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Keloid Scarring: New Treatments Ahead

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Abstract. Keloid disease presents a healthcare challenge: patients suffer from pruritus, pain, inflammation, and cosmetic disfigurement. There is no single effective therapeutic regimen for keloids. Numerous treatment options have been described including occlusive dressings, compression therapy, intralesional steroid injections, laser and radiation therapy, cryosurgery, 5-fluorouracil, interferon, and imiquimod cream, but managing keloid disease still is a considerable problem for clinicians. Better understanding of the molecular mechanisms behind keloid disease led to the development of new promising therapies like the application of recombinant TGF-β3, interleukin 10, and imatinib mesylate.
This review provides an overview of the existing therapeutic options for keloid disease and summarizes upcoming future therapies with a special focus on blocking the transforming growth factor-beta pathway.

Key words: keloid, treatment, physiopathology, molecular mechanisms, TGF-β3, interleukin 10, imatinib mesylate.

QUELOIDES: NUEVOS TRATAMIENTOS EN EL FUTURO

Resumen. Los queloides representan un reto de atención sanitaria: los pacientes padecen prurito, dolor, inflamación y desfiguración cosmética. No existe ningún tratamiento efectivo para los queloides. Se han descrito numerosas opciones terapéuticas que incluyen vendajes oclusivos, terapia de compresión, corticoides intralesionales, láser, radioterapia, criocirugía, 5-fluorouracilo, interferón e imiquimod, pero el tratamiento continúa siendo un problema considerable para los clínicos.
Se han desarrollado nuevas y prometedoras terapias, como la aplicación de TGF-β3 recombinante, interleuquina 10 y mesilato de imatinib gracias a un mayor conocimiento de los mecanismos moleculares responsables de los queloides.
Esta revisión ofrece una visión de conjunto de las opciones terapéuticas disponibles para los queloides y resume las futuras terapias, haciendo especial énfasis en los bloqueadores de la vía del factor de crecimiento transformador beta.

Palabras clave: queloides, tratamiento, fisiopatología, mecanismos moleculares, TGF-β3, interleuquina 10, mesilato de imatinib.

Introduction

The term keloid is derived from the Greek "khele", for crab claw[1]. Keloids have been mentioned for the first time in 1700 BC in the "Smith-Papyrus"[2]. In 1806 Alibert gave the first clinical description of keloids[3]. Keloids are unique to humans and are seen predominantly in darker pigmented individuals[4].

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Keloid scarring is a pathological response to dermal injury resulting in disfiguring tumors (fig. 1). Skin injuries such as burning, inflammation, surgery or minor trauma e. g. insect bites induce an excessive deposition of extracellular matrix (ECM), particularly collagen[5]. Even the spontaneous development of keloids has been discussed but may be the result of a minor, overlooked trauma[6].

The result of undisturbed wound healing is a fine line scar. However, there is a broad spectrum of abnormal scarring including widespread (stretched) scars, atrophic scars, scar contractures, hypertrophic scars and keloids. Before birth, injury of fetal skin results in scarless wound healing. Unfortunately, the mechanisms of this biologic phenomenon are unknown.

Clinically keloids extend beyond the boundaries of the original wound. This is in contrast to hypertrophic scars

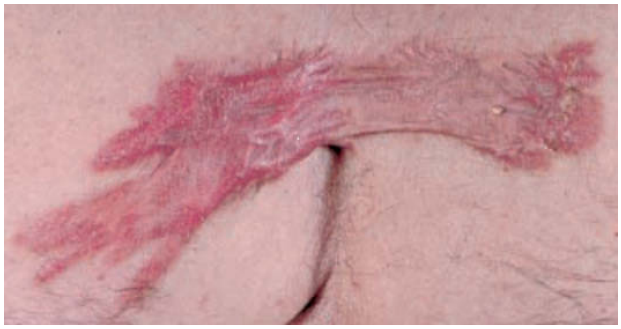

Figure 1. Typical presternal keloid. The margins are erythematous, growing into the surrounding healthy skin in a claw like appearance while the centre of the lesion has flattened and whitened.

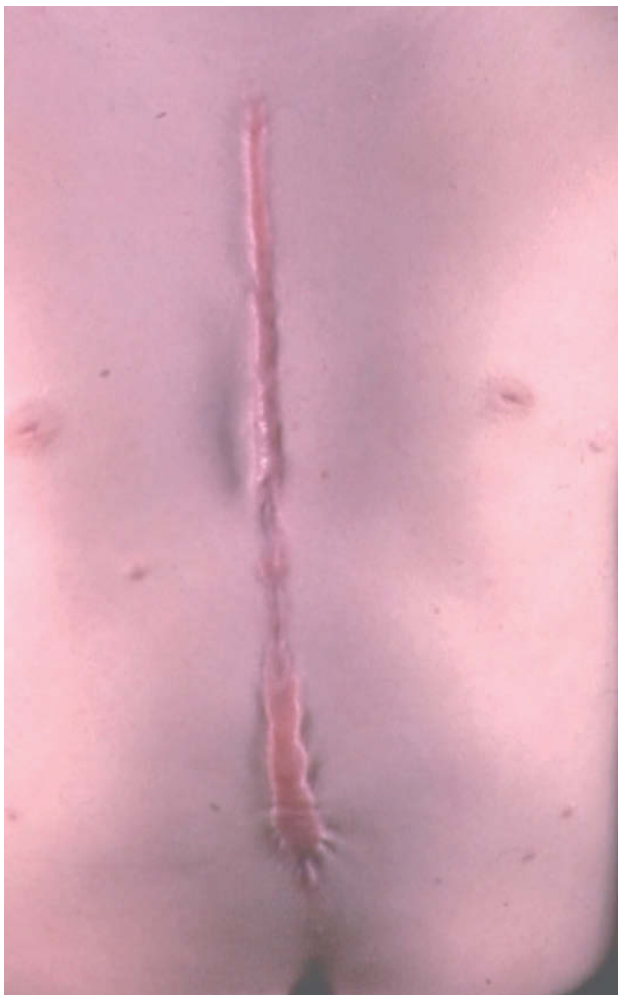

Figure 2. Presternal hypertrophic scar after surgery.

which remain within the boundaries of the original wound (fig. 2) and spontaneously regress within months to years after the initial injury[7]. Hypertrophic scars are frequently misdiagnosed as keloids.

For unknown reasons, keloids occur more frequently on the chest, shoulders, upper back, back of the neck and earlobes[8]. In one case a massive 1.8 kg keloid has been removed from the arm at the site of vaccination[9]. It has been intensively discussed whether keloids occur primarily in areas of high tension[10]. This might be an oversimplification since the most commonly affected site, the earlobe[11], is under minimal tension and keloids appear rarely on the palms or soles where significant skin tension is to be expected.

Keloids can develop at every age but have a higher incidence between 10 to 30 years. Mean age of first keloid diagnosis is 22.3 years for women and 22.8 years for men[12]. Hormones have been suggested to influence keloid formation and this is supported by data showing an elevated androgen receptor level in clinical active keloid tissue[13]. Keloids seem to have a higher incidence during pregnancy and puberty, which has been interpreted as related to the hormone profile but other explanations as increased neoangiogenesis in pregnancy are possible[14]. Although epidemiologic data are limited, there are differences among racial groups with a higher frequency of keloids in Blacks, Hispanics and Asians. The incidence of keloids in the United Kingdom is reported to be less than 1%[15], while the incidence in Blacks and Hispanics varies from 4.5 to 16%[14].

Excessive pathological scar formation as seen in keloid disease is leading to major consequences for patients such as contractures, pain, itching, paresthesia and psychological dysfunction[16]. This underlines the need for effective treatment strategies but the management of keloid disease remains a difficult problem for clinicians. Multiple treatments with varying degrees of effect have been used including established therapies as intralesional steroids and silicone gel sheeting and experimental therapies such as imiquimod cream and 5-fluorouracil (5-FU). This review gives an overview on existing treatment options and describes new treatment modalities in the future.

Current Therapies

Numerous treatments have been recommended, including established therapies (steroids, radiation, lasers, silicone gel sheets), as well as more experimental therapies such as imiquimod cream, interferon and 5-FU. An International Advisory Panel on scar management developed consensus guidelines[17] that recommended a combination of silicone gel sheeting and intralesional steroids as first-line therapy, with the use of localized pressure therapy if possible (e.g. for earlobe keloids). Second-line therapy for resistant cases includes specific wavelength laser therapy and surgery with adjunctive silicone gel sheeting, if required. Combinations or experimental methods should be conducted in units specializing in scar therapy (table 1).

Intralesional Steroids

Intralesional steroids play a central role in the treatment of keloids. Proposed mechanisms of action include inhibition of nitric oxide synthase (NOS)-transcription with subsequent inhibition of collagen synthesis in fibroblasts[18], inhibition of keloid fibroblast growth, fibroblast degeneration, and downregulation of collagen gene expression in keloids[19]. A range of steroid preparations can be used for intralesional injection, including hydrocortisone acetate, methylprednisone and dexamethasone. The most commonly used is triamcinolone acetonide (10-40 mg/ml per course every 4 weeks)[20]. Side effects are skin atrophy telangiectasias and hyper- or hypopigmentation. There are only four randomized clinical trials analyzing the efficacy of intralesional steroids. Darzi et al showed a positive effect of intralesional steroids compared to radiation therapy[21] while Layton et al concluded that intralesional triamcinolone therapy was not as effective as cryotherapy[22]. Triamcinolone acetonide treatment combined with cryotherapy was found to be more effective than steroid treatment or cryotherapy alone[23]. No significant differences in scar height or erythema were found between groups treated with intralesional triamcinolone alone, 5-FU alone or triamcinolone and 5-FU combined[24]. The level of evidence of these trials is low and further randomized clinical trials with larger study population and longer follow-up are needed[25].

Silicone-Based Therapy

Various forms of silicone sheetings and gel preparations are available for the treatment of keloids[26]. The mechanism of action of silicone therapy has not been completely determined but is likely to involve occlusion and hydration of the stratum corneum with subsequent cytokine-mediated signaling from keratinocytes to dermal fibroblasts[27]. Successful use of silicone gel sheets requires that the sheet covers the entire scar for periods of at least 12 hours each day, ideally for 24 hours[27]. An extensive Cochrane review evaluating the evidence for silicone gel sheets concluded that any effects were obscured by the poor quality of research[28].

Cryotherapy

Cryotherapy is induces an ischemic damage leading to cellular anoxia, with subsequent tissue necrosis[29]. Two freeze/thaw cycles with freezing for 10 seconds should lead to a reduction in keloid size. Treatment can be repeated every 4 -6 weeks until complete flattening of the keloid. A study including 394 patients showed a positive outcome in 64 % of patients with keloids[30] while a case series of 17 patients provided no evidence for the use of cryotherapy as monotherapy[31]. A frequent side effect of cryotherapy is hypopigmentation due to the destruction of the cold sensitive melanocytes. As cryotherapy by its nature induces tissue damage this may lead to a re-induction of keloid growth. This could explain why cryotherapy in our hands is more effective in hypertrophic scars as compared to keloids.

Table 1. Treatment options for keloid disease

Treatment	*Mechanism of action*
Occlusion	Unknown
Intralesional steroids	Anti-inflammatory, antifibrotic
Pressure	Unknown
Cryotherapy	Unknown
Dye-laser (585,595 nm)	Inhibition of angiogenesis, mast cell deactivation
Ionizing radiation	Antiproliferative
5-fluorouracil	Antiproliferative
Bleomycin	Antiproliferative
Imiquimod	Induction of interferon α and apotosis
Verapamil	Inhibition of collagen synthesis
Anti-TGFβ-antibodies	Inhibition of the TGFβ-pathway
Recombinant TGFβ3	Antagonizing TGFβ
Imatinib mesylate	Inhibition of tyrosine kinase → inhibition of TGFβ signal transduction
Anti-IL-6-antibodies	Reduction of collagen synthesis
Recombinant IL-10	Unknown
VEGF siRNA	Antifibrotic, inhibition of angiogenesis
Activin-like kinase 5	Inhibition of SMAD-activation
Mannose-6-phosphate	Inhibition of TGFβ1 and TGFβ2

Lasers

The neodymium:YAG laser (1064 nm), flashlamp pumped pulsed dye laser (PDL) (585-595 nm), CO_2 laser (wavelength 10600 nm) and argon laser (488 nm) are frequently used in the treatment of keloids. Lasers induce a thermal tissue reaction which is tissue-specific depending on the wavelength. Alster et al treated keloids and hypertrophic scars with 585 nm PDL, with an untreated half of the scar

serving as control, and found greater reduction of pruritus and erythema in the PDL-treated group[32]. The sample size was small and no distinction was made between keloids and hypertrophic scars for the purpose of analysis. Follow-up was limited to 6 months.

The main target of the dye laser is the microvasculature. However, as a frequent adverse effect of dye laser therapy is a wheal and flare reaction immediately after treatment, mast cells may also be affected.

Case series studies have provided positive evidence in favour of PDL[33], Nd:YAG laser[34] and CO_2 laser[35].

Radiotherapy

Radiotherapy is currently a second-line treatment for keloids. If indicated keloids should be primarily excised and the resulting scar irradiated afterwards to prevent recurrence[36-38]. Primary radiation therapy of keloids is only effective during the first 6 months after keloid development[39]. Irradiation is considered to influence connective tissue stem cells, ECM gene expression, and normal skin and keloid fibroblasts; radiotherapy may re-establish a balance between collagen production and degradation by destroying fibroblasts[29]. Sclafani et al showed, in a randomized controlled study including 42 patients, that radiation therapy (10 Gy or 7 Gy using either superficial X-rays or electron beams) after surgical excision is as effective as corticosteroid injections[40]. Different types of radiotherapy have been evaluated, for example superficial X-rays[41], electron beam radiation[37], orthovoltage therapy[42], beta-radiation[43], and brachytherapy[44]. Further studies are needed to determine the optimal fraction dose or schedule for radiotherapy. According to Kovalic et al the total dose of irradiation is more important than the frequency[45]. Doornbos et al suggested doses between 9 and 15 Gy as effective for the treatment of keloids[46] while other studies could not find a dose-response effect[36,45].

Pressure

The mechanism of action of local pressure application is unclear but it is thought that pressure leads to decreased capillary perfusion with subsequent hypoxia and fibroblast degeneration[47]. Pressure may even lead to accelerated collagen maturation. To achieve optimal treatment results, pressure should be applied 24 hours a day at about 20-30 mm Hg. There is positive evidence for the efficacy of pressure therapy. Rauscher et al evaluated the effect of surgical excision and postoperative pressure with steroid-impregnated tape in 57 patients with recurrent earlobe keloids. The tape was applied after excision and held in place using an earring. Four recurrences occurred in a 4 year follow-up period[48].

Imiquimod

Imiquimod cream, a topical immunomodulator that induces interferon-α, is considered to be antifibrotic[49]. Martín-García et al treated four patients with topical imiquimod cream after shave excision of earlobe keloids. Their results showed that imiquimod was more effective than steroids[50]. Other case series provided low evidence for efficacy[49,51]. Cacao et al treated nine patients with a keloid scar on the trunk with surgical excision and daily application of imiquimod 5 % cream for 8 weeks after excision. Keloid recurrence occurred in eight patients. These results suggest that short-term application of imiquimod cream is not effective in preventing recurrence of trunk keloids after surgical excision[52].

However, in an own series of patients with keloid disease at various locations including the earlobe, long-term application of imiquimod 5 % cream for more than a year was able to prevent keloid regrowth (Mrowietz et al, manuscript in preparation).

Alternative Treatments

The pyrimidine analogue 5-FU, mostly used as a chemotherapeutic agent, hinders fibroblasts proliferation and has therefore been suggested to be effective in the treatment of keloids[53,54]. Intralesional 5-FU was shown to be as effective as treatment with steroids alone, pulse-dyed laser alone or steroids combined with 5-FU[24].

Jiménez et al demonstrated that α- and γ interferons are able to inhibit fibroblasts collagen synthesis [55] and Berman et al showed that treatment with interferon-α2b resulted in normalization of collagen, glycosaminoglycan and collagenase production in keloid fibroblasts *in vitro*[56]. In one controlled comparative study with a small sample size, the use of intralesional interferon-α2b in keloids was ineffective in height reduction compared to controls[57] while Larrabee et al reported successful treatment of keloids with interferon-γ as monotherapy[58].

Another effective treatment for keloids might be the calcium-channel antagonist verapamil. Verapamil has been shown to increase collagenase activity and to inhibit collagen synthesis[59,60], and intralesional verapamil injection intra- and postoperatively prevented keloid recurrence in a case series of patients[59].

Future Developments

Elucidating the cause for keloid disease may help to develop new treatment options. At present, the pathogenesis of keloid disease is unknown. Past efforts have identified a fundamental role for TGF-β in pathological fibrogenesis[61].

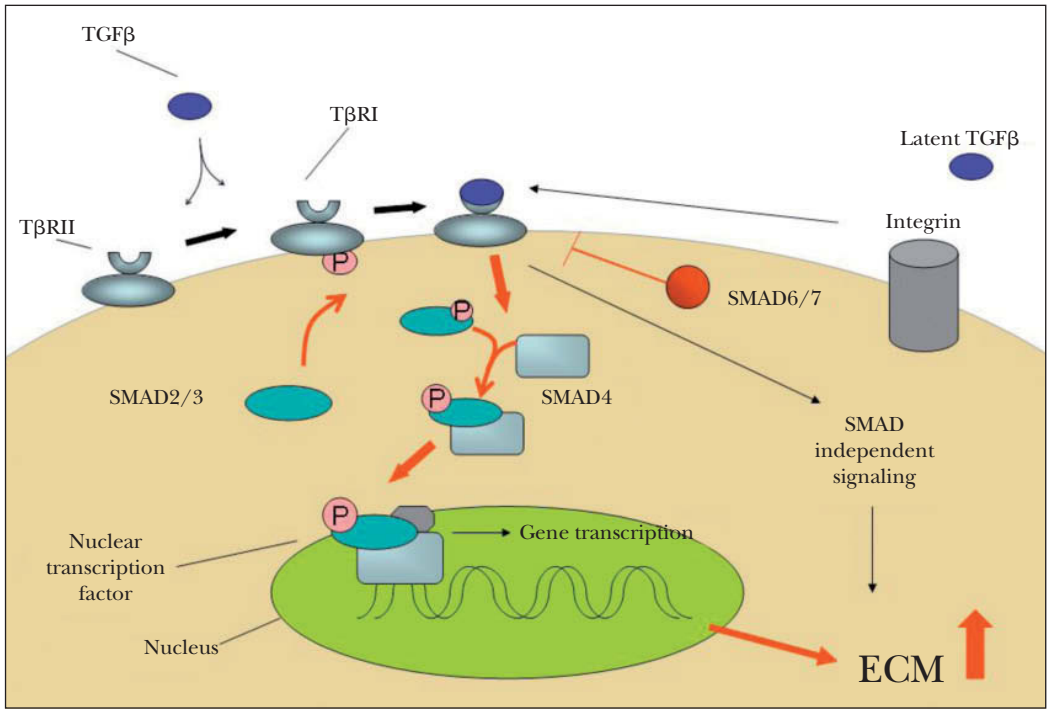

Figure 3. Mechanism of the intracellular TGF-β signaling pathway. TGF-β binds to the cell surface receptors TβRI and RII. Latent TGF-β is activated by integrin receptors. TβRI and RII activation initiates phosphorylation of SMAD2/3 with subsequent SMAD4 activation. The SMAD complex translocates into the nucleus and activates, together with transcription factors, upregulation of target genes. SMAD6 and 7 are inhibitors of SMAD signaling induced by TGF-β (RI/II, TGF-β receptor I and II).

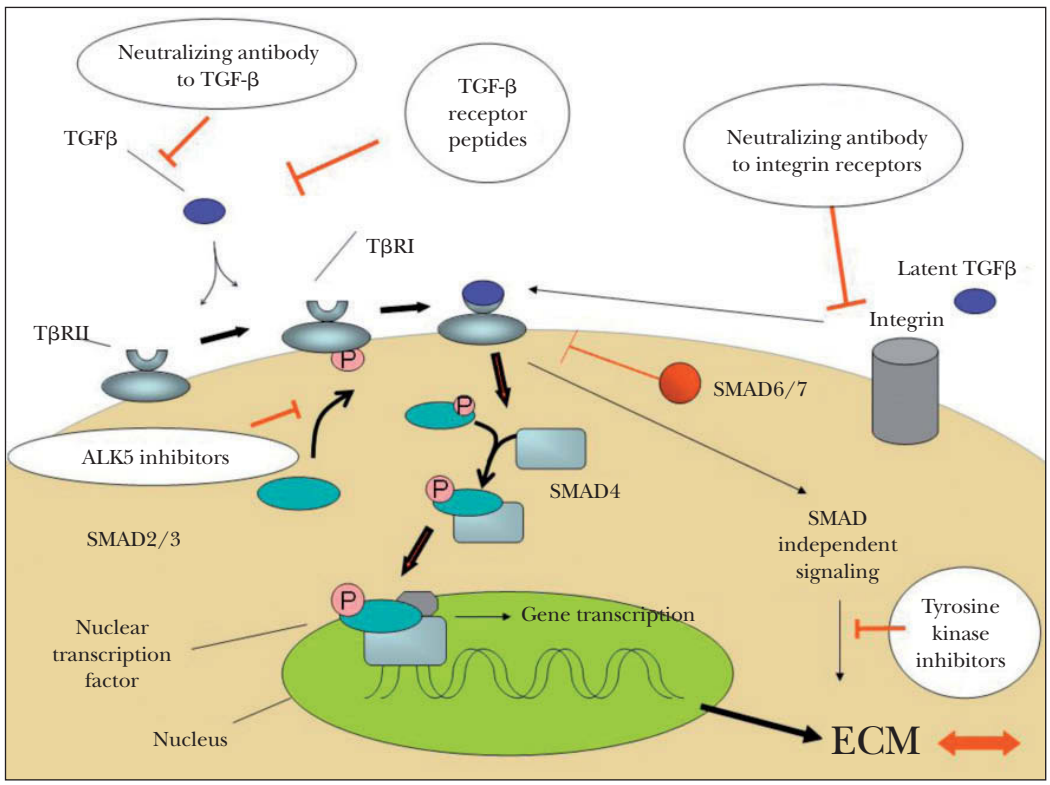

Figure 4. Different approaches blocking the TGF-β signaling pathway. Neutralizing antibodies to TGF-β seize the active ligand and the receptor peptides stop its binding to cell surface receptors. Neutralizing antibodies to integrin receptors inhibit latent TGF-β activation. Activin-like kinase (ALK5) inhibitors of TβRI block SMAD2/3 activation. Tyrosine kinase inhibitors inhibit SMAD-independent TGF-β signaling (RI/II, TGF-β receptor I and II).

This cytokine promotes fibroblast proliferation and, most importantly, upregulates the synthesis of collagen and ECM[62]. The current concept of TGF involvement in keloid disease is shown in figure 3.

There are several different possibilities to block the TGF-β pathway (fig. 4).

Neutralizing antibodies can be used to inhibit TGF-β activity and production. Shah et al injected a neutralizing

TGF-β antibody to the margins of healing dermal wounds in adult rats and found wound healing without scar-tissue formation[63]. Interestingly, clinical trials showed that monoclonal neutralizing TGF-β antibodies (metelimumab, lerdelimumab) are effective in other fibrotic conditions such as systemic sclerosis (SSc) and pulmonary fibrosis and can prevent scarring after glaucoma surgery[64,65]. As mannose6--phosphate (M6P) inhibits the activation of TGFβ-1 and TGFβ-2[66], local application of recombinant MP6 may be an alternative option to block TGF-β activity. Inhibition of TGF-β receptor activation may be achieved by applying soluble TGF-β receptor. A soluble TβRIII has been shown to be able to sequester and inactivate TGF-β preventing bleomycin-induced SSc[67]. This therapeutic strategy might be a future treatment option even in keloid scars.

Latent TGF-β is activated by cell surface integrin receptors[68]. Antibodies blocking this pathway are an interesting treatment option for keloid disease. This is emphasized by recent clinical studies showing that blocking integrin receptors prevents the development of lung fibrosis[69,70].

As shown in figure 3, phosphorylation of SMAD2/3 by TβRI is a crucial step in the activation of the intracellular TGF-β signaling cascade and increased ECM production. Small molecules (activin-like kinase, ALK5) that bind to TβRI and inhibit SMAD2/3 phosphorylation have been shown to improve experimental fibrosis[71,72] and clinical studies in keloids might reveal these molecules as an effective treatment.

Imatinib mesylate (Glivec®) is a tyrosine kinase inhibitor that blocks non-SMAD signal transduction downstream of TGF-β. Imatinib mesylate is widely used and highly effective in the treatment of chronic myeloid leukemia (CML)[73]. Distler et al showed that imatinib mesylate efficiently reduced collagen synthesis in SSc and normal dermal fibroblasts. The induction of ECM proteins after stimulation with TGF-β was strongly and dose-dependently inhibited by imatinib mesylate. The results suggest that imatinib mesylate has potent antifibrotic effects and is a promising candidate for the treatment of fibrotic diseases such as keloids and SSc[74].

Another promising therapeutic approach in keloids was developed on the basis of the previous finding that TGF-β3 is present at high levels in developing embryonic skin and in embryonic wounds that heal without scar, but by contrast, is present at low levels in keloids[75]. Application of human recombinant TGFβ-3 showed an improvement in subsequent scar appearance in rat wounds[76]. Ferguson et al conducted three double-blind, placebo-controlled phase I/II studies with avotermin, a human recombinant TGFβ-3 protein[77]. Avotermin was administered intradermally to skin incisions, before and after wounding, in healthy men and women. Visual assessment of scar formation at 6 and 12 months after wounding showed significantly improved scar scores suggesting recombinant TGFβ-3 could be a potential anti-scarring therapy.

Ghazizadeh et al showed enhanced expression of interleukin 6 (IL-6) and its receptors in keloid fibroblasts, with a concomitant increase in collagen biosynthesis[78]. Anti-IL-6 antibodies or blocking IL-6 receptors elicited reduced collagen synthesis, suggesting a role for IL-6 in the regulation of collagen gene expression. These observations imply targeting the IL-6 signaling pathway as a possible treatment for keloids.

The absence of interleukin 10 (IL-10) in fetal skin results in scar formation. The lack of IL-10 may result in continued amplification of the inflammatory cytokine cascade, continued stimulation of fibroblasts, and abnormal collagen deposition. IL-10 is necessary for scarless wound repair to occur[79]. Peranteau et al showed that overexpression of IL-10 modulates the inflammatory response at an adult wound site to more closely resemble the profile seen in the embryo. In the light of these results, applying human recombinant IL-10 may offer a potential treatment for keloids[80].

VEGF plays an important role in the regulation of angiogenesis and inflammation in wound repair. Zhang et al transfected keloid fibroblasts with siRNA against VEGF. Besides significant inhibition of VEGF expression they found significantly decreased fibroblasts growth and downregulated PAI-1 expression. Their results suggest that modulation of VEGF production by siRNA may be a potential therapeutic strategy for keloids[81].

Conclusion

Whereas in the past treatment of keloid disease was found by serendipity data from research on pathological scarring, the principles of wound healing will result in new targeted therapies. When available these treatments can be used in patients with genetic susceptibility for keloid disease to prevent the formation of pathological scars.

Conflict of interest
Authors have no conflict of interest to declare.

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