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REVIEW

Managing keloid scars: From radiation therapy to actual and potential drug deliveries

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The aetiology of keloids is becoming clearer, but many questions remain, including about the most optimal treatment. Current therapies include surgical excision, radiotherapy, and various pharmaceutical drugs. However, none of these drugs are keloid-specific. Moreover, all current interventions are associated with high recurrence rates. Here, we review the pharmaceutical interventions that are currently available. All are based on the fact that keloids are an expanding solid mass with intense chronic inflammation at its advancing edges. Consequently, current pharmaceuticals aim to reduce the mass and/or symptoms of keloids, similar to surgery and radiotherapy. They include chemotherapies, immunotherapies, volume-reducing therapies, and anti-inflammatory therapies. We also describe new advances in keloid pharmaceuticals. They include drugs that were designed to treat systemic diseases such as hypertension or breast cancer but were found to also treat keloids. Furthermore, recent progress in genetic, epigenetic, and stem cell therapies suggests that they could become useful in the keloid field. This review of pharmaceutical advances will hopefully promote additional research and the development of effective and specific pharmaceuticals for keloids.

KEYWORDS

genetic and epigenetic interventions, keloid therapy, pharmacotherapy, radiotherapy, stem cell therapy

1 | INTRODUCTION

Keloids are common pathological scars: their prevalence varies from 0.09% in the United Kingdom to 16% in the Congo.[1] They are the result of a fibroproliferative disorder[2] in which the main pathogenic mechanism is chronic inflammation of the reticular dermis that exists in the wound-healing process.[3] Clinically, keloids typically grow beyond the boundary of the original wound, thereby continuously invading the neighbouring healthy skin with a leading edge that is often erythematous and pruritic. Pathologically, they have a large number of fibroblasts and excessive accumulation of collagen fibres (mainly collagen type I) that are Hyalinized and eosinophilic.[4] Dermal nodules may or may not be present.[2]

Currently, there are no specific therapeutics that can instantly, completely, and permanently remove keloids and restore the function and aesthetics of the skin and the affected body part. Indeed, despite decades of research and clinical effort, keloids continue to be highly refractory lesions. The current treatment options include surgery with various tension-shielding techniques[5] followed by radiotherapy[6] and potentially pharmaceutical therapies, such as corticosteroid tapes/plasters/injections.[3] Other adjuvant choices include laser therapy[7] and intralesional cryotherapy.[8] The unsatisfactory results of those historical approaches and high post-therapeutic recurrence rates mean that other, more effective approaches are being expected.

This paper reviews, from a practical point of view, the latest pharmaceutical advances in keloid therapy along with the role of radiotherapy. Given that keloids remain a refractory disease, and there is a strong need for more effective therapies, the aim of this paper is to facilitate a greater awareness of the mechanisms by which radiotherapy and pharmaceutical approaches can ameliorate or eliminate

keloids along with non-cutaneous fibrotic diseases. The hope is that this will spur further exploration and the development of new interventions that can prevent, reduce, or even reverse keloid formation and progression.

2 | RADIATION THERAPY

Post-surgical radiotherapy is a widely applied component of the conventional therapeutic regimen for keloids.[9] It acts by slowing down angiogenesis and/or reducing the proliferation of new fibroblasts, thereby hampering collagen deposition.[10] The radiotherapeutic regimens that are most commonly used to achieve the desired effects while avoiding complications vary widely in terms of radiation type (eg, brachytherapy, electron beam, and X-ray), radiation parameters (eg, dosage, fractionation, field size, and treatment depth), the time point after surgery when the treatment commences, and the treatment duration.

A recent meta-analysis showed that radiotherapy of the wound bed after ear keloid excision is associated with an overall recurrence rate of 14.0% and that this is similar to the rate of 15.4% for perioperative triamcinolone acetonide (TAC) treatment ($P = 0.60$).[11] Another meta-analysis showed that radiation monotherapy is associated with a significantly higher recurrence rate (37%) than post-surgical radiation (22%; $P = 0.0046$); that brachytherapy associates with a lower recurrence rate (15%) than X-ray therapy (23%; $P = 0.04$); and that keloids on the chest and trunk have a higher rate of recurrence (34%) than keloids on other locations, such as the upper/lower extremities or the head, neck, or ears.[12]

The complications of radiotherapy for keloids include acute skin reactions (eg, erythema, pigmentation, epilation, and desquamation) during the first 7 to 10 days and sub-acute and late complications (eg, scarring, permanent pigmentation, depigmentation, atrophy, telangiectasis, subcutaneous fibrosis, and necrosis) several weeks after radiotherapy. These complications can be minimised by protecting fragile organs such as the thyroid and mammary glands and by selecting the most appropriate site-dependent dose protocol.

Our experiences suggest that, to reduce recurrence while limiting complications, postoperative electron beam irradiation therapy should be applied with a site-dependent dose. Thus, for keloids on the anterior chest wall, scapular region, and suprapubic region, 20 Gy should be given in four fractions over 4 days; for earlobe keloids, 10 Gy in two fractions over 2 days; and for keloids on other sites, 15 Gy in three fractions over 3 days.[13]

3 | CURRENT AND EMERGING PHARMACEUTICALS IN CLINICAL KELOID MANAGEMENT

The current and emerging pharmaceuticals can be classified in various ways, namely, according to their therapeutic purpose (eg, to reduce keloid mass or prevent recurrence), their target constituents (eg, cells, ECM, or cytokines), their target wound stage (eg, inflammation, proliferation, or remodelling), the administration route (eg, local or systemic), and the biological level at which they act (eg, tissue, cellular, or molecular). We classify current and emerging keloid pharmaceuticals according to the three main ways keloids are seen in the context of the therapy. Thus, (1) they can be seen as local tumours that require, for example, chemotherapy. This is because keloids resemble solid tumours in that they grow steadily beyond the original wound boundaries. Keloids can also be seen as inflammatory lesions that require, for example, corticosteroids because they exhibit the classical signs of inflammation (redness, oedema, and itching/pain during progression). (2) Keloids can also be seen as an inadvertently responding entity to other systemic drugs, such as those for hypertension. (3) Finally, keloids can be seen as a target disease for emerging translational interventions, such as genetic, epigenetic, and stem cell therapies (Table 1).

Key Messages

- Keloids are common pathological scars that are characterised by clinical continuous growth beyond the boundary of the original wound and invasion into the neighbouring healthy skin, as well as the pathological accumulations of fibroblasts and collagens. Therapeutic approaches include surgery, radiotherapy, and various pharmaceuticals, although no specific therapies are available to effectively and permanently cure keloids, with complications or recurrence commonly seen.
- In this review, we classify and summarise the current pharmaceuticals based on the recognitions of keloids as (a) locally distributed tumours (eg, chemotherapy, immunotherapy, and volume-reducing pharmaceuticals) or inflammatory lesions (eg, corticosteroid and botulinum toxin) and (b) as inadvertent responding entities to other systemic drugs (eg, anti-hypertensive and anti-breast cancer).
- Focusing on basic research frontiers, we also include emerging genetic, epigenetic, and stem cell therapies in keloid management to allow translational interventions. This review of pharmaceutical advances will hopefully promote additional research and the development of effective and specific pharmaceuticals for keloids.

3.1 | Pharmaceutical therapies that target the solid mass of keloid

3.1.1 | Chemotherapeutics

While keloids are clinically defined as benign diseases, they resemble tumours because they grow continuously and invade the adjacent normal skin. Moreover, the peripheral areas and leading edge of keloids are characterised by angiogenesis, fibroblast proliferation, and collagen production,

TABLE 1 Current pharmaceutical therapies in keloids

Viewpoints	Strategies	Classifications	Examples
Treating keloids as topical lesions	Anti-tumour	Chemotherapy	Bleomycin, 5-FU, mitomycin
		Immunotherapy	tacrolimus, imiquimod, interferons
		Volume reduction	Collagenase
	Anti-inflammatory		Corticosteroids
			Botulinum toxin A
Adopted from treatments in other systemic diseases	Anti-hypertension	Angiotensin-converting enzyme inhibitors	Captopril, enalapril
		Calcium channel blockers	verapamil
	Anti-breast cancer	Synthetic non-steroidal anti-oestrogen	tamoxifen
Emerging therapies based on advancements in other fields	Genetic	Kill fibroblasts/decrease collagen synthesis	CDglyTK, relaxin
	Epigenetic	Methylase inhibitor	5-aza-2'-deoxycytidine
		Histone deacetylation inhibitor	trichostatin A
		Non-coding RNAs	miR-196a, miR-200c, H19 siRNA
	Stem cells	Adipose tissue-derived mesenchymal stem cells	
		Mesenchymal stem cells	
		Wharton's jelly stem cells	
		Amniotic stem cells	

whereas their central areas are characterised by hypoxia, apoptosis, and abundant collagen.[2] Consequently, tumour chemotherapeutics have been applied to keloids. The main agents that have been used are bleomycin, 5-fluorouracil (5-FU), and mitomycin.

Bleomycin functions as a typical cytotoxic antibiotic that has anti-tumoural, antibacterial, and antiviral properties.[14] It delays the cell cycle in the G2 phase,[15] cleaves DNA, degrades RNAs, and induces apoptosis.[16,17] In 12 patients with 13 keloids refractory to TAC, bleomycin injections (0.1 mL of 0.15 IU per injection, 0.4 mL/cm^2/lesion, maximum volume 3.5 mL/session) using the dermojet injection technique every month for 2 to 6 sessions resulted in good flattening: 9 had complete (100%) flattening, 2 had highly significant (>90%) flattening, 1 had significant (75%-90%) flattening, and 1 had moderate (50%-75%) flattening. There were no recurrences during the mean 18.7-month follow-up period.[18] However, a prospective single-blinded randomised control study of 26 patients with keloids or hypertrophic scars showed that intralesional bleomycin injection (1 IU/mL, 0.1 mL/cm^2) every month (<6 mL/session) for 3 months did not significantly improve the lesions compared with TAC injection as measured using the Patient and Observer Scar Assessment Scale assessment. However, 50% of the patients in both treatment arms believed their treatment had resulted in a very good improvement.[19] It is likely that the therapeutic and side effects of bleomycin vary depending on the keloid location, size, cause, the skin type, the infusion technique, and whether previous treatments had been applied.[20]

5-FU is a pyrimidine analogue and a classical chemotherapeutic agent. When the moderately sized keloids (maximum dimension ≤6 cm) of 24 patients were injected with 50 to 150 mg of 5-FU every week for up to 16 sessions, the lesions of more than half of the patients exhibited >50% flattening. The side effects included pain, purpura, superficial sloughing, temporary hyperpigmentation, and the development of treatable ulcers.[21] Similarly, a prospective randomised uncontrolled trial in 28 keloid patients showed that weekly intralesional injections of 5-FU (50 mg/mL, 0.5 to 2 mL per session) for 12 weeks induced a > 50% reduction in lesion size as well as lesion flattening and regression of the scar periphery in the majority of patients. No recurrences were observed during the 24-week follow-up period. The main side effects were pain, ulceration, and burning sensation.[22]

Mitomycin is a potent DNA cross-linker that inhibits DNA synthesis and induces DNA fragmentation in the late G1 and early S phases of the cell cycle.[23] When the keloids of two patients were subjected to intralesional administration of mitomycin (1 mg/mL), the lesions worsened, and there was an increased risk of ulceration. However, when the keloids or hypertrophic scars of nine patients were resected by shaving excision, and the wound beds were topically treated with mitomycin (1 mg/mL) for 3 minutes, the pruritus and pain of the patients were markedly reduced.[23] Similarly, when the surgical wounds left by core excision of the keloids of 10 patients were first covered with a gauze soaked with mitomycin (0.4 mg/5 mL) for 4 minutes and then irrigated fully with saline, the keloid recurrence during the average 8-month follow-up period was only 10%.[24]

3.1.2 | Immunotherapies

There are many lines of evidence that suggest the immune system plays a key role in keloid development and progression. For example, keloid patients have significantly higher levels of circulating immune complexes and cells than control subjects.[25,26] Consequently, multiple immunotherapies are potentiated in keloid management.[26] The main keloid immunotherapies that have been clinically tested are tacrolimus, imiquimod, and interferons (IFNs).

Tacrolimus is a calcineurin inhibitor and an immunosuppressive drug that can inhibit T-cell activation. When keloid fibroblasts are treated with tacrolimus in vitro, their TGF-β1-induced proliferation, migration, and collagen production drop significantly.[27] However, a subsequent genome-wide microarray analysis, followed by quantitative PCR, showed that treating human keloid fibroblasts for 72 hours with 2 nmol/L tacrolimus in vitro did not directly block their collagen expression pathways; rather, tacrolimus acts by inhibiting NME/NM23 nucleoside diphosphate kinase 1 (a metastasis suppressor) and heterogeneous nuclear ribonucleoprotein H3-2H9. The latter is involved in the fibrogenic epithelial-mesenchymal interactions and the post-transcriptional control of collagens.[28] In terms of clinical evidence, a patient in a clinical trial for conventional topical treatment of atopic dermatitis with tacrolimus reported that he had also treated his keloid with the agent and had observed marked clearing of the keloid.[29]

Imiquimod is a Toll-like receptor agonist. Imiquimod 5% cream serves as an immune response modifier in keloid management.[30] Topical treatment of keloids with imiquimod cream every day for 2 to 8 weeks before surgical excision significantly up-regulated *DFFA* and down-regulated *caspase 3*; both genes are markers of apoptosis.[31] Moreover, when wounds that remained after earlobe keloid excision were treated daily with imiquimod cream for 6 weeks, the cosmetic outcome was satisfactory, and none of the keloids recurred during the 12-month follow-up period.[32] However, the same approach was much less successful for trunk keloids: of the nine patients whose post-surgical wounds were treated daily with topical imiquimod for 8 weeks, seven recurred approximately 12 weeks after surgery. The topical treatment was also associated with local skin reactions, including erythema, erosion, and crusting.[33] A meta-analysis in 2017 showed that the estimated keloid recurrence rate in patients undergoing post-surgical imiquimod cream treatment was 24.7%.[34]

IFN-γ and IFN-α2b are controversial keloid therapies perhaps because of protocol differences between studies. Intralesional IFN-γ injections (0.01 or 0.1 mg) thrice a week for 3 weeks reduced the height of keloid sites by 30.4% compared with 1.1% in control sites; this effect was associated with reductions in thickened collagen bundles and active dermal fibroblasts.[35] However, a double-blinded placebo-controlled trial showed that local IFN-γ injections (10 μg weekly for 10 weeks) after keloid excision did not reduce the keloid recurrence rate.[36] With regard to IFN-α2b, a retrospective study showed that when 16 keloid sites underwent topical post-surgical injection with IFN-α2b (1 million units in 0.1 mL/linear cm) plus an additional injection of 5 million units in 12/16 sites 1 week later, the recurrence rate during the mean 7-month post-surgical observation period was 18.7%.[37] However, a prospective clinical trial then showed that, when keloids were excised and the wound bed was injected intraoperatively and a week later with IFN-α2b (1 million units/linear cm, maximum 5 million units), the recurrence rate was not superior to that of the TAC control group (54% vs 15%).[38]

3.1.3 | Volume-reducing pharmaceuticals

Several studies have tested the keloid-clearing ability of intralesional injections of collagenase. The hypothesis was that these injections could enzymatically degrade collagen, which is the main ECM component in keloids. In one study, six recurrent earlobe keloids (≥5 mm diameter) were injected once with 0.225 mg of collagenase clostridium histolyticum in 0.195 mL of diluent and then treated daily with compression earrings. In three, the maximum volume reduction change was 91%, 83%, and 86% at 12-, 12- and 10 post-injection months, respectively. The other three patients chose keloid excision for cosmetic reasons 6, 8, and 11 months after enrolment; at the last visit before surgery, their keloid volumes had decreased by 39% (at 1 post-injection month), 58% (at 10 months), and 33% (at 1 month), respectively.[39] However, another study showed that, when five keloids underwent one or more intralesional injections with 600 to 4500 units of pure bacterial collagenase, the scar volumes did not improve satisfactorily. Moreover, significant side effects were observed, including swelling, ulceration, pain, blistering, and local bruising.[40]

3.2 | Pharmaceutical therapies targeting the prolonged inflammatory phase in keloids

A number of drugs aim to dampen the intense and prolonged inflammation in keloids, including corticosteroids and botulinum toxin A (BTA).

The classical corticosteroid application is intralesional injection of TAC. TAC doses vary from 10 to 40 mg/mL depending on the keloid volume, size, and location, as well as the characteristics of the individual patient.[41] A double-blinded clinical trial on 40 adult keloid patients showed that monthly intralesional TAC injections (40 mg/mL, 0.5 mL/cm^2) for 3 months improved symptoms such as erythema and pruritus and reduced keloid height during the 44-week follow-up period, although these effects were less significant than those of monthly 5-FU tattooing (50 mg/mL, 2 mL/cm^2) for 3 months.[42] A prospective clinical trial in 21 children also showed that monthly intralesional TAC infiltration (20 mg/cm^3, ≤40 mg/session) for 3 months decreased the average size of the 25 keloids by 82.7%. Only one keloid did not respond to treatment, even after five infiltrations.[43] The side effects of intralesional steroid administration are mainly pain, hypopigmentation, hyperpigmentation, skin atrophy, and telangiectasia.[41]

The therapeutic effects of BTA are conflicting and not convincing. When keloid fibroblasts were cultured with an optimal BTA concentration (2.5 μL/10^6 cells) for 48 hours, their numbers were reduced by 50%.[44] However, Haubner

et al failed to detect a consistent effect of BTA on the ability of keloid fibroblasts to produce IL-6, VEGF, or TGF-β or to proliferate.[45] One case report showed that an intralesional injection of BTA (100 units in 5 mL of saline) successfully treated neuropathic pain in one keloid patient.[46] However, when four keloid patients were treated with intralesional injections of 70 to 140 Speywood units of BTA/session every 2 months for up to 6 months, very little keloid regression was observed.[47]

3.3 | Therapeutic pharmaceuticals aimed at other systemic diseases that are effective for keloids

3.3.1 | Anti-hypertensive pharmaceuticals

Keloids associate closely with hypertension.[48] Our cohort study demonstrated that blood pressure correlated closely with keloid size and number. We speculate that the endothelial dysfunction, inflammation-induced hypoxia, and/or altered skin fibroblast behaviour in hypertension may amplify the cellular abnormalities in keloids.[49]

Consequently, anti-hypertensive pharmaceuticals such as angiotensin-converting enzyme inhibitors (eg, captopril and enalapril) and calcium-channel blockers (eg, verapamil) may be effective treatments for keloids. Topical application of captopril cream (5%) twice a day for 6 weeks decreased the height of a keloid on the hand while concomitantly eliminating its redness and relieving its itchiness. Topical and systemic side effects were not observed.[50] Similarly, oral administration of enalapril (10 mg daily) improved the incisional keloids of two patients with no side effects. As this low-dose enapril treatment does not associate with side effects in general (with the exception of patients with acute renal failure, chronic renal insufficiency, or collagen vascular disease), it was suggested that it may be a good treatment for keloids.[51] With regard to verapamil, a double-blinded randomised controlled trial showed that monthly intralesional verapamil injections (2.5 mg/mL) for 4 months in half of the wound bed after keloid excision was associated with more keloid recurrence 12 months after surgery than a similar regimen of TAC injections (10 mg/mL) in the other half of the wound bed ($P = 0.01$), although no side effects were found in the verapamil-treated scar halves.[52] The mechanisms by which anti-hypertensives improve keloids are not known but may involve decreasing collagen metabolism, cellular proliferation, and the expression of PDGF-BB, TGF-β1, and HSP47 by keloid fibroblasts.[53]

3.3.2 | Anti-breast cancer pharmaceuticals

Tamoxifen is a synthetic non-steroidal anti-oestrogen drug that was originally developed to treat breast cancer. It has been shown to decrease the collagen synthesis by keloid fibroblasts by decreasing TGF-β production in vitro.[54,55] A prospective clinical study showed that when the keloids of 13 patients were injected with 20 mmol/L tamoxifen (0.01 mL/cm^2) once a week for 8 weeks, the fibroblast numbers in the 8-week punch biopsy were lower than those in the pre-treatment biopsy. The collagen fibres were also reduced and atrophic. There was marked inflammatory infiltration at 8 weeks.[56]

4 | EMERGING GENETIC AND EPIGENETIC THERAPIES

Several intriguing genetic and epigenetic therapies have been proposed, although they are still in the pre-clinical stage of research.

4.1 | Genetic therapies

There are two potential anti-keloid genetic therapies: they either kill keloid fibroblasts or inhibit their collagen synthesis. One is the CDglyTK double-suicide gene. It consists of cytosine deaminase (CD) linked to thymidine kinase (TK), which convert 5-fluorocytosine and ganciclovir into toxic metabolites, respectively. When keloid fibroblasts were infected with a recombinant adenovirus that expressed CDglyTK (Ad-CMV-CDglyTK) and were then treated with 5-fluorocytosine and ganciclovir, they underwent more profound apoptosis (as indicated by positive TUNEL staining and decreased Bcl-2 and increased Bax mRNA expression) than the control cells.[57] Another genetic therapy is replication-incompetent dl-lacZ-RLX-RGD adenovirus that expresses relaxin. Relaxin is a member of insulin-like growth factor (IGF) family that has known anti-fibrotic effects.[58] When keloid fibroblasts were infected with the dl-lacZ-RLX-RGD adenovirus, their mRNA expression of collagens I and III decreased by 28% and 59%, respectively. Their MMP-1 and MMP-3 mRNA expression also decreased.[59]

4.2 | Epigenetic therapies

Epigenetic therapies that modulate the DNA methylation and histone modification in keloid fibroblasts, as well as non-coding RNAs, may be useful in keloid management.

Altering the DNA methylation of keloid fibroblasts could reduce their pathological characteristics. This is supported by the fact that DNA methyltransferase 1 (DNMT1) is expressed by 100% and only 8% of keloid and normal skin fibroblast samples, respectively. Moreover, when keloid fibroblasts were treated with the methylase inhibitor 5-aza-2′-deoxycytidine (5-aza-dC), it reduced their mRNA expression of both TGF-β1 and DNMT1.[60] Similarly, keloid fibroblasts, but not normal dermal fibroblasts, express high levels of the profibrotic gene encoding insulin-like growth factor-binding protein-5 (IGFBP5). When keloid fibroblasts were treated with 2 μM 5-aza-dC for 4 days, their IGFBP5 expression was markedly decreased than in 5-aza-dC-treated normal fibroblasts.[61]

Post-translational histone modifications such as histone deacetylation (HDACs) provide another target of epigenetic therapy. Treatment of keloid fibroblasts with the HDAC inhibitor trichostatin A (TSA) decreased proliferation, induced apoptosis, and reduced TGF-β1-induced collagen synthesis.[62] Moreover, treating keloid fibroblasts with TSA (0.33 μM) for 1 day led to a ~15-fold rise in their expression of secreted frizzled-related protein 1 (SFRP1), which functions as a WNT inhibitor and is expressed at much lower levels in keloid fibroblasts than in normal dermal fibroblasts.[61]

Non-coding RNAs such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) may also be useful in keloid management. MiRNAs are short, single-stranded, non-coding RNAs that regulate gene expression at the post-transcriptional level by targeting specific mRNAs for degradation or inhibiting mRNA translation.[63] lncRNAs (>200 nucleotides) are mRNA-like molecules that lack stable open reading frames and are known to regulate developmental processes and diseases.[64] An miRNA microarray analysis demonstrated that miR-196a was significantly down-regulated in keloid fibroblasts compared with normal fibroblasts. When miR-196a was overexpressed and knocked down in keloid fibroblasts, their secretion of type I/III collagens dropped and rose, respectively.[65] Similarly, miR-200c, which targets ZNF217, is under-expressed in keloid fibroblasts. MiR-200c RNA levels correlate inversely with the transcript levels of lncRNA-activated by TGF-β (lncRNA-ATB). When lncRNA-ATB was knocked down in keloid fibroblasts, their miRNA-200c levels rose, which decreased ZNF217 levels, which in turn suppressed the autocrine secretion of TGF-β_2. Thus, knocking down lncRNA-ATB may be a therapeutic strategy for keloids.[66] In addition, keloids have much higher levels of lncRNA-H19 than normal skin controls, and silencing of this lncRNA by small interfering RNAs significantly reduced the proliferation of keloid fibroblasts in vitro.[67]

5 | STEM CELL THERAPIES

Several studies have assessed whether stem cells can counter fibrosis by reducing inflammation, clearing reactive oxygen species, promoting the production of anti-fibrotic factors, and enhancing angiogenesis and matrix remodelling.[68,69]

Candidate stem cells that may have these anti-fibrotic effects include adipose tissue-derived mesenchymal stem cells (ASCs), mesenchymal stem cells (MSCs), Wharton's jelly stem cells (WJSC), and amniotic stem cells. Thus, ASCs-conditioned medium (ASCs-CM) inhibited the proliferation and migration of keloid fibroblasts; reduced their mRNA expression of IL-6, TGF-β1, collagen 1a1, and SMA; and decreased their contractility. Furthermore, when injected into the keloid implantation athymic mouse model, ASCs-CM induced the shrinkage of the keloid implant. These effects were associated with reduced accumulation of $CD68^+$ and CD31+ cells and lower blood vessel densities and collagen deposition.[70] MSC-conditioned medium reduced the viability, α-SMA expression, and collagen secretion of keloid fibroblasts in vitro. Moreover, intralesional injections of the BM-MSC-conditioned medium (100 μL daily for 3 weeks) into a bleomycin-induced dermal fibrosis mouse model significantly decreased skin fibrosis. These effects were potentiated via TGF-β3-dependent activation.[71] In addition, when human keloid cells were treated with human WJSC-conditioned medium or lysate every 72 hours for up to 9 days, they exhibited decreased proliferation, increased apoptosis, interruption of the cell cycle, and inhibition of migration.[72] In relation to amniotic stem cells, when a thoracotomy scar and its surrounding skin were injected with 2 million human amniotic stem cells mixed with amniotic membrane matrix, the intractable pain of the Caucasian male patient decreased significantly. Two additional injections completely eliminated the pain and improved the remodelling of the scar.[73]

6 | FUTURE DIRECTIONS

A deeper understanding of keloid aetiology potentiates new pharmaceutical interventions for keloids in the future. This is exemplified by our recent research showing the important role of mechanobiology in scar formation: this information has aided the recent development and clinical use of mechanotherapeutic interventions that promote proper wound healing by imposing mechanical stimuli at the molecular, cellular, and/or tissue level.[74] These interventions include tension-reducing surgical techniques[5] such as small-wave incision[75] and tension-reducing wound dressings such as silicone sheets.[76] Further investigations into the mechanobiology of abnormal scarring will help identify novel molecules and processes that could be targeted by specific pharmaceutical agents for keloids. Candidate molecules include mechanosignalling molecules[77] and molecules that are involved in dictating cell shape, ECM stiffness, or cell-matrix interactions. Further in vivo research, including with keloid animal models and long-term RCTs, is also needed to identify these and other target molecules to test potential anti-keloid techniques from other fields and to identify additional biochemical, histological, and genetic mechanisms that drive keloid development and recurrence. These advances are likely to spur the development of new strategies that can prevent, reduce, or even reverse keloid formation and progression.

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