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Keloids: The paradigm of skin fibrosis – pathomechanisms and treatment

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Abstract

Keloids, fibroproliferative dermal tumors with effusive accumulation of extracellular matrix (ECM) components, particularly collagen, result from excessive expression of growth factors and cytokines. The etiology of keloids is unknown but they occur after dermal injury in genetically susceptible individuals, and they cause both physical and psychological distress for the affected individuals. Several treatment methods for keloids exist, including the combination therapy of surgical incision followed by intralesional steroid therapy, however, they have high recurrence rate regardless of the current treatment method. Improved understanding of the pathomechanisms leading to keloid formation will hopefully identify pathways that serve as specific targets to improve therapy for this devastating, currently intractable, disorder.

Keywords

Fibrotic disease; inflammation; keloid; collagen; TGF-β; wound healing

1. Introduction

Keloids represent benign fibroproliferative tumors originating in response to trauma to the skin. Keloid tissue is characterized by an overabundant accumulation of extracellular matrix (ECM) components, especially collagen, in the dermis and subcutaneous tissue that extends beyond the confines of the original wound site. Keloids continue to grow over the years and

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they rarely regress spontaneously [1,2]. After surgical treatment, keloids tend to recur inevitably and the recurrence often exacerbates the condition [3]. Keloids can be a significant burden for the affected individual in terms of cosmetic harm, pruritus, pain and in severe cases, limited joint movement (Fig. 1). To date, no one specific factor has been identified as the cause for keloid development, however, several pathologic etiologies have been described. Certain regulators of the fibrotic cascade, such as transforming growth factor β (TGF-β) and fibronectin extra domain A (Fn-EDA) have been demonstrated to play a role in collagen deposition during keloid development, but how they are involved in the initiation and subsequent continuation of collagen deposition has remained unclear. Complicating matters has been the lack of appropriate animal models in which to study keloid development and potential treatment modalities [4].

2. The Cascade of Fibrotic Events

2.1 Role of trauma and genetic predisposition

The exact etiology of keloid scarring remains unknown, however recent studies have identified a number of factors needed for extensive scarring to occur. Clinically, keloids have been well documented to develop following injury or inflammation of the skin, in most cases several months or even years after initial trauma. Thus, trauma to the skin is a necessary and important inciting event. Specific skin sites are more prone to keloid development, such as ear lobes, anterior chest wall and shoulders, as these are areas more prone to trauma, caused either iatrogenically (*e.g.*, ear-piercing) or as a sequel of an inflammatory disease (*e.g.*, acne) [5]. Nevertheless, trauma to the skin is seen as a necessary factor for the abnormally sustained wound healing process to ensue, leading to keloid development.

A strong genetic component has been noted to be associated with keloids. Individuals with a darker complexion are at increased risk of developing keloid scarring following trauma, as they occur in ~15–20 % of individuals of Black, Hispanic and Asian ancestry, less commonly in Caucasians and no reported cases in patients with albinism [6,7]. To date, no single gene has been identified to contribute in a Mendelian fashion to keloid scarring, however, several susceptibility loci have been identified. In a genome-wide association study, Nakashima *et al.* (2010) found four single-nucleotide polymorphisms in three chromosomal regions in Japanese patients with keloids. One of these four loci, rs8032158 SNP in chromosome 15, located in intron 5 of the neuronal precursor cell-expressed developmentally down-regulated 4 (*NEDD4*) gene, is thought to affect keloid severity [8,9]. A study of admixture mapping identified potentially common genetic elements among a cohort of Black, Japanese and Chinese patients on chromosome 15q21.2–22.3, within which *NEDD4* resides [10]. Similar studies in families with keloids identified two susceptibility loci, one in chromosome 2q23 in a Japanese family and one in chromosome 7p11 in an African-American family [11]. Despite evidence of familial keloid formation, phenotypic presentations and scar severity vary among families, thus leading to a suggestion that polygenic inheritance pattern is likely.

2.2 Wound repair mechanisms

Following injury, hemostasis is rapidly achieved through interaction of platelets, growth factors and clotting factors. Elements involved in platelet-plug formation are activated to reduce blood loss, prevent contamination and limit systemic effects from trauma. From 24 hours after injury up to 8 days, neutrophils and macrophages characterize the inflammation that is seen during this period. In addition to their role in inflammation, these cells also help to initiate the fibrotic process through the secretion of several growth factors, such as TGF-β and platelet-derived growth factor (PDGF). For the next several weeks, the proliferative phase involves active fibroblast migration and ECM deposition. It is during this phase that collagen and ECM synthesis primarily occurs. Differentiated fibroblasts contract and pull wound edges together thereby decreasing the wound size and increasing the tensile strength of the wound. Under normal homeostatic conditions, wound repair is limited in its scope and intensity, with most wounds having fully matured within the span of several months to over a year. Fibrosis occurs when key repair processes become deregulated and/or accentuated, leading to excessive ECM accumulation, which can result in the formation of hypertrophic scars or keloids [12].

2.3 Cellular components in fibrotic processes

2.3.1 Fibroblast—A multitude of cell types have been identified that contribute to the fibrosis observed in keloid scarring (Fig. 2). While not every cell produces collagen, many stimulate those cells that do, primarily fibroblasts, leading to sustained activity. Fibroblasts are responsible for the majority of collagen and ECM deposition that occurs in both normal and abnormal wound healing. These actions are mainly driven by fibrogenic growth factors, such as TGF-β, PDGF, fibroblast growth factor β (FGF-β) and insulin-like growth factor I (IGF-I) [13]. In keloids the effects that these growth factors have on fibroblasts contribute to the enhanced scarring phenotype. This altered phenotype is thought to be central to keloid formation [14,15]. Fibroblasts isolated from keloid tissue are more sensitive to TGF-β1, PDGF and IGF-I *in vitro* than their counterparts in normal skin, leading to higher expression of collagens and other ECM-related proteins [16–18]. Additionally, keloid fibroblast density and proliferation rates are increased while the apoptotic rates are reduced, further contributing to collagen-matrix deposition [2,6]. In a recent study, the location of fibroblasts within the lesional skin also appears to contribute differentially to the fibrosis. Isolated deep fibroblasts display elevated expressions of COL1A1, TGF-β1, periostin, PAI-2, and inhibin beta A compared to their superficial and normal counterparts [19].

2.3.2 Myofibroblast—Previous classification of keloids suggested that the lesions were histologically distinct from hypertrophic scars, and specifically, keloids showed minimal presence or complete absence of a differentiated form of fibroblast, the myofibroblast [7,20]. Recent literature, however, suggests a role for the myofibroblast in keloid pathogenesis. In one study [21], the authors report the presence of cell markers characteristic of activated myofibroblasts, such as transglein, cytoglobin/STAP, and prolyl 4-hydroxylase β, which are all implicated in fibrotic conditions, in keloid tissue. Several other reports have confirmed the presence of α-smooth muscle actin (αSMA)-positive myofibroblasts within keloid tissue, suggesting a potential role in pathogenesis [22,23].

2.3.3 Keratinocyte—While fibroblasts play a central role leading to ECM overproduction, epithelial-mesenchymal cross-talk has also been implicated between keratinocytes and dermal fibroblasts [24,25]. Keratinocytes isolated from keloid tissue have been shown to induce keloid-like behavior in normal fibroblasts, and co-culturing keratinocytes and fibroblasts resulted in increased proliferation rates in both normal and keloid-derived fibroblasts [26]. These effects were found to be mediated through secretion of several growth factors, hypoxia-inducible factor-1α (HiF-1α) and release of IL-1 [27]. Keratinocytes have also been shown to contribute to the decreased apoptotic rate of fibroblasts through paracrine and double paracrine signaling [28,29].

2.3.4 Melanocyte—Melanocytes, which are located in the basal layer of the epidermis, have been postulated to have an effect on keloid formation. Evidence has accumulated citing the increased occurrence of keloids in darker pigmented individuals compared to individuals with lighter skin, while there is no report of albino patients developing the lesions. In addition, keloids tend to occur in skin areas with higher density of melanocytes and are almost absent where melanocytes are less common [2,6,7,30]. Under normal homeostatic conditions, melanocytes do not proliferate or express autocrine cytokines. During wound healing, however, melanocyte proliferation and melanin production are activated as a result of the intense inflammation that occurs [31]. Fibroblasts co-cultured with melanocytes have also been shown to have enhanced type I collagen and TGF-β expression while the suppressive effects of α-melanocyte stimulating hormone (αMSH) on collagen production appear to be deregulated in keloids compared to controls [21,32].

2.3.5 Mast cell—Mast cells, when present in the skin, secrete a variety of chemokines in response to injury during the inflammatory phase of wound healing. While our understanding of their role in keloid formation is still emerging, the mast cell density is known to be elevated in keloid tissue and degranulation results in histamine and heparin release leading to microvascular endothelial cell proliferation and pruritus that often accompany the lesions [33]. Increased activity levels of chymase, a chemokine secreted by mast cells, have been found in keloid tissue, promoting fibroblast proliferation and collagen synthesis via TGF-β activation and SMAD signaling induction [34].

2.4 Key regulator molecules of fibrosis in keloids

Keloid formation is driven by multiple cytokines and growth factors (Fig. 2). Keloid fibroblasts express increased levels of growth factors and receptors and they also respond more readily to growth factor signals [20].

2.4.1 TGF-β—TGF-β1 is a cytokine with a wide variety of biological functions ranging from proliferation and cellular differentiation to playing a role in many different conditions and disease states, including cancer [35–37]. Among its primary functions, TGF-β serves as a stimulator for wound repair and tissue regeneration, as a mediator for ECM production, and in the case of fibrosis, as a driver for excessive collagen accumulation [36,38–40]. Three isoforms of TGF-β exist, all share 70–80% sequence homology, and are produced and secreted by inflammatory cells, particularly macrophages, as well as fibroblasts and platelets [36]. The mature TGF-β protein dimerizes to produce a 25 kDa active protein that serves

many cellular functions. In active wound healing, TGF-β is involved in a number of processes, including inflammation, angiogenesis, cell proliferation, collagen and matrix production and wound remodeling [36]. During hemostasis and inflammation, TGF-β secretion attracts further macrophages and enhances chemotaxis of smooth muscle cells and fibroblasts while additionally modulating collagen and collagenase expression [12]. Many of these functions are mediated through SMAD signaling, a pathway through which TGF-β primarily acts [36].

As the active wound site begins to mature, activity levels of TGF-β decrease and consequently, collagen and matrix production diminishes [36]. In fully mature, established scars, TGF-β eventually returns to baseline levels, however in pathologic fibrotic conditions, specifically keloids, TGF-β remains active and up-regulated [36].

With respect to keloid pathogenesis, TGF-β has been shown to act as a primary modulator of fibrosis, as exogenous TGF-β stimulates keloid fibroblast proliferation and collagen synthesis while also inhibiting the collagen-degrading activity of matrix metalloproteinases (MMP) [17,36]. Additionally, TGF-β signaling induces many other effector molecules, such as Fn-EDA, vascular endothelial growth factor (VEGF) and PDGF, further promoting collagen synthesis and tissue angiogenesis [36,41–44]. Direct inhibition of TGF-β signaling proteins has been shown to reduce the effects of scarring in rodents, with varying degrees of success [45–47].

2.4.2 PDGF, VEGF—In addition to its direct, SMAD-mediated effects on gene expression, TGF-β stimulates ECM accumulation indirectly through up-regulating PDGF, another cytokine involved in wound healing. PDGF induces mitogenesis and chemotaxis of smooth muscle cells and fibroblasts to wound beds, and stimulates cell proliferation and migration. During later stages of wound healing, PDGF causes acceleration of granulation tissue formation and stimulates collagen production [13].

VEGF is a highly specific mitogen for endothelial cells that promotes both physical and pathological angiogenesis in a dose-dependent manner [48,49]. Recent literature has indicated circulating pro-angiogenic endothelial progenitor cells (EPCs) present at a higher degree in patients with keloids compared to patients without keloids [34]. VEGF binds to specific receptors, VEGFRs, on EPCs, leading to mobilization and maturation of the EPCs to endothelial cells. With increased angiogenic activity, VEGF assists in wound healing and its overactivity may promote keloid formation [50].

2.4.3 Other contributing factors—During wound healing, matrix synthesis and angiogenesis are also promoted by a myriad of other factors (Fig. 2). Heparin, FGF-β, IGF-I and IL-8 have been implicated in angiogenesis while epidermal growth factor (EGF), TGF-α and IGF-I have been shown to enhance migration of epithelial cells into the wound site [51]. In keloids, concentrations of IL-6, tumor necrosis factor- α (TNF-α) and INF-β are increased, all which promote cell migration and proliferation and signal an inflammatory response to recruit T cells to wound site [52,53]. Conversely, circulating concentrations of INF-α, INF-γ and TNF-β, molecules that act to down-regulate collagen synthesis and

fibroblast proliferation, are reduced leading to loss of inhibition and subsequent promotion of uncontrolled collagen production [52,54].

2.4.5 Proteolytic enzymes—Proteolytic degradation of ECM is an integral process that occurs during normal wound remodeling. Physiologically, proteoglycans are synthesized, collagen III is replaced by collagen I and excess fibrin and fibronectin are degraded as the wound matures. Serine proteinases, such as tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA), and matrix metalloproteinases (MMPs) are active in degrading ECM components. MMPs, which comprise a family of 25 proteinases that are zinc- and calcium-dependent, act specifically to degrade collagens I and III while also cleaving chemokines thereby limiting inflammation [55,56]. In keloid lesions, the activity of these proteolytic enzymes is elevated in the peripheral, leading edge of the original wound, thereby enhancing the degree of wound remodeling that occurs [57]. Specifically, MMP-1, MMP2, MMP3, and MMP9 have been demonstrated to be elevated in keloid-derived fibroblasts, when isolated from the superficial periphery and deep center of lesions [57]. The synthesis and activity of proteases and MMPs is a complex process largely regulated by TGF-β1 and SMADs 3 and 4 [58–60].

2.5 Fibrotic signaling cascades

2.5.1 SMAD signaling—The SMAD signal-transduction pathway is a downstream mediator of TGF-β through TGF-β type I receptor (Fig. 2). SMADs are a family of intracellular regulatory proteins that can be categorized into receptor-activated SMADs (R-SMAD 1, 2, 3, 5 and 8), common mediator SMAD (Co-SMAD 4) and inhibitory SMADs (I-SMAD 6 and 7) [61]. After phosphorylation, profibrotic R-SMAD 3 forms a complex with the common mediator Co-SMAD 4. This complex regulates the transcription of specific genes in the cell nucleus [62]. Phosphorylation of RSMAD 3 is up-regulated in keloids while down-regulation of R-SMAD 3 can significantly decrease procollagen gene expression by keloid fibroblasts [63]. I-SMAD 6 and I-SMAD 7 inhibit TGF-β actions by preventing phosphorylation of R-SMADs through a negative feedback loop by binding to activated TGF-β type-I receptor. SMAD 6 can also inhibit the binding of SMAD 4 and R-SMAD. The expression of I-SMAD 6 and 7 is decreased in keloid fibroblasts [64]. Keloid formation can be markedly reduced by the inhibition of TGF-β1-SMAD signaling pathway and the activation of TLR7 or SMAD 7 [65,66].

2.5.2 Toll-like receptor signaling—Toll-like receptors (TLRs) are transmembrane proteins that are essential to the innate immune system [67]. In addition to recognizing microbial pathogen-associated molecular patterns, such as bacterial lipopolysaccharides (LPSs), TLRs also recognize nonmicrobial covert ligands and take action [68]. Thus, TLRs are also important factors in the pathogenesis of fibrosis (Fig. 2). After skin injury, molecular patterns of endogenous TLR4 ligands, normally inaccessible to the innate system, are released passively into the extracellular space. These ligands, grouped together as damage-associated molecular patterns (DAMPs), enable the innate immune system to respond to sterile tissue damage [69]. As the concentrations of several pro-inflammatory and profibrotic cytokines increase in response to TLR stimuli in macrophages, changes in fibroblast gene expression and TGF-β response occur, leading to enhanced collagen

production [70,71]. In the case of keloids, the effects of fibronectin EDA auto-activation and feed forward systems have been proposed to act through TLR4- and surface integrin-mediated pathways [41,72–77]. Additionally it has been proposed that decreased expression of TLR7 is associated with keloid formation. This has led to a suggestion that TLR7 agonist, imiquimod, may be effective in inhibiting keloid recurrence after surgical removal, however, recurrence rates following treatment remain high [78,79].

2.5.3. Fibronectin, Fn-EDA and Fn-EDB—Fibronectins are multifunctional, high molecular weight glycoproteins involved in a variety of physiological processes, interacting with both ECM components and cell surface receptors. Fibronectin is a disulfide-linked dimer consisting of type I, II and III repeating structural domains [80]. Fns are present in both a soluble, circulating form in the plasma (pFn) and an insoluble cellular form (cFn) which is deposited into the ECM of most tissues. In humans, the primary Fn mRNA transcripts are alternatively spliced to yield up to 20 different mRNA variants [81]. Following alternative splicing, one or both of two additional Type III domains, extra domain-A (Fn-EDA) or −B (Fn-EDB) are incorporated into the final protein [82]. The role of these isoforms in tissue physiology and pathology is not well understood, however, it is known that Fns carrying the EDA domain (Fn-EDA) are virtually absent from normal adult tissue whereas in pathologic conditions, such as keloids, Fn-EDA is readily abundant [41]. In these pathologic scenarios, Fn-EDA is a structural ECM component as well as a signaling molecule that regulates adhesive, proliferative and migratory cellular processes [83]. Additionally, Fn- EDA is crucial for TGF-β driven myofibroblast differentiation from normal fibroblasts [84].

Fn-EDA plays an important role in both normal and pathologic wound healing, as Fn-EDA$^{-/-}$ mice demonstrate very poor wound re-epithelialization and lack adequate scar formation. However, there is no difference in wound healing between the Fn-EDA$^{+/+}$ and Fn-EDA$^{wt/wt}$ mice [85]. In recent reports, Fn-EDA has emerged as an endogenous ligand to TLR4. It is thought that Fn-EDA binds to TLR4, stimulating downstream TGF-β1 production, which in turn feeds-forward in up-regulating Fn-EDA further, leading to a vicious cycle of fibrosis [41,77,86]. The feed-forward cycle may serve as a suitable target for reducing and/or blocking the effects Fn-EDA has on tissue fibrosis and keloid development.

3. Treatment

3.1. Non-targeted therapies

Surgical excision remains the mainstay for the treatment of many keloid lesions. When used as the sole form of therapy, keloid lesions have been reported to recur in 70–100 % of patients, often leading to more robust collagen accumulation and larger lesion formation much to the dissatisfaction of physicians and patients alike [7]. When combined with adjuvant therapies, however, the recurrence rate is improved.

Multiple studies have been performed combining the use of surgery with several adjuvant therapies, such as pulsed-dye laser ablation, radiation therapy, pressure therapy, and CO_2 laser ablation, among others. In most instances, the lesions are effectively treated, however

with varying degrees of recurrence [87–93]. Definitive conclusive results are difficult to ascertain due to a number of factors, most notably limited patient cohort size in individual studies.

In the case of keloids located on the ear and/or earlobe, pressure therapy following surgical excision has shown promising results and is currently employed on a more widespread basis. Believed to induce localized tissue hypoxia, pressure therapy has been postulated to modulate fibroblast activity and promote collagen degradation [91]. While the exact mechanism by which pressure therapy acts is still unknown, many patients have benefited from this treatment strategy for lesions that are located on visible parts of the body.

3.2 Corticosteroids

The most effective intralesionally used corticosteroid is triamcinolone acetonide (TMC). The dosage used varies depending on the size and site of the lesion and on the age of the patient, ranging from 10 to 40 mg/ml. Injections are administrated at intervals of 4 to 6 weeks for several months or until the scar is flattened. To avoid irreversible atrophy of the epidermis, TMC should be injected at the correct depth in the mid-dermis. Corticosteroids have suppressive effects on the inflammatory process during wound healing; they reduce collagen and glycosaminoglycan synthesis, inhibit fibroblast growth, and enhance collagen degradation. TMC has been found to inhibit TGF-β1 expression and when combined with surgery, remains the most widely utilized treatment with the best reported success rates [6,60]. Recurrence rates when lesions are treated both pre- and post-surgically range anywhere from less than 10% to upwards of 30% [60]. While this still impacts a large number of patients, the addition of corticosteroid use as an adjuvant to surgery remains the gold standard for reducing the burden these lesions have on patients' lives.

3.3 Targeted therapies

Targeted therapies aimed at reducing or eliminating one or many key factors crucial to the fibrotic cascade have long been a goal in treating keloids. Several factors, both upstream and downstream that are highly expressed and play a role in fibrotic development, such as Fn-EDA, present as natural targets for pharmacotherapies.

Antisense oligonucleotide (ASO) treatment directed against TGF-β mRNA transcripts demonstrated down-regulation of MMP-9, SMAD 2, SMAD 4, and reduced secretion from fibroblasts *in vitro*, while ASO therapy targeting HiF-1α led to down-regulation of PAI-1 [60,65,94]. While ASO technology has been utilized in the laboratory setting for proof-ofprinciple experimentation, the transition to clinical practice has yet to be made.

Downstream targets in the fibrotic cascade include the molecules responsible for cross-linking of collagen fibers, namely the lysyl oxidase (LOX) family of enzymes. LOX and its constituent isoforms are copper-dependent amine oxidases that catalyze the cross-linking of collagen fibers once secreted from the fibroblast. Beta-aminopropionitrile (BAPN) is a lathyritic agent which directly inhibits all LOX enzymes, preventing cross-linking and promoting collagen degradation. In one case series performed in 1981, BAPN was used successfully in the treatment of severe keloid scarring in several patients following lesion excision [95]. In a similar fashion, other agents aimed at inhibiting collagen-deposition,

through copper ion chelation (*e.g.*, Dpenicillamine) or incorporation into collagen fibers directly (*e.g.*, proline analogues) have demonstrated varying degrees of success [96,97]. While these agents are specific for targeting key elements during collagen production, further studies are needed to translate their use to the clinical setting.

4. Conclusions

Since their first description by Alibert in 1806, keloids have remained a challenge for physicians and a significant quality of life issue for many patients. Despite the advances made over the past century, many patients still suffer from the negative effects of excessive scarring and presently are without effective treatment. We are, however, closer to understanding the molecular basis for abnormal wound healing, and with this improved understanding will come better, more effective strategies for limiting excessive scarring. Among the hurdles to translate understanding of this disease to clinical practice is the lack of appropriate model systems. By having a reliable, reproducible model that researchers can learn from, optimized treatments can be employed, leading to better patient outcomes.

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Abbreviations

ECM	extracellular matrix
Fn-EDA	fibronectin extra domain A
MMPs	metalloproteinases
PAI-I	plasminogen activator inhibitor-I
PDGF	platelet-derived growth factor
TLRs	toll-like receptors
TGF-β	transforming growth factor-β
VEGF	vascular endothelial growth factor

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Highlights

- Keloids are dermal tumor characterized by excessive accumulation of collagen.
- The key cell responsible for matrix production in activated myofibroblast.
- A number of growth factors, particularly TGF-β, play a role in excessive collagen production.
- Recent studies have supported a role for Fibronectin Extra domain A (Fn-EDA) which is markedly upregulated in keloids.
- Identification of the pathways involved in matrix accumulation allows development of effective targeted therapies for fibrotic diseases.

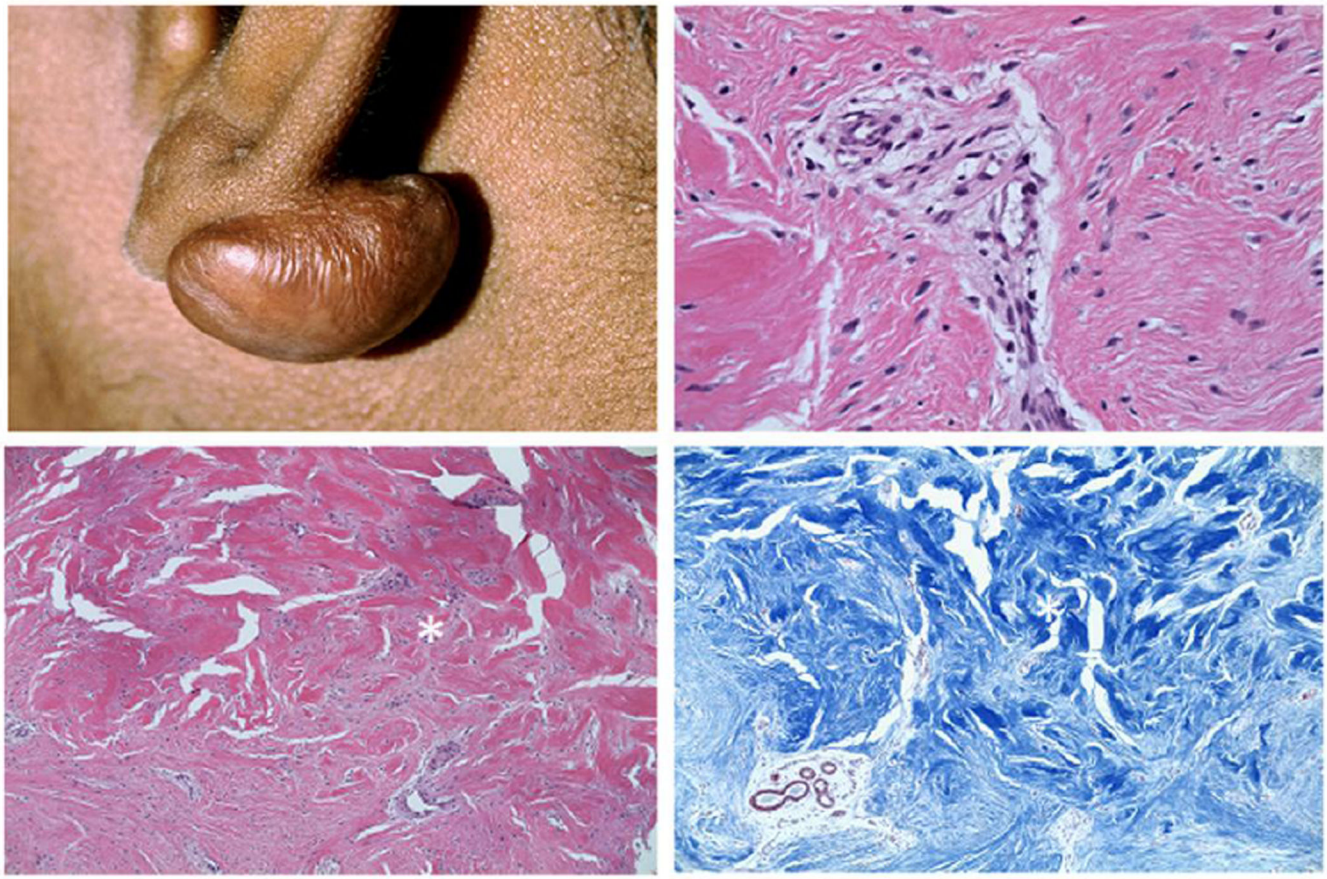

Figure 1. Clinical and histopathologic features of keloids

Note the presence of keloid formation on the earlobe as a result of trauma (upper left panel). The lesions are histopathologically characterized by accumulation of tightly packed collagen (asterisks). Some parts of the lesions demonstrate marked cellularity, as shown in the right lower panel. (Hematoxylin-Eosin stain, bottom left and upper right panels; Masson's Trichrome stain, lower left panel)

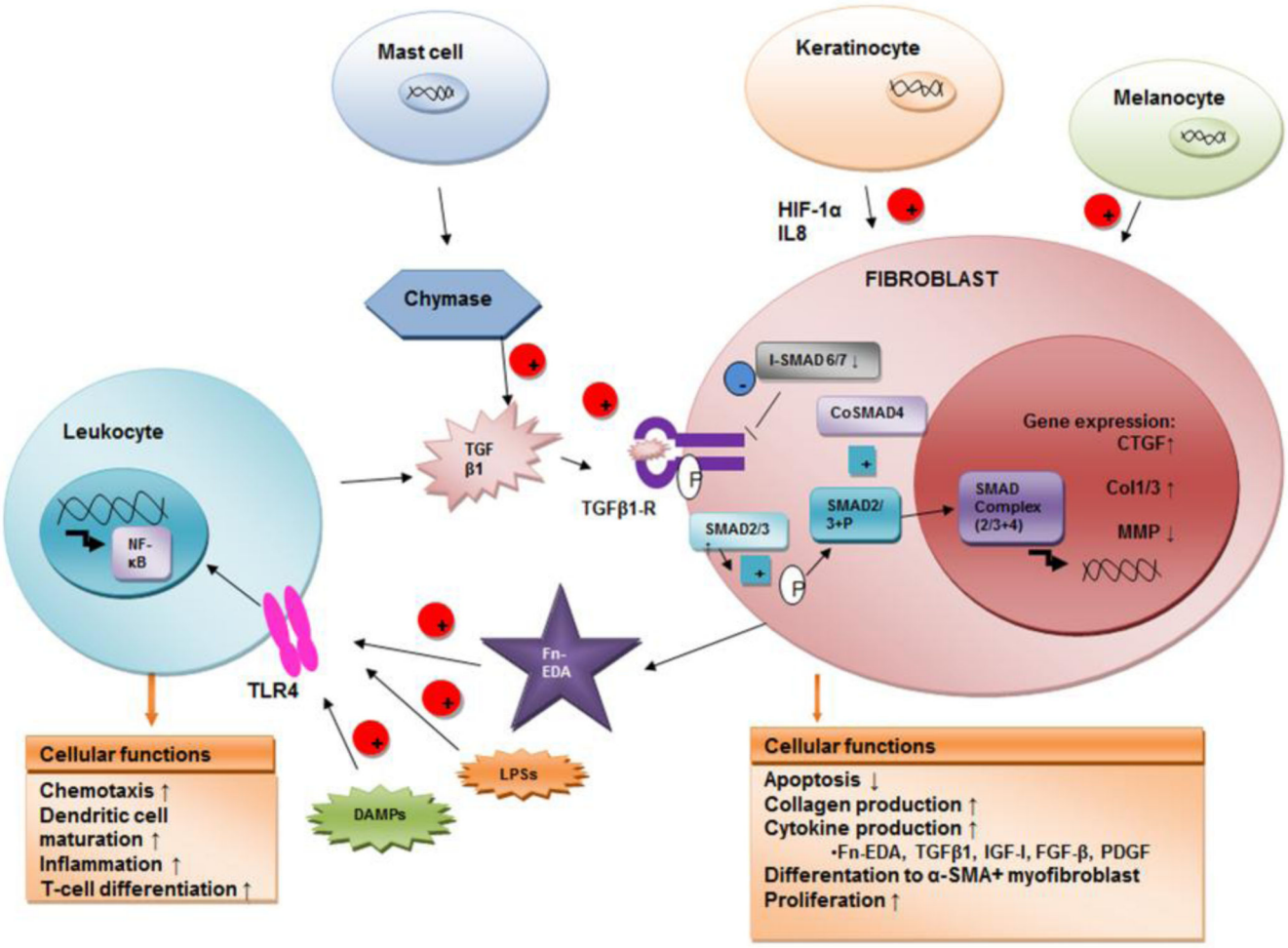

Figure 2. Fibrotic cell-signaling pathways in keloids

Fibroblasts are the centric cell type in the process of profibrotic events that leads to excessive ECM accumulation, inflammation and eventually keloid formation. Key cell-cell and cell-ECM interactions are depicted.