Fibroproliferative scars

Shahrad R. Rahban, MD\textsuperscript{a}, Warren L. Garner, MD\textsuperscript{a,b,*}

\textsuperscript{a}University of Southern California Keck School of Medicine, Division of Plastic and Reconstructive Surgery, LAC+USC Medical Center, 1450 San Pablo Street, Suite #2000, Los Angeles, CA, 90033, USA

\textsuperscript{b}Burn Unit, LAC+USC Medical Center, 1200 N. State Street, Room 12-700, Los Angeles, CA 90033, USA

The physiology of wound healing has been a topic of intense investigation during recent years. Much insight has been gained into the complex cascade of events that results in a healed wound. The aberrations in this process that result in an abnormally healed wound are less well understood. Wounds can heal excessively or inadequately. Although many investigations have examined the pathophysiology and treatment of nonhealing or chronic wounds, there is little information about why some wounds heal with excess scar, and even less information on the best ways to treat them. Recent work has suggested clues to the pathogenesis of fibroproliferative scarring, but these have not been assembled yet into a descriptive scheme that suggests mechanistic treatment. The result is that many treatments exist, but none have been proven to be consistently efficacious therefore, hypertrophic and keloid scars remain a therapeutic challenge for clinicians.

This article reviews the two forms of fibroproliferative scars and the available treatment modalities. It discusses the published literature, suggests future possible treatments, and includes comments based on personal experience. These types of information have been kept separate in the hope that readers will evaluate and distinguish between science, experience, and prejudice.

Definition

Because epithelial tissue heals by scar formation rather than regeneration, it is normal to have scar at the site of tissue repair. Two forms of scar—hypertrophic scar and keloid scar—are excessive. Although hypertrophic and keloid scars can sometimes appear morphologically similar and the terms are often used interchangeably for excessive scarring, they are clinically and histologically distinct entities with different pathophysiology and treatment approaches.

Hypertrophic scars are raised, erythematous, and often pruritic. They remain within the boundaries of the original wound \cite{1,2}. Scar formation usually begins within 6 to 8 weeks of injury \cite{3}, and can worsen for up to 6 months \cite{4}. As hypertrophic scars develop, they may produce contractures if they are located over joints or occur along the length of an extremity. The maturation phase may last 1 to 2 years, and many regress without intervention \cite{5}. The extent of scarring is related to the depth and area of the original injury \cite{6}.

Keloid scars are also raised, erythematous, and often pruritic; however, they extend beyond the original wound boundaries \cite{1,2}. Keloids infrequently regress, tend to recur after excision, and are not associated with contractures \cite{7}. The amount of scarring may far surpass the extent of the original injury \cite{2,8–12}. Despite these differences, both fibro-
proliferative scars are disfiguring and can be clinically challenging to treat (Table 1).

### Epidemiology

The incidence of keloids and hypertrophic scars has been difficult to determine because few individuals with these problems present to physicians for treatment. There are a few universally agreed upon demographic associations. Both lesions are most common in dark pigmented individuals. Cosman et al [13] reported an incidence of keloids ranging from 4.5% to 16%, based on clinical impressions as opposed to pathological diagnosis, in a predominately Hispanic and black population. Oluwasanmi [14] surveyed a small African community and found the incidence to be 6.2%. The incidence of hypertrophic scars is probably higher in the general population, although no exact number is known [11]. Fibroproliferative scars are less frequent in whites, with an estimated white to black ratio of 1:3.5 to 1:15 [15].

Keloids and hypertrophic scars may occur at any age, but are more common in younger individuals ranging from 10 to 30 years of age [8,11,13,15-17]. It is unclear whether this is due to biological differences in children or because they are more prone to trauma [15]. No gender predisposition has been proven [15,18,19]. Keloids often occur in individuals with a familial history of keloid formation, although no specific genetic markers or exact pattern of inheritance has been established [12]. In a recent study of 14 pedigrees of families with keloids, Marneros et al [20] suggested an observed pattern of inheritance consistent with an autosomal dominant mode with incomplete clinical penetrance and variable expression. This is the most comprehensive collection of families with keloid described to date, and is the first elucidation of the clinical genetic characteristics of the familial form of this wound-healing disorder. Many practitioners believe that there is an increased incidence of keloid formation during puberty and pregnancy, suggesting the influence of sex hormones [12]. In addition, there are reports that these scars soften and flatten after menopause and with advancing age [21].

Hypertrophic scars are common after significant trauma such as burns and incisions, although they can occur after minor trauma such as acne or vaccinations. Patients with keloid scars often describe a minor initial trauma, such as ear piercing, although spontaneous occurrences have also been reported [4,12,22]. Both forms of proliferative scar are more common in areas of stretch or tension. Hypertrophic scars have a predilection to occur over joints, whereas keloids are commonly found on the deltoid, upper back, and chest. Interestingly, earlobes are a common site for keloid formation; however, this is not a site of skin tension [23]. Keloids rarely occur on eyelids, genitalia, palms, or soles [15].

### Pathogenesis

The pathogenesis of keloid and hypertrophic scar formation is complex and not fully understood. Both types of scar are believed to occur secondary to an imbalance between the synthesis of extracellular matrix (ECM)—particularly collagen—and its degradation. The specific nature of the imbalance appears to be different between keloids and hypertrophic scars.

Normal wound healing is a stepwise process beginning with hemostasis, and followed by inflammation, proliferation, and ultimately remodeling. During hemostasis and the deposition of a fibrin/platelet clot, platelet-derived growth factor, transforming growth factor \( \beta \) (TGF-\( \beta \)), and many other mediators are deposited into the wound [24]. During the subsequent inflammatory phase, macrophages are activated and then release additional cytokines, which induce matrix deposition and cell proliferation and promote angiogenesis. It is at this point during wound healing that many believe that hypertrophic scar formation originates. Inflammatory mediators are present in normal wounds [25] and are increased in

<table>
<thead>
<tr>
<th>Borders</th>
<th>Keloids</th>
<th>Hypertrophic scars</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Grows beyond original wound</td>
<td>Remains within original wound</td>
</tr>
<tr>
<td>Contractures</td>
<td>Absent</td>
<td>Often develops weeks after injury</td>
</tr>
<tr>
<td>Regression</td>
<td>Infrequent</td>
<td>Often partial within 1–2 years</td>
</tr>
<tr>
<td>Pruritis/erythema</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Extent of scar</td>
<td>Can far surpass initial extent of tissue injury</td>
<td>Related to initial depth of tissue injury</td>
</tr>
<tr>
<td>Response to surgery</td>
<td>Poor, often worsening</td>
<td>Well, especially with adjuvative therapy</td>
</tr>
</tbody>
</table>
slowly healing wounds [26]. These inflammatory cytokines can induce connective tissue growth factors such as TGF-β [27]. Prolonged inflammation in large wounds, such as burns, or following infection can be expected to increase the activity of fibrogenic cytokines such as TGF-β, insulin-like growth factor-1, and PDGF, and likely contribute to the development of keloids and hypertrophic scars [28–30]. This suggests a mechanism for the clinical observation that wounds, which healed beyond 21 days with exaggerated inflammation, had a high rate of hypertrophic scar formation [31].

TGF-β is a cytokine that plays a key role in fibroproliferative scar pathophysiology. In normal wound healing, it acts as a modulator between collagen and ECM production and breakdown. TGF-β is a potent stimulator of collagen and ECM synthesis [32,33]. It has been shown to increase procollagen gene expression [30,34] and stimulate deposition of fibronectin [33,35] and proteoglycans [33,36,37] by fibroblasts. In addition to its stimulatory effects, TGF-β inhibits matrix breakdown. It increases protease inhibitor synthesis and decreases protease synthesis [37,38]. It is predominately produced by platelets [39], but is also made by activated macrophages [40], T lymphocytes [41], and fibroblasts [42].

We and other authors [43–46] have written extensively about the role of TGF-β in the pathogenesis of hypertrophic scar. This cytokine is found at high concentrations in scar tissue and is the likely proximate cause for the increase in collagen and other matrix proteins, by increasing synthesis and decreasing breakdown. Further, TGF-β increases contraction and may be the cause of contractures.

The effects of TGF-β on keloid formation are also believed to be significant. Lee et al [47] demonstrated higher levels of TGF-β1 and TGF-β2 isoforms in keloid fibroblast cultures compared with normal human dermal fibroblast cultures. Later, Chin et al [48] further demonstrated an increased expression of TGF-β1 and TGF-β2 receptors and increased phosphorylation of Smad 3—an intracellular TGF-β signaling molecule—in keloid fibroblasts relative to normal human dermal fibroblasts. Younai and colleagues [49] also suggest that keloid fibroblasts may have an enhanced sensitivity to TGF-β compared with hypertrophic or normal fibroblasts. Furthermore, underexpression of apoptosis-related genes in human keloid tissue and decreased apoptotic activity in fibroblasts derived from keloids versus normal scars have been implicated in the pathogenesis of keloids [50]. This suggests distinct but related mechanisms for the importance of TGF-β as the cause of fibroproliferative scars. This also supports the notion that control of TGF-β would be a possible future mechanism for scar treatment.

Interestingly, several studies comparing keloid or hypertrophic scar fibroblasts to fibroblasts from normal skin of the same individual showed similar doubling times [12]. Instead there was an increased synthesis of collagen and ECM by existing fibroblasts. In addition, there was a reduction in matrix degradation. Hypertrophic fibroblasts have demonstrated reduced mRNA for collagenase [51] and increased mRNA for TGF-β [46] as compared with normal skin fibroblasts from the same individual.

Cell-to-cell interactions in the skin may also play an important role in the pathogenesis of these lesions. The association between unhealed (ie, lacking an epidermis) wounds and later hypertrophic scar suggests that epidermal cells may regulate fibroblast production of matrix. We have previously documented that epidermal cells synthesize a soluble product that decreases collagen production by fibroblasts [52]. Niessen et al [53] found decreased production of interleukin-1 in the epidermis, and increased production of PDGF in the dermis of hypertrophic postmastectomy scars. They concluded that the epidermis is involved in preventing the formation of hypertrophic scars. The specific mediator or product that is involved in these effects is not yet known. Interestingly, as noted below, the absence of normal keratinocytes has been implicated in hypertrophic scar formation, whereas other studies suggest that the presence of keloid keratinocytes promotes fibrosis. Lim et al [54] demonstrated increased proliferation of fibroblasts co-cultured with keloid keratinocytes as compared with normal skin keratinocytes. This study suggest that overlying epidermal keratinocytes play a role in the pathogenesis of fibroproliferative scars, although the exact mechanism remains unclear.

Keloids and hypertrophic scars have a fourfold increase in the number of mast cells compared with normal skin. The release of histamine is believed to be responsible for the pruritis and erythema seen with these scars [55], and explains why antihistamines have been useful for symptomatic treatment [56]. After mechanical pressure treatment of hypertrophic scars the number of mast cells decreased to that of mature scar [55].

Histology

In addition to their clinical differences, keloids and hypertrophic scars have unique histological appearances. Both keloids and hypertrophic scars...
showed increased deposition of connective tissue, density of blood vessels, and number of cells, as compared with dermis and normal scar [60]. Collagen in normal skin dermis is arranged in distinct bundles that run in a basketlike weave pattern parallel to the epidermis. They are connected to one another by random, fine, fibrillar strands of collagen or elastin. The collagen bundles in hypertrophic scars are flatter, less distinct, and arranged in a wavy pattern, although they still run parallel to the epidermis. In contrast, keloids have essentially no collagen bundles. Also, the collagen fibers are composed of larger fibrils and are arranged in a randomly oriented fashion relative to the epidermal surface [11,57–59].

Ehrlich et al [60] reported further morphological and immunohistochemical differences between keloids and hypertrophic scars. The collagen fibers in keloid scars are thick and large, and made of numerous fibrils closely packed together. In contrast, hypertrophic scars exhibit a nodular structure which is made of small vessels, fibroblasts, and fine randomly organized collagen fibers. These nodules are cigar shaped, run parallel to the surface of the skin, and are oriented along the tension lines of the scar [58].

In addition, only hypertrophic scars have myofibroblasts with α-smooth muscle (α-SM) actin expression that is believed to be an important element in the pathogenesis of contractures. Myofibroblasts are differentiated fibroblasts that are found temporarily in granulating tissue during wound healing. They are present permanently in hypertrophic scars [61] but not in keloid scars (Table 2).

### Treatment

It is essential to distinguish between hypertrophic scars and keloids in order to determine the appropriate treatment. Hypertrophic scars often regress spontaneously or with local measures such as corticosteroid injections or pressure dressings. Keloids, however, are more resistant to such measures and usually require surgical excision followed by adjunctive therapy. The diversity in accepted treatment modalities reflects the challenge of fibroproliferative scars, because no one method has proven to be superior to others.

### Surgery

Excision of fibroproliferative scars is one of the oldest treatment modalities. It is associated with a high recurrence rate (50%–80%) when used alone, however [13,64–66]. Cosman et al [62] reported a median recurrence period of 12.9 months. Therefore, a 2-year minimum follow-up period is necessary to adequately assess recurrence. Because it is not a successful single modality, surgery is most often combined with other therapies, such as intralesional steroids injections, radiation, pressure dressings, or silicone gel sheeting. Excision of earlobe keloids with intraoperative steroid injections and postoperative pressure therapy is one example of improved outcomes using combination therapy [65]. Engrav et al [66] advocate an alternate method of hypertrophic scar removal in which a rim of scar tissue is not excised. They and other authors [11,66,67] suggest that intramarginal scar excision reduces recurrence rates, although this technique has not yet been evaluated by a prospective randomized trial [12]. Depending on the size and location of the scar, local flaps, serial excision, or preoperative tissue expansion may be necessary to remove the scar completely.

We believe that surgical excision is the best treatment for small-sized to moderate-sizes scars. We always utilize multimodal therapy, however, in order to decrease scar recurrence. Our experience with intramarginal scar excision has not been good thus far. Small scars are resected, usually with a z-plasty or w-plasty to reorient contraction forces. Often the incisions are injected with Kenalog at the time of surgery and again at 6 to 8 weeks. Tissue expansion has been proposed as a treatment for moderate scars. We have found that the requirement for two surgical procedures and weekly clinic visits for inflation is more time consuming than what many patients are capable of adhering to. In many cases, serial staged excision over 2 to 4 years provides the same result with less disruption of daily routine for the patient.

### Table 2

Summary of histologic differences between scars based on immunohistochemistry and light microscopy and confirmed by electron microscopy

<table>
<thead>
<tr>
<th></th>
<th>Keloids</th>
<th>Hypertrophic scars</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connective tissuea</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Collagen structurea</td>
<td>Larger fibers with closely packed fibrils</td>
<td>Flatter and less distinct bundles, fine fibers</td>
</tr>
<tr>
<td>Orientation of fibers</td>
<td>Random to epidermis</td>
<td>Wavy, but parallel to epidermis</td>
</tr>
<tr>
<td>Myofibroblasts</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>α-Smooth muscle actin</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Density of blood vesselsa</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Number of cellsa</td>
<td>Increased</td>
<td>Increased</td>
</tr>
</tbody>
</table>

*a As compared with normal skin dermis and scar.
Key principles behind surgical excision of fibro-proliferative scars:

1. Tension-free closure, which may require local flaps or reorientation of the scars to parallel lines of relaxed skin tension.
2. Removal of all inflammatory tissue that may contribute to recurrence, such as trapped hair follicles, epithelial tracts or cysts, local infection, and hematomata.
3. Avoid trauma to the surrounding tissue and completely obliterate dead space.
4. Utilize corticosteroids, pressure, or silicone-coated materials as an adjunct.

A new surgical treatment for proliferative scar involves the use of Integra (Johnson & Johnson, Summerville, NJ) dermal matrix. Although Integra was originally designed for the treatment of massive burn injuries, it has been found to be useful in the surgical treatment of scars as well. The authors and many others have had anecdotal success using this material as a replacement for the defect after excision of both hypertrophic and keloidal scars. The matrix is placed at the time of scar excision and then overgrafted several weeks later with a very thin (6/1000-inch) skin graft. Reports have documented success with improved motion, skin quality, and appearance [68,69]. The stabilized matrix appears to resist recurrence better than do traditional skin grafts, which have a reported recurrence rate of 59% [63,70]. Although there is a theoretical risk of scar formation at the donor site when the skin grafted in the second stage is harvested, this has not been a problem in the experience of those who have tried this technique.

Corticosteroids

Intralesional steroid injections are another frequently used treatment modality for FPDs. They are often used as an initial therapy, either alone or in conjunction with other treatment options. When used as single therapy, steroid injections have a highly variable response rate of 50% to 100% and a recurrence rate of 9% to 50% [10,71–76]. This treatment is most effective in younger proliferative scars. Although less effective in softening and flattening older proliferative scars, especially keloids, it often provides symptomatic relief for itching and pain [77]. The exact mechanism of action is unknown, but is likely secondary to inhibition of mediator release by tissue macrophages [12]. Steroids are believed to cause regression of fibroproliferative scars by reduction of collagen and glycoaminoglycan synthesis, increased synthesis of tissue proteinases, reduction of the inflammation, and increased hypoxia [75,78–82].

There are several different steroid preparations including hydrocortisone acetate, methylprednisolone acetate, dexamethasone, and triamcinolone acetonide. The latter is the most popular [10,72], although no particular advantage has been clearly demonstrated for any one type. Because individual clinical response is highly variable, no standard administrative protocol has been developed. There is a considerable variation among practitioners in the dose, frequency, and duration of treatment [83]. Our practice is to perform two to three injections of Kenalog, at a dose of 10 mg/mL, approximately 4 to 8 weeks apart. We have had satisfactory results with this regimen. Despite its benefits, intralesional steroid injections have several possible adverse side effects including hypopigmentation, skin and subcutaneous fat atrophy, telangiectasias, necrosis, ulcerations, and cushingoid habitus [72,77,83,84]. The risk of complication is greater when inadvertent injection of surrounding normal tissue occurs.

Combination therapy with surgery also shows variable recurrence rates of 0% to 100%, but with a mean of less than 50% [10,71,76,85,86]. We regularly inject preoperatively with steroids until no further regression of the scar is noted followed by excision. The scar edges are injected at the time of surgery and postoperatively for varying lengths of time [10,76]. Cryotherapy has also been combined with intralesional corticosteroid injections with varying results [87,88]. Some authors reported that initial treatment of the scar with cryotherapy induces edema and cellular breakdown, resulting in decreased density of the fibrous tissue, making injection easier and effective [87]. In addition, cryotherapy may provide anesthesia prior to infiltration. As a lone modality, cryotherapy has limited success [89].

Pressure therapy

Pressure therapy is a conservative treatment modality that has been utilized for many years, particularly in the treatment of hypertrophic scars after burn injury. There have been numerous studies in the past documenting that pressure therapy reduces the size as well as softens hypertrophic scars [11,55,61,90–93]. Reports also suggest a partial reduction in scar progression in 60% to 85% of reported cases [71,94,95]. In a recent, prospective, randomized study of the efficacy of pressure garment therapy in burn patients, however, Chang et al [96] demonstrated no significant difference with regard to whether garments were used. The conflict between extensive,
longstanding clinical experience in support of pressure therapy, and a randomized prospective trial showing no benefit remains unresolved. Although the Chang et al trial [97] has been criticized for containing few patients of non-European ancestry, and thus enrolling a low-risk patient group, it is the best study of this modality in print.

The mechanism of action behind pressure garments is believed to be secondary to tissue ischemia. The pressure leads to local hypoxia, which in turn decreases tissue metabolism and increases collagenase activity [75,90,97]. It also reduces fibroblast proliferation and collagen synthesis [90]. The exerted pressure is effective between 24 and 30 mm Hg [90,98], although other studies have shown response at pressures as low as 5 to 15 mm Hg [99]. At these pressures, the inherent capillary flow, but not the peripheral circulation, is overcome [90,98], and there is occlusion of the small vessels within the scar [100].

Therapy should begin as soon as re-epithelialization occurs and continued until the scar has matured [91]. To be most effective, garments can be custom fabricated to fit each patient. This can be expensive and require remeasurement in growing children. Early discontinuation of the garments is associated with rebound hypertrophy [101]. The use of prophylactic pressure garments is recommended in patients whose wounds take 14 to 21 days to heal and is required if wounds take greater than 21 days to heal.

Pressure therapy has historically had several disadvantages. Garments must be worn 24 hours per day for a minimum of 12 months in order to obtain good results [75,83,91,101–103]. Garments are also uncomfortable and often cannot provide therapeutic pressure levels in difficult anatomical locations [5]. Our practice is to treat high-risk patients and wounds such as burns around joints in children of African or Asian ancestry expectantly. Others are treated with pressure garments only if significant scar proliferation develops. Pressure garments worn after scar excision or other reconstructive procedures have proven to be an effective adjunct with an improved success rate of 90% to 100% [71,85,104].

**Topical silicone gel**

Silicone-coated material (frequently gel sheeting) is a newer treatment modality for fibroproliferative scars that has proven to be effective since its introduction by Perkins et al in 1983 [105]. Authors since then have reported relief in symptoms, decreased scar volume, and increased elasticity in 60% to 100% of scars treated with topical silicone material [5,106–112]. It is generally well tolerated and painless, although patients must maintain good hygiene in order to prevent the most frequent complications of irritation and rash. In contrast to pressure garments, silicone gel sheeting can be applied for only 12 hours per day and treatment duration can be effective when used for as little as 6 months. In addition to treatment for scars, several authors believe that application of topical silicone gel is preventive, particularly following excision [106,108].

The mechanism for these effects is unclear. Unlike pressure garments, compression is not felt to be essential. This makes topical silicone ideal for anatomical regions unsuitable for pressure garments. Differences in oxygen tension and silicone permeation into the scar have also been disproved as potential causes for the silicone’s effects [5,109–111]. Other possible unproven mechanisms include a rise in the scar temperature below the sheeting, resulting in increased collagenase activity [113], changes in skin hydration [110,114] and downregulation of wound healing by the negative charge of the silicone [115]. Multiple variations of combining silastic inserts with compression devices exist to treat concave regions. The use of pressure garments with silicone conformers is one effective method [116].

**Radiation**

Low-dose, superficial radiation therapy has also been used to treat hypertrophic scars and keloids, either alone or in combination with surgery [31,117–120]. In a 10-year follow-up study, Darzi et al [73] reported that β radiation, as a lone modality was most effective at eradicating symptoms (55%), but poor at reducing the size of the lesion (11%). In combination with surgery, results were much improved with a 67% to 75% success rate. Kovalic and Perez [119] also reported success with combination surgery and radiation therapy for keloids with reduced recurrence rates of 73%. Most patients received 1200 cGy in three fractions over 3 days in the immediate postoperative period. Despite reports of effective results with radiation therapy, it has not gained popular use due to risks of carcinogenesis [121] and long-term effects on the skin. Radiation therapy should be reserved for adults with significant symptoms and keloids that are disabling or resistant to other treatments. Generally it is avoided in adolescent patients.

**Laser**

The use of lasers to treat fibroproliferative scars was first entertained in the mid 1980s. Initial results by
multiple investigators using the CO₂ and Argon lasers on keloids and hypertrophic scars were promising [122]. Follow-up publications, however, reported significant recurrence rates and some worsening of the original scar [123–126]. Beginning in the 1990s, investigators using a vascular-specific pulsed dye laser (585 nm) to treat port-wine stains noticed its application with fibroproliferative scars. The treated scars became more pliable and less erythematous, pruritic, and hypertrophic [127–131]. Alster [127] reported clinical and textural improvement in long-standing hypertrophic and erythematous scars of 57% and 83% after one or two treatments, respectively. In addition, histological examination of laser-irradiated scars confirmed the suspected improvement in dermal collagen. The collagen was more fine and fibrillar following treatment [129].

**Calcium channel blockers**

Recent work suggests that calcium channel-blocking agents, in particular Verapamil, may trigger ECM degradation in dermal scars, resulting in scar volume reduction [132]. Their effects have been studied in an in-vitro fibroblast-populated collagen matrix and shown to reduce the incorporation of proline into the ECM [133]. Calcium channel-blocking agents are believed to work in a similar fashion to colchicine, by changing the cell shape and mediating epigenetic control of ECM remodeling [134–136]. Doong et al [137] have observed that Verapamil induces a change in the shape of fibroblasts from bipolar to spherical. This may drive fibroblasts toward ECM degradation, via increased rate of collagenase synthesis and inhibition of collagen synthesis. Initial work is promising; however, more clinical data must be collected.

**Treatments on the horizon**

As further insight is gained into the molecular basis for fibroproliferative scar formation, new therapeutic avenues are discovered. Two critical modulators of scar formation that show great promise are interferons (INF-α, INF-β, and INF-γ) and TGF-α1 and TGF-β2. Manipulation of these cytokines may allow for advances in keloid and hypertrophic scar therapy.

**INFs**

INFs (IFN – α, IFN-β, and IFN-γ) are cytokines derived from leukocytes, fibroblasts, and T lymphocytes, respectively. They are of interest because of their inhibitory affects on scar formation and therapeutic potential [12]. They have been shown in cultured fibroblasts to reduce cell proliferation [12], inhibit collagen and fibronectin synthesis [12,138,139], and promote collagenase production [138] by binding to cell membrane receptors. INF-α and INF-β have been shown to reduce glycosaminoglycan synthesis as well [139,140].

In vitro, scleroderma fibroblast collagen synthesis is inhibited by INF-γ [141], whereas clinically, patients with scleroderma who are treated with INF-γ show reduced symptoms [142]. Furthermore, intralesional injections of INF-γ in human subjects with keloids and hypertrophic scars have shown significant reduction in scar size and symptoms ranging from 30% to 50% [143,144]. Histologically, treated scars exhibited a diminished quantity of thickened collagen bundles in the dermis, a reduced amount of active fibroblasts, and an increased number of inflammatory cells [143].

In addition, intralesional INF-α2b has shown promising in vitro and in vivo results. Berman and Duncan [145] demonstrated a gradual reduction in keloid size following intralesional INF-α2b treatment. They also reported a reduced keloid recurrence rate of 8.3% to 18.7% in patients who underwent excision followed by INF-α2b injection therapy as compared with corticosteroid injection or no therapy [85,146]. Tredget and co-workers have published extensively on the ability of INF-α2b to control abnormal collagen synthesis in hypertrophic scar fibroblasts. They recently documented significant improvement in scar symptoms and appearance in patients with severe hypertrophic scar [147,148]. Finally, in a recent report, they documented that treatment with INF-α2b induces apoptosis in the fibroblasts and myofibroblasts found in these scars [149].

Unlike corticosteroids, INF-γ injections do not appear to cause changes in pigmentation, skin atrophy, and telangiectasia formation. Side effects reported are mostly constitutional, including fever, chills, fatigue, and, most commonly, malaise and headache. Laboratory abnormalities included reversible granulocytopenia and elevation of hepatic transaminase levels. All the side effects were dose-dependent and route-dependent [143,144,150].

**TGF-β**

As mentioned earlier, TGF-β production by cells within the proliferating scar is the major proximate cause for wound fibrosis. Inhibition of TGF-β may serve as a new approach to scar therapy. Soluble cytokine receptors, autoantibodies, and binding molecules are all promising regulatory mechanisms currently under investigation [151]. Soluble cytokine receptors have been isolated in human plasma and urine [152–154] and are believed to be similar to
membrane-bound receptors except that they lack the transmembrane anchor [154–156]. TGF-β-specific soluble receptors are a specific proteoglycan termed betaglycan [155]. They have been isolated from fibroblasts, epithelial cells, myoblasts, and adipocytes. Their role has not yet been fully elucidated, but they are believed to serve as a reservoir of active TGF-β. Exogenous administration of receptors might be used to scavenge excess TGF-β.

Autoantibodies are also believed to regulate cytokine activity and may serve as another treatment modality of fibroproliferative scars on a molecular level. Several cytokine-specific autoantibodies have been isolated and implicated in chronic disease and inflammatory states [157–160]. Interestingly, intravenous administration of antiserum against TGF-β has been shown to decrease excessive ECM production in an animal model of glomerulonephritis [161]. Furthermore, neutralizing antibodies to TGF-β produced an improved quality of wound healing and reduced scar tissue formation in an in-vivo model of wound healing [162].

Binding proteins isolated from human serum or plasma have also been shown to play a key role in cytokine regulation. When bound to α2 macroglobulin—the major binding protein of TGF-β—TGF-β is in a latent form. Although its exact function is unknown, α2-macroglobulin is believed to be a scavenger of TGF-β leading to rapid clearance from the plasma [163,164]. Therefore, manipulation of binding proteins may have clinical application for scar therapy.

Summary

Fibroproliferative scars remain an ongoing clinical challenge. Both hypertrophic scars and keloids require multimodal therapy to achieve partially successful treatment. At the present time incomplete understanding about the pathogenesis of fibroproliferative scars makes targeted, mechanistic treatment impossible. As understanding of these abnormal wound problems increases, more effective treatments will likely be available. Until that time, clinicians must utilize existing knowledge to treat patients while continuing to experiment with new approaches.

References

[23] O’Sullivan ST, O’Shaughnessy M. Aetiology and


[54] Lim JJ, Phan TT, Song C, et al. Investigation of the...


[90] Kischer CW, Shetlar MR, Shetlar CL. Alterations in


