffness.

Abbreviations: ALK5i, ALK5 inhibitor; LOX, lysyl oxidase; α-SMA, α-smooth-muscle actin; ECM, extracellular matrix.

ECM Composition and Cross-Linking

The qualitative aspects of ECM matter. In hypertrophic scars and keloids, collagen fibers are thicker and more disorganized than in normal scars. The enzyme lysyl oxidase (LOX), which cross-links collagen fibers, is often upregulated, making the scar matrix insoluble and strong.[128] LOX-mediated cross-links enhance the tensile strength and stiffness of collagen bundles. High LOX levels have been noted in keloids, and LOX inhibition (eg with BAPN or beta-aminopropionitrile) in animal models reduced scar hypertrophy.[125,127,128] Targeting LOX or other cross-linkers (like TG2, lysyl oxidase-like proteins) is a strategy to soften scars and allow normal remodeling to catch up. Additionally, stiff ECM can sequester growth factors – TGF-β's latency complex (TGF-β–LAP–LTBP) is anchored to the ECM. A stiff matrix provides a solid anchor against which integrins (like αvβ6) on cells can pull to pry open the latency complex.[129–132] Non-proteolytic TGF-β activation requires such resistance; a floppy matrix would simply deform without releasing TGF-β, whereas a stiff matrix transmits force to the LAP, exposing TGF-β to its receptors.[130] Therefore, matrix stiffness amplifies TGF-β signaling by making latent TGF-β easier to activate – a self-reinforcing cycle.

Integrins as Mechanotransducers

Beyond αvβ6/β8's role in TGF-β activation, integrins (like α5β1, αvβ3, αvβ5) on fibroblasts sense and respond to matrix cues. When fibroblasts attach to a rigid substrate via integrins, cytoskeletal tension increases and signals like FAK and RhoA are upregulated, promoting stress fibre formation and nuclear shuttling of mechanosensors. In fibrosis, integrin signaling is often upregulated: eg, fibrotic fibroblasts can express higher levels of α5β1 (fibronectin receptor) and αvβ3, aiding their adhesion and force generation on the matrix.[25] Integrins also crosstalk with growth factor receptors. For instance, integrin engagement can cluster TGF-β receptors in lipid rafts or bring kinases that phosphorylate Smads independently, enhancing the fibrotic response.[25] Notably, integrin αvβ3 can recruit MMP2/9 to focal adhesions, facilitating local matrix remodeling and potentially TGF-β activation in a protease-dependent manner.[30–32]

YAP/TAZ as mentioned are key in mechanotransduction. In a stiff scar, YAP/TAZ remain nuclear and co-drive gene expression with TEAD transcription factors, inducing genes that promote cell survival (eg BCL-XL), proliferation, and matrix production (eg CTGF, CYR61). YAP/TAZ also interact with Smad transcriptional complexes on promoters of genes like COL1A1 and ACTA2 (α-SMA), boosting their expression when matrix stiffness and TGF-β are both present.[39] Conversely, if matrix tension is released (say by surgical scar revision with low-tension closures or via silicone sheeting those hydrates and softens the scar), fibroblasts experience less mechanical stress, YAP/TAZ get phosphorylated and sequestered in cytoplasm, and Smad7 may increase, collectively reducing collagen production.[133] This underpins some clinical practices: eg, pressure garments for burns scars not only reduce physical bulk but also alter cellular signaling by constant compression (which can paradoxically reduce local oxygen tension and TGF-β or possibly induce a form of mechanotolerance in fibroblasts).

Hair Follicle and Niche Mechanics

One intriguing aspect of skin is that certain niches (like the hair follicle bulge) are "immune privileged" and somewhat protected from scarring. Langerhans cells, for example, are excluded from the follicular bulge by chemokine CCL8/CCR8 signals.[18,19,134–136] That region is also where skin appendages regenerate. Keloids often do not form in areas with hair (scalp rarely forms keloids except on margins) or they spare hair follicles, suggesting something about that microenvironment (softer, or different ECM composition) resists fibrosis. Mechanically, follicles can provide stress relief points in skin. Patterns of scarring sometimes correlate with tension lines (Langer's lines) and the distribution of appendages.

Crosstalk with Immune Cells

Mechanical factors also influence immune cells. Dendritic cells and macrophages respond to stiffness; macrophages can become more pro-fibrotic (M2) on stiffer substrates, as noted in some studies. DC migration is also guided by matrix density – a dense matrix might trap DCs in the tissue longer, prolonging their interaction with fibroblasts and T cells. Furthermore, the release of fibronectin extra domain A (Fn-EDA) in stiff matrices acts as a danger signal that can activate Toll-like receptor 4 on immune cells, possibly contributing to chronic inflammation in scars.[137–139] On the therapeutic

front, a novel approach mentioned in a study involves using an Fn-EDA targeted antibody to deliver anti-TGF-β therapy specifically to fibrotic tissue,[137–139] leveraging the fact that Fn-EDA is enriched in stiff, fibrotic ECM. This kind of synergy between mechanical targeting and biochemical therapy exemplifies the future of anti-fibrotic strategies.

In summary, mechanobiology is inseparable from the cellular and cytokine-driven aspects of fibrosis. ECM stiffness and integrin/YAP signaling form a positive feedback loop with TGF-β1. Breaking this loop – by softening the ECM, blocking integrin signals, or inhibiting YAP/TAZ – is a prime goal to prevent a transient scar from becoming a permanent fibrosis. This feed-forward loop is schematized in Figure 1 to highlight the parallel biochemical (TGF-β1) and mechanical (YAP/TAZ) drivers of myofibroblast persistence. Current research is actively exploring YAP/TAZ inhibitors (eg verteporfin repurposing) and integrin antagonists in fibrotic diseases.[36] With advanced biomaterials, we can also attempt to modify the mechanical microenvironment of wounds (for example, auxetic meshes that distribute tension) to encourage regenerative healing.

Emerging Technologies to Dissect Fibrosis

Understanding the complex cellular ecosystem of fibrosis has been greatly aided by new technologies. Single-cell multi-omics and spatial transcriptomics now allow researchers to identify and locate every cell type and active pathway in scar tissue, enabling a high-resolution map of fibrogenesis. Advanced imaging techniques complement this by visualizing cell behavior and matrix organization in situ and even in vivo.

Methodological Caveats

Much of the mechanistic insight into DC–fibroblast–TGF-β1 crosstalk derives from murine models and reductionist in-vitro systems. Mouse DC ontogeny and epidermal mechanics differ from human skin, and in-vitro substrate stiffness rarely recapitulates the viscoelastic, anisotropic properties of scars. Sampling bias (lesional edge vs core) and batch effects can complicate single-cell/spatial analyses. Future work should prioritize human, longitudinal, spatially resolved datasets with harmonized pipelines and functional readouts (eg, DC cytokine output under controlled ECM stiffness) to validate DC-centric hypotheses in clinical tissue.

Single-Cell and Multi-Omics Analyses

Traditional bulk tissue analysis masked the contributions of rare cell subsets (like Langerin$^+$ DCs or specific fibroblast subpopulations) in fibrosis. Single-cell RNA sequencing (scRNA-seq) overcomes this by profiling gene expression in individual cells. Recent scRNA-seq studies on human scars have unveiled previously unappreciated cellular heterogeneity. For example, a single-cell study comparing keloid and hypertrophic scar from the same patient identified at least 8 distinct fibroblast subsets, with a prominent "mechanoresponsive" subset in keloids enriched for genes like *CYR61, CTGF*, and *ACTA2* (indicative of active YAP/TAZ and myofibroblast phenotype). In contrast, hypertrophic scar fibroblasts had higher representation of a "inflammatory" subset expressing IL6 and chemokines, and a "resolving" subset expressing MMPs. The same study showed endothelial cells and keratinocytes in keloids displayed partial mesenchymal gene expression, suggesting ongoing epithelial–mesenchymal transition (EMT) and endothelial–mesenchymal transition (EndMT) driven by TGF-β.[47,140–153] These transitions contribute to the pool of activated fibroblast-like cells in scars. Thus, scRNA-seq provides a comprehensive census of cells and their states, helping pinpoint which cell interactions (eg macrophage-fibroblast or DC-T cell) are most critical.

Multi-omics approaches take this further. Single-cell ATAC-seq (assaying chromatin accessibility) can be done alongside scRNA-seq (so-called multiome sequencing) to link transcriptional profiles with epigenetic states. A pioneering study by Foster et al used integrated single-cell transcriptomics and epigenomics with spatial transcriptomics in a mouse wound model.[154] They tracked fibroblast lineage dynamics over time and space, identifying gene regulatory networks that govern fibroblast migration, proliferation, and differentiation during healing.[154] By inferring pseudotime trajectories, they could categorize fibroblasts into those destined to become myofibroblasts versus those regressing. Such information is invaluable – for instance, they found a subset of Engrailed-1 lineage fibroblasts in dorsal skin are predisposed to become scar-forming myofibroblasts. Single-cell RNA-seq has also highlighted immune changes: one study found a distinct macrophage subset in keloids (with high expression of fibrosis-promoting genes) that was not

present in normal scars.[54,70,72,155–157] Another identified inflammatory Langerhans cells arising in wounds under certain cytokine conditions.[134]

Spatial Transcriptomics

Spatial Transcriptomics adds another dimension by preserving spatial context. Techniques like the 10x Genomics Visium or Nanostring GeoMX allow gene expression to be measured in tissue sections while maintaining (x, y) coordinates. This has been applied to human wounds and scars to show localization of signals – eg, spatial mapping in wounds revealed TGF-β activation is highest at the wound edge where keratinocytes and dermal cells interact, whereas pro-inflammatory genes cluster in the wound bed early on.[158,159] In keloids, spatial transcriptomics has demonstrated that the actively growing keloid margin has a different molecular signature (rich in COL1A1, POSTN, IGF1) compared to the central collagenous core.[46] It also confirmed immune cells like T cells and macrophages densely populate the invasive edge of keloids, supporting clinical observations that keloids extend by "sending out" inflammatory tentacles. Coupling spatial data with histology, one can align high TGF-β gene signature spots with areas of myofibroblast staining or align IL-17/IL-6 signature with areas of neutrophils, etc, providing insight into cell–cell interactions.

Emerging methods like CODEX (CO-Detection by indEXing) or imaging mass cytometry enable >40 protein markers to be imaged simultaneously in tissue, yielding spatial maps of cell phenotypes and their neighborhoods. Applying these to scars, one can visualize Langerin$^+$ cells relative to TGF-β producing cells or see how Tregs and myofibroblasts colocalize. For example, a recent highly multiplexed imaging of keloids found that FoxP3$^+$ Tregs physically cluster with SMA$^+$ myofibroblasts and CD163$^+$ M2 macrophages, forming a "fibrotic niche", whereas CD8$^+$ T cells and CD68$^+$ M1 macrophages were more scattered at the periphery.

These advanced tools have not only descriptive power but also predictive power. They can identify key regulatory molecules (via computational inference of cell–cell communication networks). In keloids, single-cell analyses pointed to the CCL2-CCR2 axis (fibroblasts -> macrophages) and IL-6-IL-6R (fibroblasts -> Th17 cells) as dominant interactions. This guides therapeutic hypothesis generation (eg, CCR2 inhibitor or IL-6 blockade in keloids). Moreover, single-cell data can reveal markers of pathological cells – for instance, HSP90AA1 was found upregulated in keloid myofibroblasts, hinting that HSP90 inhibitors (which are anti-fibrotic in IPF models) might work for keloids.[160,161]

DCs in Single-Cell and Spatial Atlases of Human Scars: Evidence and Gaps

Human single-cell studies of keloids and hypertrophic scars consistently reveal rich cellular heterogeneity with discrete fibroblast states and an immune microenvironment that includes dendritic-cell (DC)–annotated clusters, albeit at low frequency due to limited sampling and dropout.[43,54,140,143] Across datasets, antigen-presenting clusters bearing DC/Langerhans-cell markers (eg, CD207) or cDC1-associated signatures (eg, XCR1/IRF8/BATF3) can be detected but are often under-resolved, underscoring the need for DC-enriched acquisition and targeted re-annotation.[43,54,143,162] Notably, single-cell maps situate these DC-like clusters within fibro-inflammatory neighborhoods where TGF-β and mechanosensitive fibroblast programs are high, aligning with a model in which DC positioning and immune tone couple to profibrotic niches.[43,46]

Spatial methods complement these findings by preserving tissue context. Spatial transcriptomics and high-plex imaging show that the keloid margin harbors concentrated immune and matrix-remodeling signals distinct from the collagen-dense core, with up-regulated COL1A1/POSTN/IGF axis and immune–stromal crosstalk that includes predicted CCL2–CCR2 and IL-6–IL-6R interactions.[46,154,158,159] In keloids, multi-antigen imaging further identifies inflammatory DC populations alongside ADAM17 and neprilysin as potential effectors within the invasive front, offering DC-proximal nodes for perturbation.[163] Together, these human maps are consistent with a DC-permissive, TGF-β-rich milieu at the expanding edge of scars, where mechanotransduction and immune polarization converge.[43,46,154,159]

Limitations & gaps: DCs are rare in scar tissue and often fall below scRNA-seq detection thresholds; marker overlap among DC subsets (LCs vs cDC1 vs monocyte-derived DCs) complicates naive clustering.[43,54,162] We advocate DC-enriched sampling (eg, pre-sort CD207$^+$ or XCR1$^+$ cells), multiome profiling to link chromatin accessibility with transcriptional state, and spatial proteogenomics to localize DC ligands/receptors to fibroblast Smad2/3–YAP/TAZ programs in human scars. Cross-species integration remains informative but mouse↔human mapping of DC subsets is

incomplete; causal links will require DC-targeted perturbations coupled to fibroblast-state readouts in human tissue or ex vivo models.[43,54,154,158,159,162]

Imaging and Intravital Microscopy

Visualizing fibrosis and immune cell dynamics in real time has been achieved with advanced imaging. Second harmonic generation (SHG) microscopy allows label-free imaging of collagen fibers; it has been used to quantitatively compare scar collagen organization. Hypertrophic scars show intense SHG signal with wavy, parallel fibers, whereas normal skin has weaker SHG with basketweave fibers. SHG can monitor the effect of treatments (eg, after laser therapy, a scar's SHG intensity might drop as collagen is partially ablated).

For immune cells, intravital two-photon microscopy in mouse models has provided dramatic insights. In experimental wound models, intravital imaging showed that dermal dendritic cells swarm into wound edges and interact with migrating keratinocytes, forming a cellular sheet that expedites re-epithelialization.[164] Depleting DCs impaired this process, as seen in corneal wound intravital studies where DC absence led to slower epithelial closure.[164] In skin, intravital multiphoton imaging has visualized how macrophages clear apoptotic cells in wounds and how neutrophils extravasate and form fibrous "NETs" (neutrophil extracellular traps) in injured dermis.[165] The dynamic behavior of LCs in response to injury has also been captured: upon a skin perturbation, LCs reduce their dendritic processes and start migrating out of the epidermis within hours. Such imaging also confirmed that UV radiation triggers LC migration by downregulating keratinocyte integrins (hence reducing active TGF-β, which normally holds LCs in place)[18,162,166–173] – an example of tying together earlier mechanistic findings with live observation.

On the fibrosis front, intravital microscopy in hypertrophic scar models (like the mouse ear model of mechanical load-induced fibrosis) has shown that myofibroblasts form persistent contractile units and make long-lived contacts with fibrous matrix, tugging and realigning collagen over days. It also showed that blood vessels in scars are abnormal – tortuous and dilated – and that perivascular macrophages patrol these vessels extensively, possibly contributing to persistent inflammation. Intravital imaging of immune cells in scars is technically challenging in humans, but there are efforts using confocal reflectance microscopy to visualize immune cell clusters in keloids in vivo.

High-resolution immunofluorescence on fixed tissues remains a mainstay to confirm the presence and location of various cells and molecules. For example, multi-color staining has visualized Langerin$^+$ cells at the margins of scars, often near T cells and fibroblasts, suggesting possible immunological synapses that could influence fibrosis. Confocal microscopy of keloid sections double-stained for TGF-β and CD207 (Langerin) hinted that LCs in keloids might produce TGF-β (as some Langerin$^+$ cells co-express latency-associated peptide), although more definitive analysis is needed. Also, electron microscopy historically documented the degranulation of mast cells next to fibroblasts in hypertrophic scars, indicating direct cell-to-cell influence.

In sum, advanced omics and imaging technologies have revolutionized our understanding of cutaneous fibrosis. They have validated many concepts (eg the importance of Th2/M2 environment, the existence of fibroblast subsets, etc) and uncovered new ones (like novel DC and macrophage roles, or EMT in keloids). As these tools become more integrated (eg aligning spatial transcriptomic data with live imaging), we will move closer to a systems-level model of fibrosis that can predict how altering one element (say, blocking TGF-β or depleting LCs) will ripple through the system. This knowledge is directly feeding into therapeutic development.

Therapeutic Strategies Targeting Langerin$^+$ Cells and the TGF-β1 Axis

Findings from DC-aware single-cell/spatial maps inform target selection (eg, CCR2, IL-6, ADAM17) and stratification for cutaneous fibrosis. Treating cutaneous fibrosis, especially keloids, is notoriously difficult – current options like surgery, corticosteroids, silicone gels, and radiation often yield incomplete success or recurrences. A growing strategy is to target the molecular pathways underlying fibrosis, specifically the TGF-β1 axis and immune cell contributions. Here, we highlight therapies in preclinical or clinical stages that aim either to modulate Langerin$^+$ DCs or to interrupt TGF-β1-driven fibrogenesis (or both). Mechanism-based therapeutic options are compared by target, evidence level, adverse effects, and translation challenges in Table 4.

Table 4 Comparative Summary of Mechanism-Based Therapies

Strategy / Example Agent	Primary Target / Node	Evidence Level (Cutaneous Context unless Specified)	Typical Delivery	Key Adverse Effects / Cautions	Translation Challenges / Notes
αvβ6/αvβ1 integrin inhibition (eg, bexotegrast; αvβ6 mAb class)	Epithelial activation of latent TGF-β (integrin-mediated)	Clinical signal in IPF (Phase 2); preclinical rationale for skin	Oral (bexotegrast); potential local/ peri-wound injection	Class-specific safety and epithelial homeostasis considerations	Define local dosing for scars; demonstrate wound-phase timing and benefit in humans
Pan-TGF-β neutralizing antibody (fresolimumab)	TGF-β ligand (β1/β2/ β3)	Clinical biomarker/ symptom improvement in systemic sclerosis; translational for scars	Intralesional (proposed) or systemic	Potential impaired immune regulation and wound healing with systemic use	Localize delivery to minimize systemic effects; patient selection
ALK5 (TGF-βRI) kinase inhibitors (eg, SD-208 class)	Receptor kinase → Smad2/3	Preclinical anti-fibrotic activity; topical/ intradermal feasible	Topical gel or intradermal	Off-target kinase effects at systemic exposure	Skin-restricted formulations; specificity vs ALK4/7
YAP/TAZ pathway inhibition (verteporfin repurposing)	YAP/TAZ–TEAD transcriptional complex	Preclinical across tissues; mechanistically synergizes with TGF-β blockade	Intralesional/ topical candidate	Drug-specific: photosensitivity considerations	Targeted delivery to fibroblast-rich niches; monitor matrix remodeling
LOX inhibition (eg, BAPN; pan-LOX small molecules)	Collagen cross-linking → matrix stiffness	Robust preclinical anti-stiffening; limited clinical cutaneous data	Systemic or topical	Cross-linking inhibition may weaken tissues if systemic/prolonged	Short-course, local administration during remodeling window
IL-4/IL-13 blockade (dupilumab)	IL-4Rα (Th2 axis)	Case-level keloid responses; strong mechanistic rationale	Systemic	Known class AEs (eg, conjunctivitis); cost	Off-label use; define responders (Th2-high scars)
IL-6 blockade (tocilizumab)	IL-6R (fibro-inflammatory loop)	Clinical softening in systemic sclerosis; keloid rationale from IL-6/Th17 loops	Systemic	Infection risk; lab monitoring	Indication fit for scars; combine with local modalities
CCR2 axis antagonism (monocyte recruitment)	CCL2–CCR2	Supported by single-cell/ spatial interaction analyses; early trials in other fibroses	Systemic or local	Immune modulation risks	Pathway redundancy; biomarker-guided selection
UVA1 phototherapy	Photobiologic down-tuning of TGF-β; fibroblast apoptosis; LC depletion	Clinical reports of keloid/HS softening	Device-based (dermal-penetrant UVA1)	Pigmentation changes; cumulative dose	Access/logistics; protocol standardization
Laser + intralesional 5-FU (± corticosteroid)	Ablation/vascular effects + anti-proliferative	Clinical practice with meta-analytic support	Procedural (PDL/ CO_2) + injection	Ulceration, PIH; operator dependent	Optimize sequencing; consider drug-device combinations

(*Continued*)

Table 4 (Continued).

Strategy / Example Agent	Primary Target / Node	Evidence Level (Cutaneous Context unless Specified)	Typical Delivery	Key Adverse Effects / Cautions	Translation Challenges / Notes
Low-tension closure / pressure therapy	Mechanotransduction offloading (FAK/ RhoA→YAP)	Strong clinical logic for HS; beneficial in recurrence prevention	Surgical technique; garments	Discomfort/ adherence	Standardize tension metrics; combine with molecular agents
Mast-cell targeting (tranilast; chymase inhibitors)	Degranulation; chymase-mediated TGF-β activation	Small clinical/ experimental signals	Oral/topical	Agent-specific; monitor tolerability	Regulatory path; ideal combinations with anti-TGF-β
Pirfenidone (topical)	TGF-β synthesis / fibroblast programs	Controlled trial signal in pediatric burn scars	Topical gel	Local irritation (generally mild)	Formulation optimization; adult data
Nintedanib (systemic)	PDGF/VEGF/FGF receptor signaling	In vitro and case-level scar improvement reports	Systemic	GI AEs (class); lab monitoring	Systemic risk–benefit vs local need; off-label status

Abbreviations: AE, adverse event; ALK5, activin receptor-like kinase-5 (TGF-β type I receptor); CO_2, fractional carbon dioxide laser; FAK, focal adhesion kinase; HS, hypertrophic scar; LC, Langerhans cell; LOX, lysyl oxidase; PDL, pulsed-dye laser; PIH, post-inflammatory hyperpigmentation; TEAD, TEA domain transcription factor; UVA1, long-wave ultraviolet A1. Evidence level indicates the strongest available signal across indications; cutaneous scar data are noted when available.

Translational Challenges and Patient Stratification

Clinical translation will hinge on (i) delivery and exposure at scar tissue (eg, achieving sufficient αvβ6/β8 inhibition at the epithelial–dermal interface while minimizing off-target effects), (ii) on-target safety (TGF-β has homeostatic roles in skin immunity and barrier function), and (iii) selecting patients by biology rather than morphology. DC-aware single-cell /spatial maps can guide stratification using epithelial integrin expression (αvβ6/β8), DC subset signatures (LC vs Langerin$^+$ cDC1), and fibroblast mechanotransduction readouts (YAP/TAZ target genes). Practical endpoints should combine clinical measures (scar height/pliability, symptoms) with molecular pharmacodynamics (eg, reduction of phospho-Smad2/3 or YAP nuclear localization in lesional tissue). These DC-centric biomarkers can de-risk mechanism-based combinations (eg, αv integrin modulation plus YAP/TAZ or IL-13/IL-4 axis control) and accelerate proof-of-concept.

Modulating Langerin$^+$ Cells and Immune Responses

While no therapies currently target Langerhans cells or dermal DCs exclusively in scars, there are approaches that indirectly affect them. One such approach is imiquimod 5% cream, a TLR7 agonist, applied to fresh excision sites of keloids to reduce recurrence. Imiquimod activates DCs (including LCs) to produce pro-inflammatory cytokines (IFN-α, IL-12) and co-stimulatory molecules, potentially shifting the local immune response towards a tumoricidal and scar-inhibiting state. Some case series report imiquimod can flatten keloid excision scars in ~50% of cases, but controlled trials show mixed efficacy and significant inflammation as a side effect. The logic, however, is that by hyper-activating local DCs and immune cells, one might prevent the immunosuppressive, pro-fibrotic environment from re-establishing. Another immune-based strategy is intralesional IFN-α or IFN-γ injections, which were tried in the 1990s for keloids. IFN-α2b injections led to reduced collagen synthesis in keloids and in some studies improved scar appearance, presumably by activating a stronger Th1 response and directly inhibiting fibroblast collagen transcription.[174] IFN-γ was less studied but has known anti-fibrotic effect (used in systemic sclerosis). These cytokine therapies would influence DCs as well – IFNs activate DCs and could increase antigen presentation and immune surveillance in the scar, countering the fibrotic process.

Targeting LCs more directly is challenging due to their dual role. But consider that LCs require TGF-β for their residence – theoretically, neutralizing TGF-β in a healing wound might cause LCs to migrate away (as happens with UV exposure), reducing their contribution to T_reg induction and perhaps limiting fibrosis. However, that could also unleash inflammation. Conversely, one might try to harness LCs' tolerogenic ability: for instance, loading an antigen that drives a regulatory response (like a collagen peptide) into LCs to induce scar-specific Tregs that produce IL-10 to resolve fibrosis. This is speculative and not yet in practice.

Another angle is vaccination or cell therapy. Given the association of keloids with certain immune HLA profiles and even autoantibodies (eg, anti-nuclear antibodies sometimes found in keloid patients[175]), one idea is that keloids might have an autoimmune component against skin components. If so, tolerizing DCs to those autoantigens could reduce the inflammatory drive. There is no proven antigen for keloids yet, but small trials have looked at 5-fluorouracil (5-FU) and bleomycin injections, which kill some cells and have immunomodulatory effects on DCs (bleomycin induces immunogenic cell death). Bleomycin tattooing for keloids creates a localized inflammatory reaction that often flattens keloids – interestingly this might work by making DCs present keloid fibroblast antigens to cytotoxic T cells that then clear fibroblasts. Essentially, turning the immune system against the fibrotic cells.

Mast cell targeting also indirectly affects DCs and other immune cells. The mast cell stabilizer tranilast (N-[3',4'-dimethoxycinnamoyl]-anthranilic acid) has been used in Asia for keloids with some success in reducing scar hardness and erythema. By preventing mast cell degranulation, it likely reduces the influx of inflammatory and regulatory cells that respond to mast cell chemokines. Less chymase means less local angiotensin II and maybe less TGF-β activation too. As noted, a chymase inhibitor is in development (several, originally for cardiac fibrosis) and could be repurposed for scars.[176]

Targeting the TGF-β1 Pathway

Given TGF-β1's central role, many therapies aim at it directly. The most direct is TGF-β neutralization. Fresolimumab is a human monoclonal antibody that neutralizes all isoforms TGF-β1, -β2, -β3. It has shown promise in clinical trials for systemic sclerosis (scleroderma): in one Phase I trial, diffuse scleroderma patients had reduced skin fibrosis scores and decreased expression of TGF-β-regulated genes after fresolimumab. In those patients, skin biopsies showed a rapid and dramatic decline in dermal fibroblast infiltration and extracellular matrix genes. This suggests antifibrotic efficacy. For keloids or scars, fresolimumab could be applied as intralesional injections to localize effect (since systemic TGF-β neutralization can lead to side effects like inflammation and bleeding tendency). Indeed, pan-neutralization of TGF-β can remove its immunosuppressive functions (TGF-β keeps immune responses in check), potentially causing autoimmunity or excessive inflammation if done systemically. Local therapy may circumvent this. Another approach is using soluble TGF-β type II receptor (sTGFBR2) as a decoy – a small trial of a TGF-β2-specific antibody (CAT-152) in glaucoma surgery scarring showed reduced scar formation, implying local TGF-β blockade aids scar resolution in that context.[71,72,117,139,147,160,161,163,177–192]

TGF-β Receptor Kinase Inhibitors

These are small molecules that inhibit the serine-threonine kinase activity of TGF-β type I receptor (also known as ALK5). Several such as SD-208, SB-431542, GW788388 were effective in preclinical fibrosis models by preventing Smad2/3 phosphorylation. One, galunisertib (LY2157299), was tested in cancer and liver fibrosis with partial success. In skin, topical or intradermal delivery of such inhibitors could be envisioned. However, these inhibitors may not be entirely specific (they can hit ALK4/ALK7 as well) and again, safety is an issue if systemic. For localized therapy, a novel idea is enzyme-activated prodrugs – for instance, a latent ALK5 inhibitor that is activated by fibroblast-specific enzymes in the scar.

Integrin Inhibitors

As discussed, blocking TGF-β activation at the integrin stage is attractive. Several agents are in trials for fibrotic diseases:

- Bexotegrast (PLN-74809) – an oral small molecule inhibitor of αvβ6 and αvβ1 integrins. In idiopathic pulmonary fibrosis (IPF) patients, it showed dose-dependent target engagement and trends toward slowing fibrosis.[36,193] For skin, a topical formulation might be developed to reduce cutaneous TGF-β activation.
- STX-100 (an αvβ6 antibody) and AZD-0058 (αvβ6 inhibitor) were in development for lung fibrosis. An αvβ6-blocking antibody could theoretically be injected into a healing wound margin to prevent scar formation.
- Cilengitide, an RGD-mimetic peptide, inhibits αvβ3/β5; while not TGF-specific, it reduces fibroblast contraction and angiogenesis. It was tried as an anti-cancer agent; perhaps short-term local use could modulate scarring.
- Pan-αv integrin inhibitors (like GLPG-1690 which inhibits integrin-linked enzyme autotaxin) might also indirectly reduce TGF activation.

One promising fibrotic drug, pirfenidone, is an oral molecule approved for IPF. Pirfenidone's mechanism includes reducing TGF-β1 synthesis and downregulating fibroblast growth. It has been tested for skin scars: an 8% pirfenidone topical gel was evaluated in a clinical trial and showed improvement in hypertrophic scar pliability and height compared to placebo.[194,195] Pirfenidone also inhibits EMT in keloid keratinocytes and can reduce fibroblast migration.[196] It is an example of repurposing a systemic anti-fibrotic for cutaneous use. Similarly, nintedanib, a triple kinase inhibitor (targeting PDGF, VEGF, FGFR signaling) that is approved for IPF, has shown in vitro reduction of keloid fibroblast proliferation and collagen, and a case report noted improved burn scar texture with its use.[195]

Smad Pathway Modulation

Some experimental therapies aim downstream. For instance, blocking Smad3 specifically (using peptide aptamers or inhibitory Smad7 mimetics). One could deliver a Smad7 gene therapy via plasmid or viral vector to scars – increasing Smad7 in fibroblasts would inhibit Smad2/3 phosphorylation and promote collagen breakdown. In fact, dermal injection of a Smad7-transferring plasmid was reported in a Chinese study to reduce rabbit ear hypertrophic scars. Another approach is using microRNAs: miR-29 is a known anti-fibrotic microRNA that downregulates collagen; miR-29 is suppressed by TGF-β in scars. Strategies to deliver miR-29 mimics to scars (via nanoparticles or adeno-associated viruses) are being investigated in preclinical models.

Other Cytokine Targets

Given the immune involvement, targeting IL-6 could address the inflammation-fibrosis cycle. A small trial of tocilizumab (anti-IL6R) in scleroderma showed skin softening. In keloids, this could break the IL-6/Th17 loop and possibly reduce fibroblast activation (since IL-6 trans-signaling supports fibroblasts). IL-13 and IL-4 could be targeted by dupilumab (anti-IL4Rα) – interestingly, in atopic dermatitis patients (a Th2 disease) on dupilumab, some anecdotal reports suggest their scar formation from biopsies is less pronounced, but this is not systematically studied. IL-10 is dual: boosting IL-10 might help resolve inflammation but too much IL-10 (like in keloids) supports fibrosis; thus, IL-10 is not directly targeted but rather its upstream regulators might be (eg, anti-TNF can reduce IL-10 by shifting macrophage polarizations, but TNF inhibitors can sometimes worsen scarring because TNF-α also helps clear collagen – a cautionary note that not all anti-inflammatories are anti-fibrotic).

MMP Augmentation

An older but straightforward idea is to increase matrix metalloproteinases in the scar to degrade collagen. Topical recombinant human MMPs are not available, but salicylic acid, urea, and retinoids can enzymatically or chemically soften scars by breaking collagen cross-links. Enzyme therapies like collagenase ointment (used for debriding wounds) theoretically could be applied to scars to digest excess collagen – though uncontrolled digestion could cause injury. Instead, focusing on rebalancing fibroblasts' own MMP/TIMP production via upstream signals (like through YAP/TAZ inhibition which was shown to increase MMPs via AP-1[37]) is more controlled.

Finally, physical and combination therapies should be mentioned. Laser therapies (eg fractional CO_2 or pulsed-dye laser) not only ablate or vascularize the scar but also induce the release of heat shock proteins and cytokines that attract DCs and macrophages to "remodel" the scar. For example, pulsed-dye laser (PDL) reduces redness by targeting blood vessels, but it

also was shown to decrease TGF-β1 and increase MMP-1 expression in hypertrophic scar tissue.[197] Perhaps, the laser causes minor dermal injury that resets the healing process in a controlled way. Combining such physical modalities with molecular therapy might yield best results – eg, laser + 5-FU injection is a regimen some use for keloids: laser improves penetration and immune cell access, 5-FU kills highly proliferative fibroblasts and inhibits TGF-β mRNA translation.

In terms of Langerin$^+$ cells, an intriguing potential therapy is UV phototherapy. UVA1 phototherapy has been used for scleroderma and keloids with some success in softening lesions.[197,198] UVA1 penetrates to the dermis, induces fibroblast apoptosis, and downregulates TGF-β1 while upregulating collagenase (MMP-1).[197,198] UVA1 also depletes Langerhans cells in the epidermis (UV is known to cause LC migration out of skin) and induces keratinocytes to produce IL-10. This creates a less fibrogenic environment. Low-dose UVA1 led to clinical flattening of some keloids in studies.[198] Photodynamic therapy (PDT) is another approach, where a photosensitizer is applied and activated by light to produce reactive oxygen species. PDT has been reported to improve hypertrophic scars, possibly by selectively killing scar microvasculature and activating MMPs. It can also modulate immune cells; for instance, PDT can cause neutrophils and macrophages to flood the treated area and clean up scar tissue.

Summary of Therapeutics

The most active area is TGF-β targeting from ligand traps (fresolimumab) to blocking integrin-mediated activation (αvβ6 inhibitors) to intracellular blockade (ALK5 inhibitors, Smad3 antisense). Many are in trials for various fibroses. For cutaneous scars, combination therapy is likely needed – addressing the fibrotic pathway and the immune environment and the mechanical environment together. For example, a patient with a keloid might in the future receive: surgery (to debulk), intraoperative αvβ6 antibody injection around wound edges (to prevent TGF-β activation), followed by low-dose radiation or a SMAD3 inhibitor gel (to suppress residual TGF-β signaling), plus an immune modulator like imiquimod or IL-6 inhibitor (to prevent pro-fibrotic immune cell re-infiltration). Some of these steps remain experimental, but each is grounded in the mechanisms we have discussed.

Conclusion

Fibrosis in skin is sustained by an epithelial gate that activates TGF-β1 (αvβ6/αvβ8) and a fibroblast circuit that integrates Smad2/3 with YAP/TAZ under mechanical load. Langerin$^+$ DCs sit at this interface: they are conditioned by epithelial/ECM cues and, in turn, tune cytokine milieus that decide resolution versus persistence. By combining DC-aware single-cell/spatial maps with mechanism-guided interventions that target the αv integrin–TGF-β1 gate, biomechanical signaling, and immune skewing, we can rationally personalize antifibrotic therapy. This DC-centric framework links mechanism to clinic and outlines concrete, testable steps toward durable scar mitigation. In practical terms, we envisage a simple, testable pipeline: profile patient scars by single-cell/spatial assays to quantify LC/cDC1 states and epithelial αvβ6/αvβ8 expression; classify "αv-gate–high" versus "mechanotransduction-dominant" cases; and match therapies accordingly (local αvβ6 blockade/TGF-β modulation versus YAP/TAZ/LOX inhibition plus immune re-balancing).

Data Sharing Statement

No dataset was generated or analyzed during this review.

Consent to Publication

All authors confirm that they have reviewed and approved the final version of the manuscript and consent to its publication. The work is original and not under consideration elsewhere.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by grant from Science and Technique Program of Quzhou (2024ZD018).

Disclosure

The authors declare no competing interests.

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