CLINICAL MANAGEMENT extra

# Insights into the Pathophysiology of Hypertrophic Scars and Keloids: How Do They Differ?

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The authors, faculty, staff, and planners, including spouses/partners (if any), in any position to control the content of this CME activity have disclosed that they have no financial relationships with, or financial interests in, any commercial companies pertaining to this educational activity. This work was partly supported by a research grant from the Canadian Dermatology Foundation.

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## GENERAL PURPOSE:

**To provide information about the clinical presentation of hypertrophic scars and keloids based on their varied structural components.**

## TARGET AUDIENCE:

**This continuing education activity is intended for physicians, physician assistants, nurse practitioners, and nurses with an interest in skin and wound care.**

## LEARNING OBJECTIVES/OUTCOMES:

**After completing this continuing education activity, you should be able to:**

**1. Distinguish between the clinical presentations of hypertrophic scars and keloids.**

**2. Identify their underlying mechanisms of scarring and the treatments available.**

## ABSTRACT

Hypertrophic scars and keloids are firm, raised, erythematous plaques or nodules that manifest when the cicatrix fails to properly heal. They result from pathologic wound healing and often cause pain and decreased quality of life. The appearance of such cosmetically unappealing scars affects the confidence and self-esteem of many patients. These scars can also cause dysfunction by interfering with flexion and extension across joints. Both possess some unique and distinct histochemical and physiologic characteristics that set them apart morphologically and at the molecular level. While these entities have been the focus of research for many years, differentiating between them remains challenging for clinicians.

This article reviews the clinical presentation of aberrant scars and illustrates how they can be differentiated. It outlines their pathophysiology and emphasizes the unique molecular mechanisms underlying each disorder. It also examines how altered expression levels and the distribution of several factors may contribute to their unique clinical characteristics and presentation. Further research is needed to elucidate optimal treatments and preventive measures for these types of aberrant scarring.



**Keywords:** aberrant scarring, collagen, elastin, fibrillin 1, hypertrophic scars, keloids, TGF-β

ADV SKIN WOUND CARE 2018;31:582–95.


## INTRODUCTION

Every year, millions of patients worldwide develop scars after burns, trauma, and surgery. The fibrotic scarring process is initiated following cutaneous injury, which under normal circumstances results in wound closure with a flat scar. In certain circumstances, however, the scar continues to grow, causing pain, pruritus, functional impairment, cosmetic distortion, and psychological distress.

The process of wound healing is dynamic and complex and can be divided into 4 overlapping phases of hemostasis, inflammation, proliferation, and remodeling.[1] The process of scarring and wound healing is highly regulated and involves various cells and molecular factors in sequence. Therefore, alterations in any of the wound healing steps can predispose an individual to excessive scarring, which can take different forms, including hypertrophic scars and keloids. Table 1 highlights the characteristics of different scarring types.[2–4]

## CLINICAL AND HISTOPATHOLOGIC FEATURES

Keloids and hypertrophic scars can be hard to distinguish from each other clinically.[5] They are equally prevalent in both genders, with the highest incidence in the second decade of life.[6] Hypertrophic scars usually form 4 to 8 weeks after trauma and are estimated to occur in 40% to 70% of patients following surgery and up to 91% of patients following burn injuries, depending on the wound depth.[7] Hypertrophic scars are confined to the wound margin and usually regress within a year. Keloids, on the other hand, grow abnormally beyond wound boundaries and can appear years after skin injury[8]; they also can form spontaneously without predisposing cutaneous trauma.[9,10]

The terms *hypertrophic scar* and *keloid* were used interchangeably to describe excessive scarring until the histologic distinction between hypertrophic scars and keloids was recognized. Histologically, both hypertrophic scars and keloids are characterized by a thick, highly vascularized dermis that is highly infiltrated with inflammatory cells[11] and marked by collagen abundance.[7] The epidermal layer is generally normal in both. The reticular layer of the dermis of normal skin consists mainly of fibroblasts and unordered collagen fibers that appear relaxed;

**Table 1.**
**DIFFERENT TYPES OF SCARS**

| Scar Type | Description |
|---|---|
| Mature scar | Flat, light-colored scar |
| Immature scar | Slightly elevated, red scar. Recovers in time and becomes similar in color to surrounding skin |
| Pitted (atrophic or "ice pick") | Pitted, with a sunken appearance. Associated with acne and chickenpox |
| Scar contractures | Shrunken and tight appearance. Usually caused by skin burns |
| Linear hypertrophic scar | Elevated, red, and sometimes pruritic scar, associated with surgery or trauma. Scar is confined to the border of the surgical incision or trauma, occurs weeks after cutaneous insult, and can grow in size for 3 to 6 mo before maturing progressively to an elevated, rope-like appearance |
| Widespread hypertrophic scar | Elevated, widespread, and sometimes pruritic, usually associated with burns. Scar is confined to the borders of the burn injury |
| Minor keloid | Elevated (<0.5 cm), small/focal scar. It invades surrounding tissue and can grow and spread for years and can occur up to 1y after cutaneous insult. Does not regress on its own, and surgical excision is often followed by recurrence. Common sites: anterior chest and earlobes |
| Major keloid | Elevated (>0.5 cm), large, and sometimes pruritic and/or painful scar. It invades surrounding tissue and can grow and spread for years. |

injury to this layer is believed to be one of the primary reasons for excessive scarring.[3]

Hypertrophic scars demonstrate fine, wavy, well-organized, and parallel-oriented collagen fibers and bundles, whereas keloids are characterized by large, thick, wavy, hyalinized collagen fibers and closely arranged collagen bundles.[3,11] Keloids also express high levels of both low-density chondroitin sulfate proteoglycans (PGs) and low-density dermatan sulfate PGs, whereas hypertrophic scars express high levels of low-density dermatan sulfate PGs.[12]

Another difference between hypertrophic scars and keloids is the change in histology over time seen only in hypertrophic scars. Hypertrophic scars in the early stages of maturation (<6 months in duration) are characterized by the presence of many collagenous-cellular nodules that are composed of α-smooth muscle actin (α-SMA)–positive fibroblasts and are fibronectin (FN) positive, whereas in older hypertrophic scars (between 1 and 3 years) the cellular component is inconspicuous and mainly α-SMA negative and FN negative.[13] In keloids, however, the histology remains constant irrespective of the scar maturation and composed primarily of α-SMA negative spindle-shaped cells and FN; there are few α-SMA positive and FN positive in prominent collagenous nodules.[13,14] Table 2 provides a summary of the unique features of keloids and hypertrophic scars in terms of epidemiology, morphology, symptoms, time course, genetics, histology, and therapeutic potential.

## EPIDEMIOLOGIC AND GENETIC FEATURES

Strong evidence suggests that genetic factors are involved in the etiology of keloid formation, including common occurrence in twins and siblings[15,16] and increased rates of keloid formation in certain populations. Keloids occur in approximately 15% to 20% of patients of African, Hispanic, and Asian descent and much less commonly in whites.[2] Keloids apparently do not occur in patients with albinism, indicating that melanocytes play a possible role in keloid formation.[17]

The predisposition to keloids is an inheritable trait, expressed in an autosomal dominant mode.[18–20] Keloid formation has been associated with different alleles of human leukocyte antigen (HLA), namely HLA-DRB1*15, HLA-DQA1*0104, DQ-B1*0501, and DQB1*0503, as well as loci on chromosomes 2q23 and 7p11, among others.[21,22] Further, several single-nucleotide polymorphisms that are associated with keloid formation were identified in the Chinese Han population.[23] The roles of gene loci in the context of keloids formation are detailed elsewhere by Shih and Bayat.[21]

## MOLECULAR MECHANISMS AND FACTORS

The pathophysiology of hypertrophic scars and keloids can be addressed with 4 major categories that intersect at many levels of wound healing: proliferation, inflammation, extracellular matrix (ECM) formation, and other factors. Table 3 and the Figure (Supplemental Digital Content 1, http://links.lww.com/NSW/A11) summarize and compare the different factors involved in the pathogenesis of hypertrophic scars and keloids.

### Proliferation

Perhaps not surprisingly, the proliferative capacity of fibroblasts from hypertrophic scars is greater than that of normal skin.[24] However, compared with normal skin and hypertrophic scars, keloid fibroblasts possess higher proliferating cell nuclear antigen expression and display apoptosis resistance.[25,26] This indicates that keloids form as a result of an abnormal wound-healing process with a prolonged proliferative phase because of an apoptosis-resistant phenotype that in turn allows a state of continued production of excessive collagen beyond the amount expected in normal scar or cicatrix formation. It is likely that the formation of aberrant scarring is mediated through a combination of enhanced proliferation and collagen production capacity as well as apoptosis resistance, among other molecular factors that can be implicated in the process.

Although hypertrophic scars and keloids share common anomalies in some apoptotic gene expression, they differ in others. Their different apoptotic-resistance profiles may account for their different manifestations. The level of the tumor suppressor p53 protein found in fibroblasts isolated from hypertrophic scars is significantly higher than in normal and keloid fibroblasts, and keloid fibroblasts possess mutations in exons 5, 6, and 7, whereas hypertrophic scars possess mutations in exon 7.[27] Further, fibroblasts derived from keloids are significantly resistant to Fas-mediated apoptosis.[28]

It is likely that the delay of apoptosis of resistant fibroblasts in keloids may account for the uncontrolled production of large amounts of collagen.[29] In fact, the expression of the antiapoptotic protein B-cell lymphoma 2 (Bcl-2) was quantified by immunohistochemical methods in normal skin and different scar tissues, and it was found that the expression rate of Bcl-2 protein in both hypertrophic scar fibroblasts and keloid fibroblasts was higher than in normal skin; however, it was significantly higher in keloids than in hypertrophic scars.[30] Further, levels of Bcl-2 proteins in peripheral blood mononuclear cell fractions of burn patients with hypertrophic scars were quantified by enzyme-linked immunosorbent assay.[31] These fractions expressed significantly higher levels of Bcl-2 proteins compared with peripheral blood mononuclear cell fractions from a control cohort. These data suggest that increased levels of Bcl-2 proteins may be implicated in the pathogenesis of hypertrophic scarring by delaying fibroblast apoptosis.[31] However, increased activated caspases 3 and 9 and apoptosis were reported in keloid fibroblasts compared with hypertrophic scar and normal skin fibroblasts.[32] In addition, Lee et al[33] found that Bcl-2 levels were decreased in keloid tissues, leading to apoptotic dysregulation.

**Table 2.**
**SUMMARY OF DISTINCT FEATURES OF HYPERTROPHIC SCARS AND KELOIDS**

| | Hypertrophic Scars | Keloids |
|---|---|---|
| **Epidemiology** | | |
| Incidence | Frequent | Rare |
| Rates | Up to 40%–70% following surgery and up to 91% following burn injury | 6%–16% in patients of African descent |
| Distribution | Equal in both genders with highest incidence in the second to third decade of life | |
| **Morphology** | | |
| Scar boundaries | Scar is confined to the borders of the original cutaneous insult | Scar grows beyond the borders of the original cutaneous insult |
| Predominant anatomical sites | No predominant anatomical sites but usually occurs on joints' extensor surfaces | Predominant anatomical sites include the neck, earlobes, chest, shoulders, upper back, sternum, knees, and ankles |
| Unaffected sites | Anatomical sites that are less likely to be affected include mucous membranes, genitalia, palms, soles, and eyelids | |
| Association to trauma | Only posttraumatic | Posttraumatic or (less commonly) spontaneous |
| **Symptoms** | | |
| Pain and pruritus | Rarely painful and less pruritic | Painful and pruritic |
| **Time Course** | | |
| Chronology | Usually appear 1–2 mo following trauma, grow rapidly for up to 6 mo, and then regress (often within 1 y) | Typically appear 3 mo or up to a few years posttrauma, or appear spontaneously, and proliferate for many years or indefinitely |
| Improvement | Improvement with time, in which scar either regresses or stabilizes | Do not usually improve with time |
| Regression | Spontaneous | Not spontaneous |
| **Genetics** | | |
| Predisposition | Less genetic predisposition | More established genetic predisposition |
| Association with skin pigmentation | Less association | More association |
| **Histology** | | |
| Low-power microscopy | Absence of a tongue-like advancing edge underneath normal-appearing epidermis and papillary dermis. No horizontal cellular fibrous band in the upper reticular dermis and no prominent fascia-like fibrous band | Marked by the presence of a tongue-like advancing edge underneath normal-appearing epidermis and papillary dermis. Appearance of horizontal cellular fibrous band in the upper reticular dermis and prominent fascia-like fibrous band. |
| Orientation of collagen fibers | Fine, well-organized, wavy, type III collagen bundles parallel to epidermis surface. Presence of abundant nodules containing myofibroblasts and acidic mucopolysaccharide | Disorganized, large, thick, and hyalinized types I and III hypocellular collagen bundles with no nodules or excess myofibroblasts. Poor vascularization with widely scattered dilated blood vessels |
| Amount of connective tissue | Increased | Increased |
| Amount of immune-cell infiltrate | Related to the age and clinical behavior of the scar (more is seen in fresh scars) | Large numbers persist |
| Density of blood vessels | Increased | Decreased |
| No. of cells | Increased | Increased at the periphery but decreased in nodules |
| Collagen distribution | Flatter and less distinct bundles, fine fibers | Larger collagen fibers with closely packed fibrils |
| α-Smooth muscle actin | Significantly increased compared with normal skin | Increased compared with normal skin, but not as much as in hypertrophic scars |

*(continues)*

**Table 2.**
**SUMMARY OF DISTINCT FEATURES OF HYPERTROPHIC SCARS AND KELOIDS, CONTINUED**

| | Hypertrophic Scars | Keloids |
|---|---|---|
| Myofibroblasts | Excess myofibroblasts | No excess myofibroblasts |
| Proteoglycans | Low-density dermatan sulfate proteoglycans are present | Low-density chondroitin and dermatan sulfate proteoglycans are present |
| **Therapeutic Potential** | | |
| Overall prognosis | Better | Worst |
| Surgical prognosis | Improved with appropriate surgery | Often worsened by surgery |
| Recurrence following surgical excision | Low | High |

The differences in Bcl-2 expression trends that are reported by different studies can be explained, at least in part, by findings from a study by Ladin et al[34], where the apoptotic rates and expression levels of Bcl-2 and Fas protein levels were measured and compared between fibroblasts extracted from both the hypocellular central regions and hypercellular peripheral regions of keloid scars. The study found that the hypercellular peripheral regions and those immediately below the epidermis of keloid scars had high Bcl-2 expression, consistent with increased proliferation in the newer expanding regions of the scar. This was in contrast with hypocellular central, deep dermal, and older areas of the keloids, which showed the opposite trend (high expression of Fas antigen and low Bcl-2 levels) consistent with increased apoptotic rate, likely as a control mechanism to regulate scar growth.[34] Therefore, impairment in the fine regulation of apoptosis contributes to abnormal scarring, and this occurs even within different sites in scar tissues. More research is needed to determine precise factors regulating apoptosis in the abnormal scarring.

## Inflammation

An impaired inflammatory response to skin injury is implicated in the development of hypertrophic scars and keloids.[7,35] The type of immune response is an important modulator of fibrogenesis, in which a type 1 T-helper cell (TH1) response attenuates skin fibrosis through secretion of interleukin 12 (IL-12) and interferon γ,[36] whereas a TH2 response has been strongly linked to fibrogenesis.[7] Consistently, TH2 cytokines secreted by $CD4^+$ T cells such as IL-4, IL-5, IL-10, and IL-13 have been implicated in the development of keloids.[7]

Both the intensity and the type of the immune response significantly contribute to abnormal scar formation. In fact, the dermis in both keloids and hypertrophic scars is infiltrated by $CD3^+$, $CD45RO^+$, and HLA-antigen D–related $CD4^+$ T cells, as well as $CD1a^+$/$CD36^+$/intercellular adhesion molecule–positive dendritic cells.[13] However, in hypertrophic scars, the amount of infiltrate is variable with the age of the scar (proportional with severity), and it is extremely elevated and insignificantly variable with age in keloids.[13] Collectively, it is likely that the infiltration by immune cells contributes to excessive scarring, and consistent presence of these immune cells contributes to keloid formation.

Aberrant cytokine secretion from chronic infiltration of immune cells in keloids significantly contributes to the development of pathogenic scars.[13] Several cytokines are dysregulated in keloids and hypertrophic scars, such as IL-1β,[37] tumor necrosis factor α,[38] vascular endothelial growth factor, connective tissue growth factor, platelet-derived growth factor, and particularly transforming growth factor β (TGF-β).[39,40] Transforming growth factor β is the principal stimulator of collagen production and is overexpressed in keloids and hypertrophic scars.[41] There are 5 conserved isoforms of TGF-β, with β1 to β3 being the principal mammalian forms.[7] Transforming growth factor β1 and TGF-β2 stimulate the synthesis of collagen and PGs, whereas TGF-β3 plays key roles in decreasing the deposition of connective tissue.[7] Therefore, it is not surprising that inhibiting the activity of TGF-β1 by injecting animals with neutralizing antibodies to TGF-β1 resulted in decreased fibrosis and deposition of scar tissue.[42]

The mRNA expression of TGF-β1, TGF-β2, and TGF-β3 and their receptors I and II in hypertrophic scars, keloids, and normal skin was measured in dermal fibroblasts from freshly taken skin biopsies and confirmed that the levels of the 3 isoforms of TGF-β were dysregulated in the aberrant scarring disorders compared with normal skin. However, comparing hypertrophic scars with keloids, there were significantly less TGF-β1 and TGF-β2 and more TGF-β3 mRNA in hypertrophic scars.[43] Further, the ratio of TGF-β receptor I (TGF-βRI) to TGF-βRII in keloid fibroblasts was higher compared with hypertrophic scarring,[43] and the increased ratio of TGF-βRI to TGF-βRII was reported in another study to promote collagen synthesis.[44] Ultimately, the differences in TGF-β isoforms and receptors expression could at least partially account for the onset of either disorder.

**Table 3.**
**SUMMARY AND COMPARATIVE ANALYSIS OF DIFFERENT FACTORS UNDERLYING HYPERTROPHIC SCARS AND KELOIDS**

| | Hypertrophic Scars | Keloids |
|---|---|---|
| **Proliferation** | | |
| Proliferation | Higher proliferative capacity and apoptosis resistance than normal skin but lower than keloids' | Greater proliferative capacity and apoptosis resistance |
| Fas-mediated apoptosis | Not resistant | Resistant |
| p53 expression | Higher than normal skin and keloids, with mutations in exon 7 | Lower than hypertrophic scarring, with mutations in exons 5, 6, and 7 |
| Caspases 3 and 9 | Higher than normal skin but lower than keloids | Higher |
| B-cell lymphoma 2 | Higher than normal skin | Higher than normal skin |
| **Inflammation** | | |
| Immune cell infiltration | Less infiltration of immune cells | Greater infiltration of immune cells |
| TGF-β expression | Significantly less TGF-β1 and TGF-β2 and higher TGF-β3 mRNA | More TGF-β1 and TGF-β2 and lower TGF-β3 mRNA |
| TGF-β:receptor ratio | Lower ratio of TGF-βRI/TGF-βRII | Higher ratio of TGF-βRI to TGF-βRII (ratio consistent with promoting collagen synthesis and fibrosis) |
| **Extracellular Matrix** | | |
| Fibronectins | Dispersed diffusedly throughout the dermis in a linear or curling arrangement | Dispersed in the intercellular matrix |
| Integrins | Higher α1β1 and α2β1 than normal skin but lower than keloids | Higher α1β1 and α2β1 integrin expression |
| MMPs | Lower MMP-19 expression than keloids but comparable with normal skin | MMP-19 is significantly up-regulated |
| Fibrillin 1 | Comparable levels (reduced) | Comparable levels (reduced) |
| Elastin | Elastin level is reduced in the deep dermis | Elastin level is increased in the deep dermis |
| Collagen | Type III > I ratio (17:1) | Type I > III ratio (6:1) |
| | Lower overall expression than keloids but higher than normal skin | Higher overall expression |
| Connexin 43 | Significantly reduced compared with normal skin, but levels are higher than keloids | Significantly reduced |
| Hyaluronan | Lower than normal skin<br>Mainly distributed in the papillary dermis | Lower than normal skin<br>Mainly distributed in the reticular layer |
| Decorin | Decreased proportional to the severity of the hypertrophic scar, and levels recover as it heals | Persistent decrease |
| Dermatopontin | Lower than normal skin | Lower than normal skin |
| Periostin | Lower than keloids | Higher expression |
| Tenascin expression | Not increased compared with normal scars and skin | Significantly increased in keloids |
| Laminin expression | Not increased compared with normal fibroblasts | Significantly increased in keloidal fibroblasts |
| **Other Factors** | | |
| Mast cells | Number is significantly increased | Number and their activity is significantly increased |
| COX | COX-1 overexpression | COX-2 overexpression |
| HSP27 | Higher levels than normal skin but lower than keloids | Significantly higher levels |
| HSP47 | Significantly higher levels | Higher levels than normal skin but lower than hypertrophic scars |

*(continues)*

**Table 3.**

**SUMMARY AND COMPARATIVE ANALYSIS OF DIFFERENT FACTORS UNDERLYING HYPERTROPHIC SCARS AND KELOIDS, CONTINUED**

| | Hypertrophic Scars | Keloids |
|---|---|---|
| CGRP | No significant differences in protein expression compared to normal skin | Higher expression |
| PAI-1 | Higher expression compared with normal skin | Higher expression compared with normal skin |
| PAI-2 | Comparable expression with normal skin | Higher expression |
| ROS | Higher expression | Lower than hypertrophic scars (but higher than normal skin) |
| Nrf2 | Expression between keloids and hypertrophic scars not compared yet | Lower expression compared with normal skin |
| Inducible NOS | Similar expression compared with normal skin | Higher expression compared with normal skin |
| $Ca2^{+}$-responsive NOS | Lower expression compared with normal skin | Expression between keloids and hypertrophic scars not compared yet |

Abbreviations: COX, cyclooxygenase; CGRP, calcitonin gene-related peptide; HSP, heat shock protein; MMPs, matrix metalloproteinases; NOS, nitric oxide synthase; Nrf2, nuclear factor erythroid 2–related factor 2; PAI, plasminogen activator inhibitor; ROS, reactive oxygen species; TGF, transforming growth factor.

The anti-inflammatory cytokine IL-10 attenuates the inflammatory response following an inflammatory process such as skin injury.[45] The attenuation by IL-10 is mediated through several mechanisms, including down-regulation of the profibrotic cytokines IL-6 and IL-8[46,47] and inhibition of the key regulator of inflammation, the transcription factor nuclear factor B.[48,49] The mechanisms by which IL-10 modulates antifibrotic effects have been an important focus of research, particularly in the past decade, for potential therapeutic application against aberrant scarring. In fact, IL-10 was administered in an animal model 3 days before wounding, and compared with the control group, the wounds of IL-10–treated animals had lower levels of proinflammatory mediators and demonstrated normal collagen deposition and normal dermal architecture.[50] More recently, IL-10 was demonstrated to promote regenerative healing and improve dermal architecture by mediating antifibrosis in skin scarring.[51] It is still not completely understood whether there are significant differences in the levels of IL-10 and IL-10 receptors in keloids and hypertrophic scars. More research is required to optimize IL-10 therapy for pathologic scarring.

## Extracellular Matrix

Extracellular matrix is the noncellular component of all tissues and organs and plays pivotal roles in the structural and biochemical support of the tissue and facilitates cell-to-cell communication. The 2 primary macromolecule constituents of the ECM are PGs, such as chondroitin sulfate, heparan sulfate, and keratan sulfate, and fibrous proteins, including FN, collagen, elastin, and laminin. It is not surprising that components of the ECM are implicated both in aberrant wound healing processes and in explaining the differences between keloids and hypertrophic scarring.[52]

**Fibronectin**. Fibroblasts are the principal cells of scar tissue and are responsible for the synthesis of matrix proteins that are involved in the remodeling process.[2] Fibronectin, a product of fibroblasts, is a key glycoprotein constituent of the ECM that binds to the membrane-spanning receptor proteins integrins, as well as other components including collagen and fibrin.[53] The expression of FN is tightly regulated during wound healing. In the early stage of wound healing, there is an increased availability of FN with low expression of collagen fibers, and this trend reverses in the maturation and remodeling phase of wound healing.[54,55]

Levels of FN are significantly higher in hypertrophic scars and keloids compared with normal skin.[56] The overproduction of FN in hypertrophic scars and keloids suggests a dysregulated healing process. In fact, as already discussed, TGF-β1 levels are augmented in hypertrophic scars and keloids, and 1 of the downstream effects of such an increase is a significant increase in the biosynthesis of FN and ECM.[54] The distribution of FN is different between the 2 different types of scars. In hypertrophic scars, FN is dispersed diffusely throughout the dermis in a linear or curling arrangement,[57] but in keloids FN is localized in high density in the intercellular matrix.[58]

**Integrin**. Fibroblasts interact with other cells in the ECM through integrin proteins that function as bridges for cell-to-cell communication.[59] In response to skin injury, integrin proteins facilitate the binding of their ligand collagen to matrix metalloproteinases (MMPs), which in turn re-epithelialize the wound and help to form a scar.[60]

Integrins are composed of 1α and 1β subunit. There are 18 α and 8 β subunits in mammals,[61] and various combinations of these subunits produce different integrin proteins, each with their own signaling properties.[62] It is likely that different integrins

recruit different signaling molecules and differentially control cell signaling and cellular tension.[63]

The integrins α1β1, α2β1, and α3β1 bind to laminin, collagen, FN, and other ECM components.[64] In fibroblasts, collagen is recognized by α1β1 and α2β1 integrins that regulate collagen synthesis through a negative feedback mechanism.[2] Consistently, neutralizing antibodies against α11 integrin proteins block the down-regulation of collagen synthesis.[65]

Integrin expression is influenced by cytokines such as TGF-β1 that significantly up-regulate its expression,[54] so it is not surprising that integrin expression is affected in hypertrophic scars and keloids. In fact, expression of α1β1 integrin is significantly increased in keloidal fibroblasts, and increased but to a lesser extent in hypertrophic scars, compared with normal skin.[66] The collagen-binding α2β1 integrin is the most abundant collagen receptor on the surface of keratinocytes that reside primarily in the stratum basale layer of the epidermis.[67] The α2β1-integrin mRNA, which mediates several processes including wound healing,[68] was quantified in keloids, hypertrophic scars, and normal skin.[69] The α2β1-integrin mRNA expression was significantly augmented in fibroblasts from hypertrophic scars and keloids compared with normal skin, and protein expression was significantly higher in keloids than in hypertrophic scars.[69]

**Matrix metalloproteinases**. Matrix metalloproteinases are endopeptidases with the primary function of degrading an array of ECM proteins.[70] Along with serine proteinases such as tissue plasminogen activator and urokinase plasminogen activator, MMPs counteract fibroblast production of ECM proteins and provide a balance by preventing excessive matrix synthesis.

The degradation of collagen types I, II, and III is mediated by MMP-1 (collagenase 1), MMP-8 (collagenase 2), and MMP-13, respectively.[2] The activity and function of MMPs are also dependent on several factors that are dysregulated in aberrant scarring pathologies such as hypertrophic scarring and keloids. For instance, the expression of MMPs is regulated at least in part by TGF-β, so it is not surprising that expression of the different isoforms of MMP is affected in keloids and hypertrophic scars. In fact, compared with normal skin, the mRNA and protein expression are significantly higher for MMP-13 and lower for MMP-1 and MMP-8 in keloids.[71]

Potential differences in the expression of all MMP isoforms between hypertrophic scars and keloids are yet to be completely elucidated. Collectively, while excessive collagen synthesis plays a role in excessive scar formation, a reduced breakdown of collagen because of the dysregulation of proteinases such as MMP-1 and MMP-8 may also contribute to the pathology.

**Fibrillin 1 and elastin**. These components of the ECM allow tissue to resist tensile or stretching forces. The major components of elastic fibers are elastin and fibrillin-rich microfibrils.[72] The distribution of elastin and fibrillin 1 is reduced in normal scars and more significantly in both hypertrophic scars and keloids.[73] Although the expression of fibrillin 1 is reduced in both types of scars in comparison with normal skin, there are no significant differences in fibrillin 1 expression between hypertrophic scars and keloids in either the superficial or deep dermis. Elastin levels, however, are reduced in both hypertrophic scars and keloids compared with normal skin in superficial dermis, but in deep dermis, elastin levels are reduced only in hypertrophic scars and actually significantly increased in keloids.[73] The disruption of elastic system components likely contributes to the distinct biomechanical properties of hypertrophic scars and keloids.[73]

**Collagen**. Collagen proteins, secreted by fibroblasts, are the most abundant fibrous protein within the interstitial ECM, and through their association with elastin, they provide tensile strength and regulate cellular development, adhesion, and migration.[74,75] Collagen deposition is a key determinant for scar formation, particularly in the case of hypertrophic scars and keloids where collagen types I and III are thought to account for the excessive scarring.[8] While collagen expression is increased in both hypertrophic scars and keloids compared with normal skin, the ratio of type I to type III collagen is significantly increased in keloids compared with hypertrophic scars (approximately 17:1) and with normal skin.[76] Conversely, collagen III/I expression is significantly higher in hypertrophic scars (approximately 6:1) compared with keloids.[77] The differential expression of collagens may allow the distinction between the 2 entities through immunohistochemistry and confocal microscopy.[77]

**Connexin**. Gap junctions are organized aggregates of protein channels in cell membranes that serve as passageways to adjacent cells and allow for communication and exchange of proteins, ions, and other signaling molecules.[78] The core constituents of gap junctions are the connexin proteins.[78] Connexin proteins play important roles in the intercellular communication between fibroblasts and other cell types, and dysregulation of connexin expression has been implicated in tumorigenesis.[79] In fact, connexin-43 expression and gap junctional intercellular communication are reduced in keloid and hypertrophic tissues compared with normal skin, and keloids had significantly lower connexin-43 expression than hypertrophic scars.[80] It has been postulated that because of the reduced gap-junctional intercellular communication in hypertrophic scars and keloids, fibroblasts do not receive sufficient inhibitory and apoptotic signals from adjacent cells, and this partially accounts for the abnormal proliferation in these scars.[80] In fact, gap junctions play important roles in modulating intercellular communications and dynamic reciprocity among fibroblasts and mast cells as demonstrated by the knockdown of connexin-43 in both, which blocked transformation of fibroblasts into α-SMA–expressing myofibroblasts.[81]

**Decorin**. Decorin is a small dermal ECM PG that plays important roles in regulating the assembly and organization of

the ECM by binding to several components such as collagen and FN.[82] Decorin expression in hypertrophic scars is reduced by approximately 75%.[83] Consistently, the measurement of decorin in burn wounds at various stages of healing has revealed that its expression is decreased in hypertrophic scarring and that levels recover as hypertrophic scarring resolves.[84] Similarly, decorin expression is also dysregulated in keloids.[85] In fact, recombinant human decorin down-regulates TGF-β1 production and induces growth suppression in keloid fibroblasts, suggesting its therapeutic potential as an antifibrotic agent.[86] Aberrant expression of decorin and other small leucine-rich PGs likely contributes to the altered physical properties of hypertrophic scars and keloids, and proper scar healing may depend on appropriate expression of PGs.[83]

**Hyaluronan**. Hyaluronan is a high-molecular-mass glycosaminoglycan (polysaccharide) component of the ECM that plays pivotal roles in cell proliferation and migration.[87] It is active in the proliferative phase of wound closure and scar formation. Hyaluronan levels increase quickly following skin injury to orchestrate the appearance and maintenance of myofibroblasts, and then degrades in a highly regulated process involving hyaluronidases and reactive oxygen species (ROS).[87] Hyaluronan levels are abnormally decreased in aberrant scars, suggesting a regulatory role of hyaluronan in mediating normal wound closure and scar formation.[87–89] Hyaluronan expression is regulated by TGF-β–mediated proliferation of fibroblasts, and therefore alterations in TGF-β levels and subsequent variation in hyaluronan expression may contribute to the development of either hypertrophic scars or keloids.[90] In hypertrophic scars, hyaluronan is distributed mainly in the papillary dermis, similar to normal skin and indicating a better capacity to recover like normal skin over time, whereas keloids lack the accumulation of hyaluronan in the papillary dermis, and hyaluronan is mainly distributed in the reticular layer.[89]

**Dermatopontin**. A noncollagenous component of the ECM, dermatopontin binds small dermatan sulfate PGs, decorin, and collagens; is involved in modification of collagen fibrillogenesis; and promotes cell adhesion by integrin binding.[91] Decreased expression of dermatopontin is associated with abnormal scarring. In fact, fibroblasts from hypertrophic scars show a 2- to 3-fold reduction of dermatopontin mRNA and protein compared with fibroblasts from normal skin.[92] Keloid fibroblasts express low levels of dermatopontin.[93] Exogenous treatment of fibroblasts in vitro with TGF-β1 increased dermatopontin mRNA expression, whereas IL-4 treatment reduced dermatopontin mRNA expression compared with untreated samples.[92] Therefore, it is likely that altered levels of TGF-β, and consequently dermatopontin, contribute to the pathogenesis of hypertrophic scarring and keloid formation.

**Periostin**. This ECM protein is involved in tissue remodeling by promoting the differentiation and activation of fibroblasts.[94] Levels of periostin typically increase a few days following wound repair, peaking after 7 days and decreasing thereafter.[94] Periostin is significantly induced by TGF-β1 in vitro.[95] Perhaps not surprisingly, the expression of periostin is increased in hypertrophic scars and keloids compared with normal skin.[95] The mRNA expression of periostin, however, is higher in keloids than in hypertrophic scars,[96] highlighting periostin as an additional contributing factor in keloid formation.

**Tenascin**. Tenascins are multifunctional ECM glycoproteins expressed during fetal development and in wound repair but very limited in adult tissue, which modulate cellular adhesion through antagonizing cell attachment to FN. They play a critical role in initiating keratinocyte and fibroblast migration to wound sites.[97] Tenascin proteins are present at wound margins within 4 and 24 hours after injury in fetal and adult skin tissue, respectively, consistent with their role in the rapid epithelialization seen in wound healing.[98] There appears to be differential tenascin expression in different scar tissue. There are no significant differences in tenascin protein levels in fibroblasts from hypertrophic scars and normal scars.[99] However, tenascin C expression levels are significantly higher in keloids compared with normal scars and skin.[100] Further, the distribution of tenascin C is different in keloid tissue; it infiltrates the reticular and papillary dermis, whereas in normal skin tenascin is restricted to the dermal-epidermal junction in the superficial papillary dermis.[100]

**Laminin**. This integral glycoprotein component of the basal lamina mediates cell adhesion by binding to several cell surface receptors and other ECM molecules.[101] It is only recently that an understanding of its role in angiogenesis, scar formation, and wound repair has emerged.[102] No significant differences were found in the protein expression of laminin in fibroblasts from hypertrophic scars compared with normal scars over a 1-year period.[99] However, laminin β2 protein expression is significantly increased in keloid fibroblastic cell lines compared with normal fibroblasts.[103]

## Other Factors

**Mast cells**. There is a significant elevation in the number of mast cells in hypertrophic scars compared with mature scars and normal skin.[104–107] Similarly, the number of mast cells in keloids is significantly increased.[108] The activation of mast cells results in the release of several fibrogenic mediators such as histamine that mediate collagen fiber synthesis, tryptase (which stimulates the synthesis of type I collagen), and chymase (a protease that cleaves procollagens, aids in fibril synthesis, and contributes to scar formation).[29] Further evidence of the roles of mast cells in aberrant scar formation comes from experiments where the skin of pigs that are prone to hypertrophic scarring after wounding had reduced collagen fiber deposition and scarring when treated with ketotifen, a second-generation noncompetitive H1-antihistamine and mast cell stabilizer.[109] More research is needed to fully elucidate

differences in mast cell activation between the 2 pathologic scarring entities discussed in this article.

**Cyclooxygenases**. Prostaglandins are metabolites of arachidonic acid produced by the catalytic action of cyclooxygenase 1 (COX-1) and COX-2.[110] In normal skin, COX-1 is localized throughout the epidermis, and COX-2 is present predominantly in suprabasal keratinocytes.[111] A significant up-regulation of COX-1 protein exists in hypertrophic scars compared with keloids and normal skin, and in keloids there is significant up-regulation of the COX-2 protein, highlighting the distinct pathophysiology of both entities.[112] Further, COX-2 has been detected in lymphocytes and macrophages from keloid tissue, suggesting that inflammatory cells may also contribute to the development of keloids by COX-2 expression.[110] The expression of COX-1 is induced by TGF-β, whereas COX-2 is induced by tumor necrosis factor α.[113] This suggests that different cytokine milieus and inflammatory cells may influence the expression of each COX and predispose the scar to develop a specific form of aberrant scarring.

**Heat shock proteins**. Heat shock proteins (HSPs) function as molecular chaperones to stabilize new protein synthesis and are involved in posttranslational modification processes to ensure correct folding.[114] These HSPs are involved in the synthesis of ECM proteins: for instance, HSP47 is a collagen-specific factor that stabilizes procollagen during protein synthesis and ensures proper folding of the protein.[115] Irregular HSP expression is implicated in abnormal wound healing.[116] In fact, in keloids, compared with normal skin, there is a significant overexpression of HSP27, HSP47, and HSP70 and no differences in HSP60 and HSP90 protein expression, indicating that the dysregulation of specific members of HSPs may be implicated in keloid scar formation.[117] Several studies[69,118,119] reveal interesting findings that may implicate the differential expression of HSPs in the pathogenesis of hypertrophic scars and keloids, and more research is needed to fully elucidate the roles of each HSP in these disorders.

**Calcitonin gene-related peptide and plasminogen activator inhibitors**. Recently, the mRNA and protein expression levels of 2 other genes, calcitonin gene-related peptide and plasminogen activator inhibitor 2 (PAI-2), were found to be elevated in keloids compared with hypertrophic scars and normal skin.[69] These genes are implicated in wound healing, and their overexpression could contribute to the pathology seen in aberrant scars.[120–122] Elevated levels of PAI-1 play an important role in a decreased capacity for fibrinolysis and excessive collagen accumulation in keloids.[123–125] Recently, elevated levels of PAI-1 were also reported in hypertrophic scar–derived fibroblasts as compared with normal skin.[126] More studies that compare the differential expression of PAIs and calcitonin gene-related peptide may reveal important differences that may contribute to keloid and hypertrophic scarring pathogenesis.

**Reactive oxygen species, nuclear factor erythroid 2–related factor 2, and nitric oxide**. Elevated levels of ROS have been implicated in many fibrotic disorders, including fibrotic skin diseases. In fact, elevated levels of ROS were reported in both keloid and hypertrophic scar fibroblasts, compared with normal fibroblasts, with higher levels in hypertrophic scars than keloids.[27]

A key transcription factor, nuclear factor erythroid 2 (Nrf2), regulates the expression of many genes, including those involved in apoptosis and in the mediation of the protective cellular response against oxidative stress, triggered by different processes including inflammation and injury.[127] Indeed, in comparison with normal skin tissue, keloid tissues are associated with significantly elevated levels of oxidative stress.[33] Consistently, levels of Nrf2 in keloid tissue were significantly lower than in normal skin.[33] Currently, possible roles of Nrf2 in the formation of hypertrophic scars are still to be investigated.

Nitric oxide is one of the few recognized gaseous signaling molecules (gasotransmitters) and a mediator of a wide array of physiologic and pathologic processes.[128,129] It is produced by nitric oxide synthase (NOS). There are 3 human isoforms of NOS, the inducible NOS (iNOS), and 2 constitutive $Ca2^{+}$-responsive NOS (cNOS).[130] Nitric oxide plays a role in wound remodeling by mediating keratinocyte proliferation and modulating collagen synthesis in fibroblasts.[131] Elevated levels of iNOS mRNA and proteins were detected in keloid tissues compared with normal skin tissue controls, although cNOS was not examined in the study.[132] Further, exposure of keloid fibroblasts to exogenous nitric oxide resulted in up-regulation of type I collagen synthesis, confirming the functional relevance of iNOS in regulating collagen synthesis in keloid scars.[132] On the other hand, the expression of iNOS is not altered in hypertrophic scar fibroblasts.[133] However, dermal fibroblasts derived from hypertrophic scar tissue were shown to express lower levels of cNOS and produce less nitric oxide than normal fibroblasts.[133] It is likely that contributions of different NOS isoforms contribute to the pathogenesis of aberrant scar formation, and more research in this avenue could help to better delineate the mechanisms of keloids versus hypertrophic scars.

## TREATMENT

There are a number of available surgical options as well as topical, oral, and systemic therapies for aberrant scarring. However, research has not yet defined a cure for keloids and hypertrophic scars, and the search for one further highlights the current knowledge deficit around the molecular mechanisms underlying these disorders. The available therapeutic modalities include silicone gel sheeting, compression therapy, surgical excision followed by radiation therapy, occlusive dressings, intralesional corticosteroid injections, cryotherapy, laser therapy, and interferon therapy, among others. Detailed reviews on the available treatments

modalities of hypertrophic scarring and keloids are discussed in the following references.[4,7,134–136] It is important to note that currently most of the indicated therapeutic modalities are generally used for both aberrant scarring entities.[7] Therefore, better understanding of the pathophysiology of hypertrophic scars and keloids will allow for the development of specific and targeted therapies for each condition.[137–138]

## CONCLUSIONS

Numerous pathophysiologic and clinical factors are implicated in the pathogenesis of aberrant scars, hypertrophic scars, and keloids. Researchers and clinicians should strive to identify and understand the specific causal mechanisms in the pathogenesis of hypertrophic scars and keloids. This knowledge will potentially help in developing specific and effective therapeutic modalities and better treatment outcomes.

## PRACTICE PEARLS

- Millions of patients each year develop hypertrophic scars and keloids following trauma or surgery. They result from pathologic wound healing and often cause pain, dysfunction, and decreased quality of life.
- There are important differences between hypertrophic scars and keloids in terms of clinical presentation, epidemiology, and histologic findings.
- The underlying molecular mechanisms and factors of keloids and hypertrophic scarring are distinct and unique to each.
- Current treatment options remain incompletely effective, most likely because of a lack of understanding of the pathophysiology of the different types of aberrant scars.

## REFERENCES


1. Diegelmann RF, Evans MC. Wound healing: an overview of acute, fibrotic and delayed healing. Front Biosci 2004;9:283-9.
2. Bran GM, Goessler UR, Hormann K, Riedel F, Sadick H. Keloids: current concepts of pathogenesis [review]. Int J Mol Med 2009;24(3):283-93.
3. Butler PD, Longaker MT, Yang GP. Current progress in keloid research and treatment. J Am Coll Surg 2008;206(4):731-41.
4. Mustoe TA, Cooter RD, Gold MH, et al. International clinical recommendations on scar management. Plast Reconstr Surg 2002;110(2):560-71.
5. Van den Broek LJ, Limandjaja GC, Niessen FB, Gibbs S. Human hypertrophic and keloid scar models: principles, limitations and future challenges from a tissue engineering perspective. Exp Dermatol 2014;23(6):382-6.
6. Bayat A, Bock O, Mrowietz U, Ollier WE, Ferguson MW. Genetic susceptibility to keloid disease and hypertrophic scarring: transforming growth factor beta1 common polymorphisms and plasma levels. Plast Reconstr Surg 2003;111(2):535-43.
7. Gauglitz GG, Korting HC, Pavicic T, Ruzicka T, Jeschke MG. Hypertrophic scarring and keloids: pathomechanisms and current and emerging treatment strategies. Mol Med 2011;17(1-2):113-25.
8. Niessen FB, Spauwen PH, Schalkwijk J, Kon M. On the nature of hypertrophic scars and keloids: a review. Plast Reconstr Surg 1999;104(5):1435-58.
9. Mandal A, Imran D, Rao GS. Spontaneous keloids in siblings. Ir Med J 2004;97(8):250-1.
10. Goodfellow A, Emmerson RW, Calvert HT. Rubinstein-Taybi syndrome and spontaneous keloids. Clin Exp Dermatol 1980;5(3):369-70.
11. Atiyeh BS, Costagliola M, Hayek SN. Keloid or hypertrophic scar: the controversy: review of the literature. Ann Plast Surg 2005;54(6):676-80.
12. Swann DA, Garg HG, Jung W, Hermann H. Studies on human scar tissue proteoglycans. J Invest Dermatol 1985;84(6):527-31.
13. Santucci M, Borgognoni L, Reali UM, Gabbiani G. Keloids and hypertrophic scars of Caucasians show distinctive morphologic and immunophenotypic profiles. Virchows Arch 2001;438(5):457-63.
14. Ehrlich HP, Desmouliere A, Diegelmann RF, et al. Morphological and immunochemical differences between keloid and hypertrophic scar. Am J Pathol 1994;145(1):105-13.
15. Bayat A, Arscott G, Ollier WE, Ferguson MW, McGrouther DA. "Aggressive keloid": a severe variant of familial keloid scarring. J R Soc Med 2003;96(11):554-5.
16. Ramakrishnan KM, Thomas KP, Sundararajan CR. Study of 1,000 patients with keloids in South India. Plast Reconstr Surg 1974;53(3):276-80.
17. Baisch A, Riedel F. Hyperplastic scars and keloids. Part I: basics and prevention [in German]. HNO 2006;54(11):893-904.
18. Chen Y, Gao JH, Liu XJ, Yan X, Song M. Characteristics of occurrence for Han Chinese familial keloids. Burns 2006;32(8):1052-9.
19. Clark JA, Turner ML, Howard L, Stanescu H, Kleta R, Kopp JB. Description of familial keloids in five pedigrees: evidence for autosomal dominant inheritance and phenotypic heterogeneity. BMC Dermatol 2009;9:8.
20. Marneros AG, Norris JE, Olsen BR, Reichenberger E. Clinical genetics of familial keloids. Arch Dermatol 2001;137(11):1429-34.
21. Shih B, Bayat A. Genetics of keloid scarring. Arch Dermatol Res 2010;302(5):319-39.
22. Brown JJ, Bayat A. Genetic susceptibility to raised dermal scarring. Br J Dermatol 2009;161(1):8-18.
23. Teng G, Liu C, Chen M, Ma K, Liang L, Yan T. Differential susceptible loci expression in keloid and hypertrophic scars in the Chinese Han population. Ann Plast Surg 2015;74(1):26-9.
24. Song R, Bian HN, Lai W, Chen HD, Zhao KS. Normal skin and hypertrophic scar fibroblasts differentially regulate collagen and fibronectin expression as well as mitochondrial membrane potential in response to basic fibroblast growth factor. Braz J Med Biol Res 2011;44(5):402-10.
25. Nakaoka H, Miyauchi S, Miki Y. Proliferating activity of dermal fibroblasts in keloids and hypertrophic scars. Acta Derm Venereol 1995;75(2):102-4.
26. Calderon M, Lawrence WT, Banes AJ. Increased proliferation in keloid fibroblasts wounded in vitro. J Surg Res 1996;61(2):343-7.
27. De Felice B, Garbi C, Santoriello M, Santillo A, Wilson RR. Differential apoptosis markers in human keloids and hypertrophic scars fibroblasts. Mol Cell Biochem 2009;327(1-2):191-201.
28. Lu F, Gao J, Ogawa R, Hyakusoku H, Ou C. Fas-mediated apoptotic signal transduction in keloid and hypertrophic scar. Plast Reconstr Surg 2007;119(6):1714-21.
29. Huang C, Murphy GF, Akaishi S, Ogawa R. Keloids and hypertrophic scars: update and future directions. Plast Reconstr Surg Glob Open 2013;1(4):e25.
30. Liu Y, Ren LS, Cen Y. Experimental study of Bcl-2 and Fas gene expression in fibroblast of scar [in Chinese]. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi 2001;15(6):351-3.
31. Wassermann RJ, Polo M, Smith P, Wang X, Ko F, Robson MC. Differential production of apoptosis-modulating proteins in patients with hypertrophic burn scar. J Surg Res 1998;75(1):74-80.
32. Akasaka Y, Ito K, Fujita K, et al. Activated caspase expression and apoptosis increase in keloids: cytochrome c release and caspase-9 activation during the apoptosis of keloid fibroblast lines. Wound Repair Regen 2005;13(4):373-82.
33. Lee YJ, Kwon SB, Kim CH, et al. Oxidative damage and nuclear factor erythroid 2-related factor 2 protein expression in normal skin and keloid tissue. Ann Dermatol 2015;27(5):507-16.
34. Ladin DA, Hou Z, Patel D, et al. p53 and apoptosis alterations in keloids and keloid fibroblasts. Wound Repair Regen 1998;6(1):28-37.
35. Hunasgi S, Koneru A, Vanishree M, Shamala R. Keloid: a case report and review of pathophysiology and differences between keloid and hypertrophic scars. J Oral Maxillofac Pathol 2013;17(1):116-20.
36. Wynn TA. Fibrotic disease and the T(H)1/T(H)2 paradigm. Nat Rev Immunol 2004;4(8):583-94.
37. Salgado RM, Alcantara L, Mendoza-Rodriguez CA, et al. Post-burn hypertrophic scars are characterized by high levels of IL-1beta mRNA and protein and TNF-alpha type I receptors. Burns 2012;38(5):668-76.

38. Messadi DV, Doung HS, Zhang Q, et al. Activation of NFkappaB signal pathways in keloid fibroblasts. Arch Dermatol Res 2004;296(3):125-33.
39. Khoo YT, Ong CT, Mukhopadhyay A, et al. Upregulation of secretory connective tissue growth factor (CTGF) in keratinocyte-fibroblast coculture contributes to keloid pathogenesis. J Cell Physiol 2006;208(2):336-43.
40. Ong CT, Khoo YT, Tan EK, et al. Epithelial-mesenchymal interactions in keloid pathogenesis modulate vascular endothelial growth factor expression and secretion. J Pathol 2007; 211(1):95-108.
41. Jagadeesan J, Bayat A. Transforming growth factor beta (TGFbeta) and keloid disease. Int J Surg 2007;5(4):278-85.
42. Border WA, Noble NA. Transforming growth factor beta in tissue fibrosis. N Engl J Med 1994;331(19):1286-92.
43. Bock O, Yu H, Zitron S, Bayat A, Ferguson MW, Mrowietz U. Studies of transforming growth factors beta 1-3 and their receptors I and II in fibroblast of keloids and hypertrophic scars. Acta Derm Venereol 2005;85(3):216-20.
44. Centrella M, Casinghino S, Kim J, et al. Independent changes in type I and type II receptors for transforming growth factor beta induced by bone morphogenetic protein 2 parallel expression of the osteoblast phenotype. Mol Cell Biol 1995;15(6):3273-81.
45. Moore KW, de Waal Malefyt R, Coffman RL, O'Garra A. Interleukin-10 and the interleukin-10 receptor. Ann Rev Immunol 2001;19:683-765.
46. Chen CC, Manning AM. TGF-beta 1, IL-10 and IL-4 differentially modulate the cytokine-induced expression of IL-6 and IL-8 in human endothelial cells. Cytokine 1996; 8(1):58-65.
47. Dagvadorj J, Naiki Y, Tumurkhuu G, et al. Interleukin (IL)-10 attenuates lipopolysaccharide-induced IL-6 production via inhibition of IkappaB-zeta activity by Bcl-3. Innate Immun 2009;15(4):217-24.
48. Wang P, Wu P, Siegel MI, Egan RW, Billah MM. Interleukin (IL)-10 inhibits nuclear factor kappa B (NF kappa B) activation in human monocytes. IL-10 and IL-4 suppress cytokine synthesis by different mechanisms. J Biol Chem 1995;270(16):9558-63.
49. Schottelius AJ, Mayo MW, Sartor RB, Baldwin AS, Jr. Interleukin-10 signaling blocks inhibitor of kappaB kinase activity and nuclear factor kappaB DNA binding. J Biol Chem 1999;274(45):31868-74.
50. Peranteau WH, Zhang L, Muvarak N, et al. IL-10 overexpression decreases inflammatory mediators and promotes regenerative healing in an adult model of scar formation. J Invest Dermatol 2008;128(7):1852-60.
51. Shi JH, Guan H, Shi S, et al. Protection against TGF-beta1-induced fibrosis effects of IL-10 on dermal fibroblasts and its potential therapeutics for the reduction of skin scarring. Arch Dermatol Res 2013;305(4):341-52.
52. Sidgwick GP, Bayat A. Extracellular matrix molecules implicated in hypertrophic and keloid scarring. J Eur Acad Dermatol Venereol 2012;26(2):141-52.
53. Pankov R, Yamada KM. Fibronectin at a glance. J Cell Sci 2002;115(Pt 20):3861-3.
54. Babu M, Diegelmann R, Oliver N. Keloid fibroblasts exhibit an altered response to TGF-beta. J Invest Dermatol 1992;99(5):650-5.
55. Grinnell F. Fibronectin and wound healing. J Cell Biochem 1984;26(2):107-16.
56. Kischer CW, Wagner HNJr, Pindur J, et al. Increased fibronectin production by cell lines from hypertrophic scar and keloid. Connect Tissue Res 1989;23(4):279-88.
57. Nagata H, Ueki H, Moriguchi T. Fibronectin. Localization in normal human skin, granulation tissue, hypertrophic scar, mature scar, progressive systemic sclerotic skin, and other fibrosing dermatoses. Arch Dermatol 1985;121(8):995-9.
58. Kischer CW, Hendrix MJ. Fibronectin (FN) in hypertrophic scars and keloids. Cell Tissue Res 1983;231(1):29-37.
59. Eckes B, Zigrino P, Kessler D, et al. Fibroblast-matrix interactions in wound healing and fibrosis. Matrix Biol 2000;19(4):325-32.
60. Saarialho-Kere UK, Kovacs SO, Pentland AP, Olerud JE, Welgus HG, Parks WC. Cell-matrix interactions modulate interstitial collagenase expression by human keratinocytes actively involved in wound healing. J Clin Invest 1993;92(6):2858-66.
61. Humphries MJ. Integrin structure. Biochem Soc Trans 2000;28(4):311-39.
62. Giancotti FG, Ruoslahti E. Integrin signaling. Science 1999;285(5430):1028-32.
63. Cukierman E, Pankov R, Stevens DR, Yamada KM. Taking cell-matrix adhesions to the third dimension. Science 2001;294(5547):1708-12.
64. Humphries JD, Byron A, Humphries MJ. Integrin ligands at a glance. J Cell Sci 2006; 119(Pt 19):3901-3.
65. Ravanti L, Heino J, Lopez-Otin C, Kahari VM. Induction of collagenase-3 (MMP-13) expression in human skin fibroblasts by three-dimensional collagen is mediated by p38 mitogen-activated protein kinase. J Biol Chem 1999;274(4):2446-55.
66. Szulgit G, Rudolph R, Wandel A, Tenenhaus M, Panos R, Gardner H. Alterations in fibroblast alpha1beta1 integrin collagen receptor expression in keloids and hypertrophic scars. J Invest Dermatol 2002;118(3):409-15.
67. Grenache DG, Zhang Z, Wells LE, Santoro SA, Davidson JM, Zutter MM. Wound healing in the alpha2beta1 integrin-deficient mouse: altered keratinocyte biology and dysregulated matrix metalloproteinase expression. J Invest Dermatol 2007;127(2):455-66.
68. Dumin JA, Dickeson SK, Stricker TP, et al. Pro-collagenase-1 (matrix metalloproteinase-1) binds the alpha(2)beta(1) integrin upon release from keratinocytes migrating on type I collagen. J Biol Chem 2001;276(31):29368-74.
69. Suarez E, Syed F, Alonso-Rasgado T, Bayat A. Identification of biomarkers involved in differential profiling of hypertrophic and keloid scars versus normal skin. Arch Dermatol Res 2015;307(2):115-33.
70. Lee DE, Trowbridge RM, Ayoub NT, Agrawal DK. High-mobility group box protein-1, matrix metalloproteinases, and vitamin d in keloids and hypertrophic scars. Plast Reconstr Surg Glob Open 2015;3(6):e425.
71. Uchida G, Yoshimura K, Kitano Y, Okazaki M, Harii K. Tretinoin reverses upregulation of matrix metalloproteinase-13 in human keloid-derived fibroblasts. Exp Dermatol 2003;12 Suppl 2:35-42.
72. Kielty CM, Sherratt MJ, Shuttleworth CA. Elastic fibres. J Cell Sci 2002;115(Pt 14):2817-28.
73. Amadeu TP, Braune AS, Porto LC, Desmouliere A, Costa AM. Fibrillin-1 and elastin are differentially expressed in hypertrophic scars and keloids. Wound Repair Regen 2004; 12(2):169-74.
74. Rozario T, DeSimone DW. The extracellular matrix in development and morphogenesis: a dynamic view. Dev Biol 2010;341(1):126-40.
75. Frantz C, Stewart KM, Weaver VM. The extracellular matrix at a glance. J Cell Sci 2010; 123(Pt 24):4195-200.
76. Friedman DW, Boyd CD, Mackenzie JW, Norton P, Olson RM, Deak SB. Regulation of collagen gene expression in keloids and hypertrophic scars. J Surg Res 1993;55(2):214-22.
77. Oliveira GV, Hawkins HK, Chinkes D, et al. Hypertrophic versus non hypertrophic scars compared by immunohistochemistry and laser confocal microscopy: type I and III collagens. Int Wound J 2009;6(6):445-52.
78. Giepmans BN. Gap junctions and connexin-interacting proteins. Cardiovasc Res 2004; 62(2):233-45.
79. Eghbali B, Kessler JA, Reid LM, Roy C, Spray DC. Involvement of gap junctions in tumorigenesis: transfection of tumor cells with connexin 32 cDNA retards growth in vivo. Proc Natl Acad Sci U S A 1991;88(23):10701-5.
80. Lu F, Gao J, Ogawa R, Hyakusoku H. Variations in gap junctional intercellular communication and connexin expression in fibroblasts derived from keloid and hypertrophic scars. Plast Reconstr Surg 2007;119(3):844-51.
81. Pistorio AL, Ehrlich HP. Modulatory effects of connexin-43 expression on gap junction intercellular communications with mast cells and fibroblasts. J Cell Biochem 2011; 112(5):1441-9.
82. Iozzo RV. The biology of the small leucine-rich proteoglycans. Functional network of interactive proteins. J Biol Chem 1999;274(27):18843-6.
83. Scott PG, Dodd CM, Tredget EE, Ghahary A, Rahemtulla F. Chemical characterization and quantification of proteoglycans in human post-burn hypertrophic and mature scars. Clin Sci (Lond) 1996;90(5):417-25.
84. Sayani K, Dodd CM, Nedelec B, et al. Delayed appearance of decorin in healing burn scars. Histopathology 2000;36(3):262-72.
85. Mukhopadhyay A, Wong MY, Chan SY, et al. Syndecan-2 and decorin: proteoglycans with a difference—implications in keloid pathogenesis. J Trauma 2010;68(4):999-1008.
86. Zhang Z, Li XJ, Liu Y, Zhang X, Li YY, Xu WS. Recombinant human decorin inhibits cell proliferation and downregulates TGF-beta1 production in hypertrophic scar fibroblasts. Burns 2007;33(5):634-41.
87. Aya KL, Stern R. Hyaluronan in wound healing: rediscovering a major player. Wound Repair Regen 2014;22(5):579-93.
88. Sidgwick GP, Iqbal SA, Bayat A. Altered expression of hyaluronan synthase and hyaluronidase mRNA may affect hyaluronic acid distribution in keloid disease compared with normal skin. Exp Dermatol 2013;22(5):377-9.
89. Bertheim U, Hellstrom S. The distribution of hyaluronan in human skin and mature, hypertrophic and keloid scars. Br J Plast Surg 1994;47(7):483-9.
90. Meran S, Thomas DW, Stephens P, et al. Hyaluronan facilitates transforming growth factor-beta1–mediated fibroblast proliferation. J Biol Chem 2008;283(10):6530-45.
91. Okamoto O, Fujiwara S. Dermatopontin, a novel player in the biology of the extracellular matrix. Connect Tissue Res 2006;47(4):177-89.

92. Kuroda K, Okamoto O, Shinkai H. Dermatopontin expression is decreased in hypertrophic scar and systemic sclerosis skin fibroblasts and is regulated by transforming growth factor-beta1, interleukin-4, and matrix collagen. J Invest Dermatol 1999;112(5):706-10.
93. Russell SB, Russell JD, Trupin KM, et al. Epigenetically altered wound healing in keloid fibroblasts. J Invest Dermatol 2010;130(10):2489-96.
94. Conway SJ, Izuhara K, Kudo Y, et al. The role of periostin in tissue remodeling across health and disease. Cell Mol Life Sci 2014;71(7):1279-88.
95. Zhou HM, Wang J, Elliott C, Wen W, Hamilton DW, Conway SJ. Spatiotemporal expression of periostin during skin development and incisional wound healing: lessons for human fibrotic scar formation. J Cell Commun Signal 2010;4(2):99-107.
96. Song ZH, Qin ZL. Expression of periostin and the effect of hydrocortisone on it in human fibroblasts of scar [in Chinese]. Beijing Da Xue Xue Bao 2008;40(3):301-5.
97. Hsia HC, Schwarzbauer JE. Meet the tenascins: multifunctional and mysterious. J Biol Chem 2005;280(29):26641-4.
98. Whitby DJ, Longaker MT, Harrison MR, Adzick NS, Ferguson MW. Rapid epithelialisation of fetal wounds is associated with the early deposition of tenascin. J Cell Sci 1991;99(Pt 3): 583-6.
99. Andriessen MP, Niessen FB, van de Kerkhof PC, Schalkwijk J. Hypertrophic scarring is associated with epidermal abnormalities: an immunohistochemical study. J Pathol 1998;186(2):192-200.
100. Dalkowski A, Schuppan D, Orfanos CE, Zouboulis CC. Increased expression of tenascin C by keloids in vivo and in vitro. Br J Dermatol 1999;141(1):50-6.
101. Durbeej M. Laminins. Cell Tissue Res 2010;339(1):259-68.
102. Iorio V, Troughton LD, Hamill KJ. Laminins: roles and utility in wound repair. Adv Wound Care 2015;4(4):250-63.
103. Lim IJ, Phan TT, Tan EK, et al. Synchronous activation of ERK and phosphatidylinositol 3-kinase pathways is required for collagen and extracellular matrix production in keloids. J Biol Chem 2003;278(42):40851-8.
104. Kischer CW, Bunce H 3rd, Shetlah MR. Mast cell analyses in hypertrophic scars, hypertrophic scars treated with pressure and mature scars. J Invest Dermatol 1978;70(6):355-7.
105. Harunari N, Zhu KQ, Armendariz RT, et al. Histology of the thick scar on the female, red Duroc pig: final similarities to human hypertrophic scar. Burns 2006;32(6):669-77.
106. Wang J, Ding J, Jiao H, et al. Human hypertrophic scar–like nude mouse model: characterization of the molecular and cellular biology of the scar process. Wound Repair Regen 2011;19(2): 274-85.
107. Wilgus TA, Wulff BC. The importance of mast cells in dermal scarring. Adv Wound Care 2014;3(4):356-65.
108. Ong CT, Khoo YT, Mukhopadhyay A, et al. Comparative proteomic analysis between normal skin and keloid scar. Br J Dermatol 2010;162(6):1302-15.
109. Gallant-Behm CL, Hildebrand KA, Hart DA. The mast cell stabilizer ketotifen prevents development of excessive skin wound contraction and fibrosis in red Duroc pigs. Wound Repair Regen 2008;16(2):226-33.
110. Lee JL, Mukhtar H, Bickers DR, Kopelovich L, Athar M. Cyclooxygenases in the skin: pharmacological and toxicological implications. Toxicol Appl Pharmacol 2003;192(3): 294-306.
111. Leong J, Hughes-Fulford M, Rakhlin N, Habib A, Maclouf J, Goldyne ME. Cyclooxygenases in human and mouse skin and cultured human keratinocytes: association of COX-2 expression with human keratinocyte differentiation. Exp Cell Res 1996;224(1):79-87.
112. Rossiello L, D'Andrea F, Grella R, et al. Differential expression of cyclooxygenases in hypertrophic scar and keloid tissues. Wound Repair Regen 2009;17(5):750-7.
113. Diaz A, Chepenik KP, Korn JH, Reginato AM, Jimenez SA. Differential regulation of cyclooxygenases 1 and 2 by interleukin-1 beta, tumor necrosis factor-alpha, and transforming growth factor-beta 1 in human lung fibroblasts. Exp Cell Res 1998; 241(1):222-9.
114. De Maio A. Heat shock proteins: facts, thoughts, and dreams. Shock 1999;11(1): 1-12.
115. Nagata K. Hsp47: a collagen-specific molecular chaperone. Trends Biochem Sci 1996; 21(1):22-6.
116. Naitoh M, Hosokawa N, Kubota H, et al. Upregulation of HSP47 and collagen type III in the dermal fibrotic disease, keloid. Biochem Biophys Res Commun 2001;280(5):1316-22.
117. Totan S, Echo A, Yuksel E. Heat shock proteins modulate keloid formation. Eplasty 2011;11:e21.
118. Barrow RE, Dasu MR. Oxidative and heat stress gene changes in hypertrophic scar fibroblasts stimulated with interleukin-1beta. J Surg Res 2005;126(1):59-65.
119. Chen J, Cen Y. Detection of expression of heat shock protein 47 mRNA in pathological scar tissue by using real-time fluorescent quantitative RT-PCR [in Chinese]. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi 2005;19(8):613-6.
120. Zhou Y, Zhang M, Sun GY, et al. Calcitonin gene-related peptide promotes the wound healing of human bronchial epithelial cells via PKC and MAPK pathways. Regul Pept 2013;184:22-9.
121. Romer J, Lund LR, Eriksen J, et al. Differential expression of urokinase-type plasminogen activator and its type-1 inhibitor during healing of mouse skin wounds. J Invest Dermatol 1991;97(5):803-11.
122. Chan JC, Duszczyszyn DA, Castellino FJ, Ploplis VA. Accelerated skin wound healing in plasminogen activator inhibitor-1-deficient mice. Am J Pathol 2001;159(5):1681-8.
123. Tuan TL, Wu H, Huang EY, et al. Increased plasminogen activator inhibitor-1 in keloid fibroblasts may account for their elevated collagen accumulation in fibrin gel cultures. Am J Pathol 2003;162(5):1579-89.
124. Tuan TL, Zhu JY, Sun B, Nichter LS, Nimni ME, Laug WE. Elevated levels of plasminogen activator inhibitor-1 may account for the altered fibrinolysis by keloid fibroblasts. J Invest Dermatol 1996;106(5):1007-11.
125. Tuan TL, Hwu P, Ho W, et al. Adenoviral overexpression and small interfering RNA suppression demonstrate that plasminogen activator inhibitor-1 produces elevated collagen accumulation in normal and keloid fibroblasts. Am J Pathol 2008;173(5):1311-25.
126. Li C, Zhu HY, Bai WD, et al. MiR-10a and miR-181c regulate collagen type I generation in hypertrophic scars by targeting PAI-1 and uPA. FEBS Lett 2015;589(3):380-9.
127. Kensler TW, Wakabayashi N, Biswal S. Cell survival responses to environmental stresses via the Keap1-Nrf2-ARE pathway. Annu Rev Pharmacol Toxicol 2007;47:89-116.
128. Moncada S, Palmer RM, Higgs EA. Nitric oxide: physiology, pathophysiology, and pharmacology. Pharmacol Rev 1991;43(2):109-42.
129. Bruch-Gerharz D, Ruzicka T, Kolb-Bachofen V. Nitric oxide in human skin: current status and future prospects. J Invest Dermatol 1998;110(1):1-7.
130. Feng C. Mechanism of nitric oxide synthase regulation: electron transfer and interdomain interactions. Coord Chem Rev 2012;256(3-4):393-411.
131. Frank S, Kampfer H, Wetzler C, Pfeilschifter J. Nitric oxide drives skin repair: novel functions of an established mediator. Kidney Int 2002;61(3):882-8.
132. Hsu YC, Hsiao M, Wang LF, Chien YW, Lee WR. Nitric oxide produced by iNOS is associated with collagen synthesis in keloid scar formation. Nitric Oxide 2006;14(4):327-34.
133. Wang R, Ghahary A, Shen YJ, Scott PG, Tredget EE. Nitric oxide synthase expression and nitric oxide production are reduced in hypertrophic scar tissue and fibroblasts. J Invest Dermatol 1997;108(4):438-44.
134. Leventhal D, Furr M, Reiter D. Treatment of keloids and hypertrophic scars: a meta-analysis and review of the literature. Arch Facial Plast Surg 2006;8(6):362-8.
135. Wolfram D, Tzankov A, Pulzl P, Piza-Katzer H. Hypertrophic scars and keloids—a review of their pathophysiology, risk factors, and therapeutic management. Dermatol Surg 2009; 35(2):171-81.
136. Viera MH, Amini S, Valins W, Berman B. Innovative therapies in the treatment of keloids and hypertrophic scars. J Clin Aesthet Dermatol 2010;3(5):20-6.
137. Berman B, Maderal A, Raphael B. Keloids and hypertrophic scars: pathophysiology, classification, and treatment. Dermatol Surg 2017;43 Suppl 1:S3-S18.
138. Slemp AE, Kirschner RE. Keloids and scars: a review of keloids and scars, their pathogenesis, risk factors, and management. Curr Opin Pediatr 2006;18:396-402.

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