Clinical, Cosmetic and Investigational Dermatology Dovepress

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Future Directions About Keloid Scars Based on Pathogenesis and Therapies

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Abstract: Keloids are pathologic scars that pose a significant functional and cosmetic burden. While the literature on keloid management continues to expand, the absence of standardized guidelines or treatment protocols endorsed by academic governing bodies remains a significant challenge. The pathogenesis of keloid scars is not fully elucidated. This review delves into the intricate pathogenesis of keloids, exploring the molecular and cellular mechanisms underlying their formation. Conventional therapies are analyzed in-depth considering their efficacy and limitations, including surgical excision, pharmacotherapies, radiotherapy, cryotherapy, silicone-based product, pressure therapy, and light-based therapy. The emergence of novel therapeutic approaches is discussed, including pharmacotherapies, physical therapies, and biological therapies, shedding light on their potential in treating keloid scars. We also contemplate future directions in the field, encompassing the application of targeted therapies, gene-editing tools, tissue engineering, and regenerative medicine, together with psychosocial support and patient education. In synthesizing current knowledge, scrutinizing therapeutic modalities, and envisioning future avenues, this review aims to provide a comprehensive reference for clinicians, researchers, and stakeholders engaged in the intricate field of keloid management.

Keywords: keloid scars, pathogenesis, therapies

Introduction

Keloid scars represent a perplexing challenge in dermatology, characterized by an abnormal wound healing process that extends beyond the original injury site.[1] The raised, often painful, and cosmetically disfiguring scars pose both clinical and psychological burdens for affected individuals. Despite their prevalence, the precise etiology of keloids remains elusive, and their pathogenesis involves intricate interactions between genetic, immunologic, and environmental factors.[2] Understanding the underlying mechanisms driving keloid formation is essential for developing effective therapeutic strategies. In addition, there is a need to revisit rapidly evolving therapies. In this review, we delve into the intricate cellular processes and molecular pathways implicated in the pathogenesis of keloid scar formation. Additionally, we scrutinize the current landscape of therapeutic interventions, ranging from conventional therapies to emerging innovative approaches, with a focus on their efficacy and potential side effects. Through a nuanced exploration of both the molecular intricacies and therapeutic modalities, this review aims to contribute to the advancement of our knowledge and the refinement of strategies for the management of keloid scars.

Pathogenesis

Keloid pathogenesis is a multifaceted process involving a dynamic interplay of various cells, cytokines, and signaling pathways (Figure 1). A deeper understanding of these mechanisms opens avenues for targeted therapeutic interventions aimed at disrupting the cascade of events leading to keloid formation. By dissecting the intricacies of keloid pathology, we move closer to more effective and personalized approaches for the management of this challenging dermatological condition.

Received: 25 March 2024
Accepted: 4 September 2024
Published: 25 October 2024

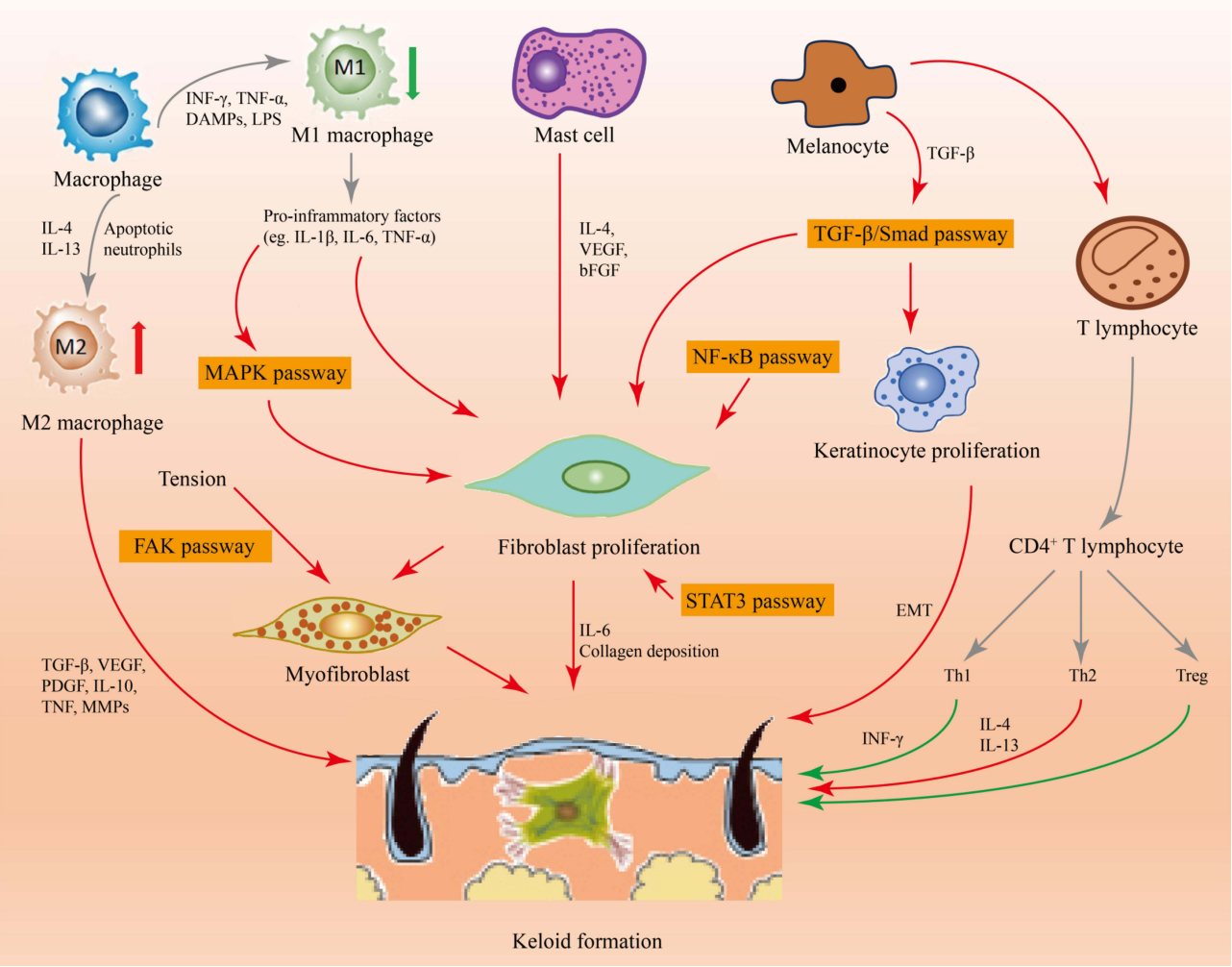

Figure 1 Schematic diagram of interactions between various cells, cytokines, and signaling pathways leading to keloid formation. Red arrows represent facilitation and green arrows represent inhibition. Macrophages can polarize into two main phenotypes depending on different microenvironments. The infiltration of M2 macrophages is significantly higher than that of M1 macrophages in keloid tissue. CD4+ T cells can be categorized into Th1, Th2, and regulatory T cells (Tregs). Th1 cells can attenuate the tissue fibrosis by releasing IFN-γ. IL-4 and IL-13 secreted by Th2 cells facilitate to the synthesis of collagen, which consequently result in deposition of reticular fibrin. Tregs can inhibit the immune function other effector T cells and maintain peripheral immune tolerance. Mast cells can increase type I collagen synthesis by stimulating fibroblast proliferation through the release of VEGF, IL-4, as well as bFGF. Fibroblasts are one of the major cells in keloid tissues. The fibroblast density in keloids is higher and the proliferation rate is increased, but the apoptosis rate is reduced, which further leads to the deposition of collagen matrix and overproduction of cytokines such as IL-6. Myofibroblasts are the key effector cells causing keloid development and growth. Aberrant expression of EMT-related genes in keratinocytes promotes keloid formation. Melanocytes in the skin can promote the TGF-β secretion, stimulate the proliferation of fibroblasts, and promote the development of pathological scarring. TGF-β/Smad, NF-κB, STAT3, MAPK and FAK are the key signaling pathways for keloid formation.

Abbreviations: IFN-γ, interferon gamma; TNF-α, tumor necrosis factor-α; DAMPs, damage-associated pattern molecules; LPS, lipopolysaccharide; IL, interleukin; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor; MMPs, matrix metalloproteinases; bFGF, basic fibroblast growth factor; Th, helper T cell; EMT, epithelial–mesenchymal transition.

Inflammatory Cells and Cytokines in Keloid Formation

Macrophages play a crucial role in the complex process of keloid formation, contributing to both the initiation and perpetuation of the abnormal wound healing response. Macrophages can polarize into two main phenotypes depending on different microenvironments. Monocytes could polarize into activated M1 macrophages in the presence of some cytokines and factors such as lipopolysaccharide (LPS), interferon gamma (IFN-γ), damage-associated pattern molecules (DAMPs) and tumor necrosis factor-α (TNF-α).[3] M1 macrophages function in enhancing immune responses and stimulating the proliferation of keratinocytes and fibroblasts by releasing pro-inflammatory cytokines (eg interleukin-6 (IL-6), IL-1β and TNF-α).[4] M2 macrophages exert its biological properties through releasing growth factors such as platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and transforming growth factor-β (TGF-β).[5] Specifically, M2 macrophages suppress inflammation by triggering IL-10 overexpression, together with

secreting TNF and different matrix metalloproteinases (MMPs).[4] In the early stage of scar formation, also known as inflammatory and early proliferative stage, M1 is the prominent macrophage population. In contrast, in the late proliferative and remodeling stages, M2 is the predominant type.[6]

T lymphocytes are part of the initial immune response to tissue injury. They are recruited to the site of injury, contributing to the inflammatory cascade. In keloids, this early immune response becomes dysregulated, leading to prolonged inflammation. $CD4^+$ T cells were categorized into Th1, Th2, and regulatory T cells (Tregs) according to the effector cytokines and transcriptomes. IL-4 and IL-13 secreted by Th2 cells have been reported to facilitate to the synthesis of collagen, which consequently result in deposition of reticular fibrin.[7] Th1 cells could attenuate the tissue fibrosis by releasing IFN-γ.[8] Moreover, Tregs can inhibit the immune function other effector T cells and maintain peripheral immune tolerance. These immunosuppressive effects directly affect the collagen deposition during the pathogenesis of keloid.

Mast cells are inflammatory cells that drive fibroblast activation and excessive collagen deposition. Mast cells number and activation status show a positive correlation with scar severity.[9,10] Mechanistically, mast cells could increase type I collagen synthesis by stimulating fibroblast proliferation through the release of VEGF, IL-4, as well as basic fibroblast growth factor (bFGF).[9]

Fibrosis-Related Cells in Keloid Formation

Fibroblasts, one of the major cells in keloid tissues, involve in extracellular matrix (ECM) synthesis and remodeling, together with scar healing after burns, trauma and surgery. A wide variety of cytokines and inflammatory mediators have been shown to significantly downregulate the expression of IL-6 in fibroblasts. During the wound healing process, fibroblasts could release massive collagen, resulting in collagen matrix deposition. The fibroblast density in keloids is higher and the proliferation rate is increased, but the apoptosis rate is reduced, which further leads to the deposition of collagen matrix and overproduction of cytokines. In addition, fibroblasts in keloids can differentiate into myofibroblasts, which possess contractile properties. Myofibroblasts contribute to tissue contraction, leading to the tightening and firmness of keloid scars.

Myofibroblasts are also thought to be a cell type that contributes to scarring[11] because abnormal persistence of activated myofibroblasts can lead to dermal fibrosis.[12] Therefore, the keloid research community generally believes that myofibroblasts are the key effector cells causing keloid development and growth.[13]

Keratinocytes have been shown to further enhance the proliferative and anti-apoptotic phenotype of fibroblasts in keloid lesions, resulting in a prolonged proliferative phase and delayed remodeling phase, allowing continued excess collagen production.[14] In a study focused on expression of keloid keratinocytes, *Hahn* et al reported aberrant expression of epithelial–mesenchymal transition (EMT)-related genes.[15] This implied that EMT in keratinocytes may be associated with keloid formation.

Individuals with darker skin tones, rather than fairer-skinned counterparts, are more prone to develop keloid.[16] Moreover, the incidence of keloids varies in different tissues, and adolescents and pregnant women with increased hormone secretion and skin pigmentation are more likely to develop keloids.[17] These suggest that the formation of keloids is associated with the number, distribution and activity of melanocytes. In addition, melanocytes have been reported to stimulate fibroblast proliferation, collagen synthesis and ECM deposition, and activate the TGF-β signaling pathway, promoting the development of pathological scars.[18]

Signaling Pathways in Keloid Formation

TGF-β1 stands out as the predominant known factor driving fibrosis, and the TGF-β/Smad signaling pathway serves as the quintessential route regulating collagen formation in fibroblasts and myofibroblasts. This pathway orchestrates fibroblast proliferation and collagen production through the upregulation of target gene expression, constituting the primary mechanism underpinning keloid formation.[19,20]

NF-κB family member function as transcriptional factors, regulating a multitude of crucial inflammatory genes. The NF-κB pathway have a close association with abnormal proliferation and excessive ECM production in keloid fibroblasts.[21]

The STAT3 signaling pathway serves as a crucial regulator of cell differentiation, apoptosis, inflammation, and fibrosis. This pathway has been observed to be activated in keloid tissues.[22,23] Diminishing STAT3 expression or inhibiting its phosphorylation has demonstrated a notable reduction in collagen synthesis, as well as keloid fibroblasts proliferation.[23] These substantiate the pro-fibrotic role attributed to STAT3.

Mitogen-activated protein kinase (MAPK), a member of serine-threonine protein kinases, can be activated by various stimuli such as neurotransmitters, cytokines, cellular stress, hormones, as well as cell adhesion. The downstream elements of the MAPK pathway encompass p38 kinase, c-Jun N-terminal kinase (JNK), and extracellular regulated protein kinase (ERK). Among these, JNK and p38, with similar biological properties, are implicated in apoptosis and inflammation. ERK is primarily associated with cell differentiation and proliferation. Research by Li et al[24] revealed that heightened TNF-α activity could further activate the NF-κB, JNK, and p38 MAPK pathways, fostering the excessive proliferation of keloid fibroblasts. These findings underscore the significant role of the MAPK pathway in the pathogenesis of keloids.

Elevated local mechanical forces are linked to the emergence of atypical skin fibrosis, with keloids commonly manifesting in regions subjected to continual tension, such as the chest. Focal adhesion kinase (FAK) pathway, recognized for its role in mechanotransduction, has been found to be aberrantly activated in keloid tissues,[25] contributing to the acceleration of skin fibrosis.[26]

Conventional Therapies

Surgical Excision

Surgical excision is a conventional approach for keloid scar removal,[27] offering various methods tailored to factors such as keloid size, patient age, skin type, and anatomical location.[28] The surgical methods include excision with grafting, flap coverage and linear closure, W-plasty, as well as Z-plasty.[29] Despite its widespread use, excision introduces new wounds and may lead to the development of similarly sized or even larger keloid scars.[30] Consequently, surgical excision has not been adopted as a standalone therapy due to a high recurrence rate of 45% to 100%.[31,32] To mitigate recurrence and enhance postoperative outcomes, surgical excision is often complemented by additional therapies, such as pharmacotherapy,[33,34] radiotherapy,[35] cryotherapy,[36,37] silicone and pressure dressings or devices,[38,39] and light-based therapy.[40]

Pharmacotherapy

Intralesional corticosteroid treatment stands as the first-line therapy for keloids. Study have shown that corticosteroids could down-regulate the collagen I and TGF-β expression at the translational level.[41] Currently, triamcinolone acetonide (TAC) is a commonly used drug in clinical practice. It (concentration: 10 to 40 mg/mL) is typically injected every 3 to 6 weeks over a period of 3 to 6 months to ameliorate keloid scars, resulting in reduced hardness, diminished volume, and improved symptoms.[42] However, the injection process will be accompanied by severe pain. A study of Park et al[43] involved intralesional TAC injections on 40 patients with 58 keloids, employing vibration anesthesia for half of each lesion while the other half received standard injections. Evaluation revealed the effectiveness of vibration anesthesia in alleviating pain during the treatment process. Corticosteroids are frequently utilized in combination with other regimens such as 5-fluorouracil (5-FU).[44] A clinical trial has demonstrated that the combined intralesional injection of TAC and botulinum toxin type A (BTX-A) within the lesion yielded more substantial improvements in thickness and volume compared to TAC or BTX-A administered alone. Importantly, this combination therapy exhibited a low recurrence rate.[34]

Although keloids are benign tumors, they display many cancer-like characteristics. Consequently, various anti-tumor drugs were used in keloid treatment, such as 5-FU,[44] paclitaxel,[45] bleomycin,[46] and mitomycin C.[47] These drugs are commonly employed for the management of small keloid scars. As a pyrimidine analogue, 5-FU enhances the resolution of keloid scars by inhibiting fibroblasts proliferation and collagen synthesis.[48] It has been indicated that 5-FU effectively diminished the size of keloids and alleviated symptoms like itching, with more pronounced effects observed when combined with TAC.[44] This combination therapy is currently prevalent in clinical practice. A study on hypertrophic scars in a rabbit model demonstrated the therapeutic response of paclitaxel, highlighting its potential in keloid management.[49] However, its notable hydrophobicity poses challenges in clinical applications as it does not easily penetrate the skin. To

enhance the aqueous solubility of paclitaxel, Wang et al[45] prepared paclitaxel-cholesterol-loaded liposomes using thin film evaporation fashion and found that this formulation effectively inhibited the proliferation of keloids. It has been reported that bleomycin could inhibit collagen production, activate apoptosis and inhibit DNA and RNA synthesis of fibroblasts.[50,51] Kim et al[46] found that bleomycin reduced the recurrence of keloid scars, but it should be used with caution in the treatment of keloid scars due to complications such as hyperpigmentation, pain, and ulceration. Mitomycin C can inhibit the proliferation of fibroblasts by inhibiting DNA and cellular synthesis.[47] Sonia et al[52] loaded mitomycin C to a cyclodextrin polymer system and found that the inhibitory effect of incorporated and released mitomycin C on fibroblast proliferation lasted much longer than a one-time application. This controlled mitomycin C delivery technology could have a greater therapeutic impact on keloids than the one-time applications of mitomycin C.

Verapamil is a L-type Ca^{2+} channel blocker, which facilitates the degradation of scar tissue by releasing procollagenase. This action leads to alterations in fibroblast shape, induction of TGF-β1 apoptosis, reduction in ECM, and actin filament depolymerization.[53] To date, intralesional verapamil has been employed for treating keloid scars.[54] However, recent evidence from a double-blind randomized controlled trial (RCT) suggested that verapamil may be less effective in preventing keloid recurrence compared with TAC following surgical excision.[55] A study by Robabeh et al, which divided patients with two or more keloids into TAC and verapamil treatment groups, revealed that significant improvement of scar height and hardness was observed only in the TAC group, not in the verapamil group.[56] Due to the limited efficacy of verapamil as a standalone treatment, it is often utilized in combination therapies. Combination of verapamil with pressure therapy has shown improvements in pigmentation, vascularity, elevation, flexibility, and pruritus in burn-induced keloids.[57] Studies by Khattab et al[58] and Morelli et al[1] demonstrated the superiority of combining verapamil with photodynamic therapy or TAC, respectively, overusing verapamil alone in treating keloid scars. These findings suggest the safety of intralesional verapamil with less adverse events, but its efficacy is enhanced when incorporated into combination therapies, offering stable and long-term results.

As a component derived from *Clostridium botulinum*, BTX-A has been considered as a potent neurotoxin that impedes neuromuscular transmission. BTX-A may affect wound healing through multiple mechanisms, including acting on tensile forces, inhibiting fibroblast differentiation, and downregulating TGF-β1 and collagen expression.[59] In a prospective, uncontrolled study involving twelve patients with keloids, intralesional injection of BTX-A (35 units/mL) resulted in favorable treatment outcomes, high patient satisfaction, and an absence of serious adverse events or indications of keloid recurrence.[60] Besides, BTX-A treatment were reported to be effective in treating keloids in two prospective clinical studies[61,62] and one RCT.[63] However, conflicting findings exist in other studies, with some showing no significant benefits of BTX-A in keloid treatment.[64,65] Ongoing research in this field underscores the need for more comprehensive clinical studies to establish the safety, effectiveness, and optimal protocols for utilizing BTX-A in the management of keloids.

Hyaluronic acid (HA) plays a crucial role in ECM, offering moisturizing and lubricating properties while influencing cell proliferation, adhesion, and migration.[66] It is commonly injected to enhance skin contours and maintain a smooth and tender skin texture in the field of plastic surgery. Study has indicated that HA with a high molecular weight could diminish the characteristic cellular proliferation activity and TGF-β1 expression in fibroblasts. By supplementing HA deposition in fibroblasts, it reduced fibrosis and ultimately curbed keloid formation.[67] It has been reported that the combined use of HA and TAC could significantly decrease keloid size.[68] However, further objective data are required to solidify the application of HA in keloid treatment.

Radiotherapy

Radiotherapy is employed as the primary preventive measure following surgical excision, which predominantly involves superficial radiation therapy. This technique primarily targets fibroblasts and vascular endothelial cells using ionizing radiation, disrupting fibroblast migration, proliferation, and synthetic secretion functions, thereby impeding fibroblast growth.[69] Presently, radiotherapy encompasses two primary modalities: external and internal. External-beam radiotherapy is represented by electron-beam radiation therapy (EBRT) and X-ray, both extensively explored in the literature. Internal radiotherapy takes the form of interstitial brachytherapy, utilizing a hollow catheter positioned in the keloid dermis to deliver localized radiation therapy.[70,71] Numerous studies have investigated surgical excision followed by

radiotherapy and advocated for the administration of radiotherapy within 24 hours of resection.[72–75] Currently, consensus on the optimal radiotherapy dose and the overall recurrence rate remains elusive. Research indicated that radiation doses below 30 Gy significantly mitigated potential risks associated with radiotherapy.[76]

While radiotherapy has been proved to significantly reduce the recurrence rate, it exposes patients to various skin-related complications, for example, short-term desquamation, erythema, and transient pigmentation changes.[77,78] The long-term complications include depigmentation, permanent dyspigmentation, atrophy, subcutaneous fibrosis, telangiectasias, chronic wounds, as well as radiation-induced malignancies.[78,79] Therefore, to minimize the risk of cancer development following keloid radiotherapy, it is imperative to adequately shield surrounding tissues, including radiosensitive breast and thyroid tissues. Additionally, efforts should be directed towards identifying the overall cancer risk factors of patients, and radiotherapy should be performed cautiously in young children.[78,80]

Cryotherapy

Cryotherapy involves subjecting keloid scars to freezing temperatures to diminish scar volume and recurrence. The temperature for the cryotherapy in treating keloid scar is lower than −22°C, inducing vascular damage, cellular anoxia, cryonecrosis, and coagulative necrosis.[81,82] Keloid tissue exposed to cryotherapy shows reduced myofibroblasts, mast cells, and TGF-β production by dermal fibroblasts.[83,84] Currently, cryotherapy options include spray, contact, and intralesional therapies. External cryotherapy tends to produce more shallow patterns of freezing and usually only partially freezes of the scar.[85] To minimize these effects, intralesional cryotherapy has been introduced. Intralesional cryotherapy involves inserting a needle, with or without a cryoprobe, into the keloid scar, allowing the vaporized liquid nitrogen to freeze the tissue.[85] According to the previous studies, intralesional cryotherapy can reduce keloid volume by 51.4% to 67.4% 12 months after the last treatment.[81,82,86–88] Evidence suggests intralesional cryotherapy is superior in treating individuals with keloids of <10 cm^2 or those with ear keloids.[86,89] Generally, despite some side effects have been reported, such as persistent hypopigmentation in non-Caucasian patients[88] and rare cases of scar recurrence,[87,88] intralesional cryotherapy outperforms spray and contact cryotherapy due to its larger internal frozen area and fewer treatment sessions.[81,90]

Silicone-Based Products

Since the 1980s, silicone-based products have been employed in keloid scar treatment, among which the silicone gel or silicone gel sheeting (SGS) has been recognized as first-line therapy for minor keloids.[37,91] Although the exact mechanism is still not well defined, SGS can enhance hydration and create a closed environment, influencing fibroblast regulation and reducing collagen synthesis.[92] SGS exhibits minimal side effects, including quickly resolvable local irritation.[93] A significant improvement up to 90% has been reported in keloid scars following SGS use.[91] However, the use of SGS demands a high level of patient compliance, as treatment regimens typically require wearing the SGS for at least 12 hours a day over 12 months.[37,94] Additionally, continuous SGS application in hotter climates may lead to increased humidity levels, potentially promoting bacterial abscess formation.[95]

Pressure Therapy

Pressure therapy has been widely used in the management of keloid scars for decades. The mechanisms underlying pressure therapy involve mechanoreceptor-induced cellular apoptosis and rigidity increase in the ECM that have been shown to affect migration, proliferation, and differentiation of fibroblasts.[96] Various pressure therapies are available, including custom pressure ear molds, elastic wrap bandages, earrings, as well as magnets.[96–98] It is recommended to apply pressure in the range of 20–40 mmHg immediately after wound re-epithelialization, preferably at the lower end, for 12–23 hours per day for over 6 months.[7,99,100] The effectiveness of pressure therapy varies according to the lesion sites of the keloids, with extremity areas and trunk being more suitable for the treatment. A pressure garment is primarily utilized in auricular keloids where pressure clips are employed after surgery.[101,102] Such pressure garment has shown success as an adjunctive therapy, reducing the risk of keloid recurrence.[101,103] However, pressure therapy is contingent on patient compliance, which could be affected by discomfort associated with continuous pressure application.[100] Taken together, pressure therapy is a well-tolerated and valuable adjunctive therapy for keloid scars.

Light-Based Therapy

Laser therapy and photodynamic therapy are two common light-based treatment modalities that show promise in alleviating keloid symptoms. Ablative lasers, such as erbium-doped yttrium aluminum garnet (Er:YAG) and CO_2 lasers, could cause localized tissue destruction and lesion size reduction through water absorption.[1] To date, there are no published RCTs on the effectiveness of CO2 laser or Er:YAG lasers to treat keloid scars. Non-ablative lasers, like pulsed dye laser (PDL) and neodymium-doped: yttrium-aluminum garnet (Nd:YAG) laser, induce thermal damage to scar capillaries, resulting in thrombosis, ischemia, collagen denaturation, and fiber rearrangement.[104–106] PDL monotherapy has reported to be effective in treating keloid or hypertrophic sternotomy scars.[107] However, according to a case series study, PDL monotherapy required 12–14 sessions for moderate to excellent outcomes.[108] To shorten the treatment sessions and reduce the recurrence rate, laser therapy has been combined with other treatments (eg cyanoacrylate glue[109] and topical corticosteroids[110]), which showed promising results.

Photodynamic therapy (PDT) for keloid scars involves applying a photosensitizer and exposing the area to specific-wavelength light, activating the photosensitizer to generate reactive oxygen species.[111] Study has shown that this therapy could inhibit fibroblast activity, restrain keloid growth, and reduce blood vessel density.[112] A case-series study evaluated the effect of PDT (light wavelength: 630 nm) in 20 patients who either had small (≤ 2 mm high) existing keloids (n =10), keloids that had been debulked surgically to a height of ≤ 2 mm (n = 6) and keloids that had been excised completely (n = 4). Three topical methyl aminolevulinic acid-PDT treatments at weekly intervals significantly reduced scar formation in keloid disease evidenced by decreased blood flow, increased pliability, decreased collagen and haemoglobin levels. Only one case of recurrence was observed at the nine-month follow-up.[113] In another case report, a female presented with chin keloid scar underwent five sessions of methyl aminolevulinate PDT (light wavelength: 633 nm) over a period of 5 months. This treatment resulted in an overall acceptable cosmetic outcome and there was no recurrence at 1-year follow-up.[114] PDT is considered a selective treatment modality because it primarily affects the treated area without harming surrounding healthy tissue. However, the choice of photosensitizer and light parameters significantly influences its effectiveness.

Both laser therapy and PDT aim to regulate collagen production and promote normal healing responses. However, their effectiveness varies among individuals, and further controlled clinical studies are required to assess their safety and effectiveness comprehensively.

Emerging Innovative Therapies

In the ever-evolving landscape of keloid scar management, a paradigm shift is underway, with a focus on novel and promising treatments. This section explores emerging innovative pharmacotherapies, physical therapies, and biological therapies poised to redefine keloid care.

Pharmacotherapies

Recently, a plethora of promising drugs has surfaced, demonstrating potential efficacy in the treatment of keloid scars. Notable among these are angiotensin-converting enzyme (ACE) inhibitors, calcineurin inhibitors, imidazoquinolines, and tamoxifen.

ACE is a peptidyldipeptide hydrolase responsible for the conversion of angiotensin (Ang) I to Ang II. This enzymatic process is crucial in blood pressure regulation and fibrous remodeling.[120,121] ACE inhibitors, recognized for their impact on blood pressure control, are now being considered as a viable avenue for the treatment of keloids.[122,123] The study of Fang et al[124] indicated that ACE inhibitors involved in the reduction of fibroblast proliferation, suppression of expression of collagen and TGF-β1, as well as downregulating the phosphorylation of SMAD2/3 and TAK1. In comparison to controls treated with water, scars in rats treated with ramipril or losartan not only exhibited reduced width but also demonstrated improved re-epithelialization and neovascularization. Additionally, the treated scars displayed the formation of well-organized granulation tissue. Lannello et al reported two cases featuring postoperative abdominal keloid scars, and the results demonstrated significant improvement in severe keloid scars following treatment with low-dose enalapril (10 mg daily).[115] In addition, over a six-week period of application, captopril cream (5%) resulted in a reduction in the height of the scar, redness and itchiness. Notably, this improvement was achieved without inducing cutaneous or systemic side effects.[116] However, as these medications have only been reported to be effective in a few cases, it's

essential to consult with a healthcare professional before use them for keloids, as they are not standard treatment strategies and may not be suitable for everyone.

Derived from *Streptomyces tsukubaensis*, the cyclic depsipeptide tacrolimus (FK-506) exerts its effects by inhibiting the calcineurin complex with FK-binding proteins.[132] Furthermore, it disrupts TGF-β/SMAD signaling pathways in keloid fibroblasts through down-regulation of TGF-β receptors expression.[133] Sirolimus (rapamycin), a cyclic depsipeptide derived from *Streptomyces hygroscopicus*, exhibits antifungal, anti-tumor and immunosuppressive properties.[132,134] It could down-regulate the expression of cytoplasmic proliferating cell nuclear antigen, collagen fibronectin, cyclin D1, as well as α-SMA. These findings highlight the anti-cancer effects of sirolimus, underscoring its potential as a therapeutic agent for keloid treatment.[135] Sirolimus also exhibited multifaceted functions, including the inhibition of ECM deposition, down-regulation of collagen I and III over-expression, and platelet-derived growth factor-induced collagen synthesis in keloid fibroblasts.[136] Since most of the studies are laboratory-based, further clinical studies are necessary to recommend FK-506 and Sirolimus.

Imiquimod could be administered after surgery through diverse treatment regimens. One approach involves initiating treatment on the night of the surgery with daily applications. Alternatively, treatment can commence at postoperative two weeks, with applications on alternate nights spanning an eight-week period.[118,141,142] In a pilot study, imiquimod 5% cream administration for 6 weeks following tangential shave excision was efficacious for the treatment of earlobe keloids.[117] Chuangsuwanich et al[118] investigated the efficiency of imiquimod cream in averting the recurrence of excisional keloids. The research involved 35 patients with keloids situated on various regions, including the pinna, back or shoulders, chest wall, and neck. The findings revealed that the application of imiquimod 5% cream significantly hindered keloid recurrence post-resection, showcasing a recurrence rate of 28.6%. However, side effects including skin abrasions and hyperpigmentation were found in 37.1% patients. Longer follow up periods should be studied for recurrence of keloids and whether re-application of imiquimod could treat the newly formed keloids.

Tamoxifen, a versatile agent, exerts its influence on keloidal fibroblasts through multiple mechanisms. Notably, it modifies RNA transcription, effectively hindering fibroblast proliferation. Furthermore, Hu et al[143] demonstrated that tamoxifen inhibited the contraction of collagen lattices by fibroblasts in a dose-dependent manner (10–20gM). These actions underscore its potential as a valuable intervention in the modulation of keloid formation. One study suggested that tamoxifen could decreased the levels of TGF-β1 in keloid fibroblasts.[144] In a prospective study, Soares-Lopes et al[119] reported that intralesional administration of tamoxifen could trigger the reduction of collagen fiber, inflammatory stimulus, and the number of fibroblasts (Table 1). Nevertheless, there is scarcity of publications on the effects of intralesional tamoxifen on keloids. More research is needed to demonstrate that it is a promising drug.

Table 1 Emerging pharmacotherapies Used in Clinical Studies

Study Type	N	Whether Hypertrophic or Other Scars were Included	Treatment	Outcome	Adverse Event	Potential Bias	First Author, Year
Case report	2	No	Enalapril (10 mg/day) for 4 or 6 months	Keloid scar showed marked improvement.	None	Selection bias	Lannello, 2006[115]
Case report	1	No	5% captopril solution in cold cream (twice-daily) for 6 weeks	Lesion height decreased from 9–11 mm to 2–4 mm, redness and scaling were noticeably eliminated with no itchiness.	None	Selection bias	Ardekani, 2009[116]
Pilot study	4	No	Imiquimod 5% cream for 6 weeks	Excellent cosmetic result, no recurrence, itchy and painful.	None	Publication bias	Stashower, 2006[117]
Retrospective study	35	No	Imiquimod 5% cream (alternate night for 8 weeks)	Recurrence rate of keloid scars was reduced.	Skin abrasions and hyperpigmentation	Selection bias	Chuangsuwanich, 2007[118]
Prospective study	13	No	Intralesional tamoxifen	Tamoxifen was effective for the topical treatment of keloid.	Not stated		Soares-Lopes, 2017[119]

Abbreviation: N means the number of patients.

Physical Therapies

As research progresses, electrical stimulation stands out as a non-invasive and potentially effective intervention for keloid scar management.[126] In a recent study, the Fenzian system served as an electro biofeedback device that generated degenerate waves, could reduce symptoms related to abnormal skin scarring.[145] Besides, the Fenzian wave electrical stimulation significantly reduced the pain and pruritus in patients with raised dermal scars[125]. Perry et al[126] demonstrated the efficacy of the Fenzian system in alleviating pain, itching, and scar scores in a cohort of 30 patients with 140 scars. The notable reduction in excessive formation of collagen I served as a key mechanism underlying the anti-keloid efficiency of electrical stimulation. Additionally, its cytotoxic effects on keloid fibroblasts may be significantly increased by degenerate wave stimulation.[154] As there were no device-related complications or adverse events, researchers are more apt to propose that ES therapy is considered safe and easy to use. However, it is relatively cost effective compared to other comparative treatments.

Several studies have evaluated the efficiency of extracorporeal shockwave therapy (ESWT) in treating post-burn, hypertrophic, and keloid scars.[127–129] The pain, itching, and scar appearance could be improved using ESWT.[127,128] ESWT triggered significant reduction in collagen fibers and increases of MMP-13 enzyme.[129] The efficacy of ESWT can be attributed to shock waves influencing the physiology of pain receptors and the generation of micro-trauma by these waves, leading to the release of cytokines that facilitate tissue repair.[127] However, further large-scale controlled studies are warranted to elucidate its overall efficacy.

Recognizing the discomfort associated with hypodermic needles and the limited effectiveness of transdermal patches, researchers have developed microneedle drug delivery systems. This technology offers advantages such as a faster onset of action, enhanced patient compliance, self-administration capability, and improved penetration and efficacy.[146] Yeo et al explored the potential of FDA-approved liquid crystal polymer-based microneedles to impede keloid fibroblast proliferation. Following a 12-hour treatment period, the non-viable fraction of keloid fibroblasts in cell culture exhibited a notable increase, reaching 83.8 ± 11.96%.[147] In a single-blinded intra-individual controlled clinical trial, daily utilization of dissolving TAC-embedded microneedles could significantly attenuate the keloids volume.[130] Xue et al[148] investigated the role of microneedle patch based on the comparison of encapsulating 5-FU and polyethylene glycol diacrylate in keloid fibroblast proliferation, which showed that microneedles effectively abolished the proliferation of keloid fibroblast proliferation. However, it is essential to acknowledge that microneedle drug delivery systems come with certain limitations. These include the potential for skin irritation or allergies, particularly in individuals with sensitive skin, and the risk of small, delicate microneedle tips breaking and possibly remaining in the skin. It is worth noting that such limitations are infrequent and can be effectively addressed using advanced microneedle materials.

Laser-assisted drug delivery (LADD) is a novel approach that combines the benefits of laser technology with the targeted delivery of therapeutic agents to treat keloid scars. This technique involves the use of lasers to create microscopic channels or pores in the skin, enhancing the penetration and absorption of drugs or active substances applied topically.[149] Cavalie et al investigated the efficacy of using the Er:YAG laser every other week and applying topical betamethasone cream twice daily in 23 patients with 70 keloids, which yielded a median percentage of improvement of 50% (range −43 to 84), together with recurrence in 8 (22%) lesions.[110] Park et al[131] conducted a comparative analysis of the effectiveness of Er:YAG LADD combined with intralesional corticosteroid injection and Er:YAG LADD combined with topical corticosteroid application for treating keloid scars. Four treatment sessions were carried out with a treatment frequency of once every 6 weeks. Patient satisfaction in both groups was rated as "moderate". Nevertheless, the mean pain score was 1.1 out of 10 on the topical side versus 6.1 on the corticosteroid injection site. These findings suggested that ablative fractional laser therapy combined with topical corticosteroid holds promise for keloid scar treatment. In addition, the combination of 5-FU and imiquimod with LADD in in vitro porcine skin has demonstrated enhanced drug penetration and a reduced required dosage for optimal efficacy (Table 2).[150,151] More prospective clinical studies with larger sample sizes are warranted to identify the optimal parameters for laser treatment and for application of therapeutic agents in the treatment of keloid scars.

Table 2 Emerging Physical Therapies Used in Clinical Studies

Study Type	N	Whether Hypertrophic or Other Scars were Included	Treatment	Outcome	Adverse Event	Potential Bias	First Author, Year
Prospective noncontrolled case series	18	Yes, raised dermal scars	Fenzian wave electrical stimulation	Pain and pruritus were reduced in patients with raised dermal scars	Not stated	Selection bias	Ud-Din, 2013[125]
Retrospective study	30	Yes, symptomatic abnormal skin scars	Fenzian electrical stimulation	Pain, itching, and scar scores were reduced.	Not stated	Selection bias	Perry, 2010[126]
Prospective quasi-experiment	17	Yes, burn scar	ESWT (once a week for 6 weeks)	The pain, itching, and appearance of the burn scar were improved.	Not stated		Taheri, 2018[127]
Retrospective study	16	Yes, hypertrophic and contracture scars	ESWT (twice a week for 6 weeks)	All treated scars obtained a more acceptable appearance.	Not stated	Selection bias	Fioramonti, 2012[128]
Retrospective study	22	No	3 ESWT treatments in 6 weeks	Significant decreases in collagen fibers and increases in MMP-13 enzyme.	Not stated	Publication bias	Wang, 2018[129]
Single-blind intra-individual controlled two-phase clinical trial	27	No	Triamcinolone-embedded dissolving microneedles (2min daily, 4 week/phase)	Keloid volume showed significant reduction	Not stated	Selection bias	Tan, 2019[130]
Retrospective study	23	No	Er:YAG laser every other week, topical betamethasone cream twice daily	Median percentage of improvement: 50%; recurrence: 22%	Not stated	Selection bias	Cavalie, 2015[110]
Retrospective study	10	No	Er:YAG laser plus intralesional or topical corticosteroid (once every 6 weeks, four sessions)	Both two therapies are effective for keloids mean pain score: 1.1 of topical site versus 6.1 of intralesional site	No	Selection bias	Park, 2017[131]

Abbreviations: N means the number of patients; ESWT, extracorporeal shock wave therapy; Er:YAG, erbium:yttrim-aluminum-garnet.

Biological Therapies

Platelet-rich plasma (PRP) is a concentrated platelet solution obtained through the centrifugation of autologous whole blood. Its primary constituents include platelets, fibrin, complete coagulation factors, and a rich array of growth factors and cytokines.[152] Studies have reported that PRP could enhance the proliferation of fibroblast, increase collagen expression, and promote the synthesis of matrix proteins.[153,155] In a study by Hewedy et al,[137] 40 patients were randomly divided into two groups, both receiving intralesional TAC injection at a concentration of 20 mg/mL. One group additionally received intralesional PRP injection one week after the TAC injection. Results indicated that the group receiving additional PRP exhibited significant improvement in symptoms such as lesion volume, pigmentation, and hardness compared to the control group. When utilized as adjuvant therapy alongside procedures such as surgical excision and radiotherapy, PRP has shown the potential to significantly reduce recurrence rates.[138–140] Overall, as an autologous material, PRP proves to be safe, cost-effective, and an efficacious adjunctive treatment for keloids.

Mesenchymal stem cells (MSCs), possessing regenerative and immunomodulatory properties, have promising efficiencies in treating keloids in preclinical studies. The potential mechanisms underlying MSC therapy involve the modulation of inflammatory responses, coupled with anti-fibrotic effects. This is achieved by decreasing the production of collagen while simultaneously increasing angiogenetic activity.[156] Adipose-derived stem cell-conditioned medium (ADSC-CM) could attenuate the gene expression of tissue inhibitor of metalloproteinases 1 (TIMP-1), plasminogen activator inhibitor-1, as well as collagen type I in keloid fibroblasts. This resulted in a significant inhibition of bioactivities in keloid fibroblasts.[157] Fang et al[158] demonstrated that bone marrow derived MSC-conditioned medium (BMSC-CM) markedly upregulated anti-fibrotic genes in hypertrophic scar fibroblasts and keloid fibroblasts, such as TGF-β3 and decorin. Simultaneously, it significantly downregulated the expression of pro-fibrotic genes, including plasminogen activator inhibitor-1, connective tissue growth factor, TGF-β1, as well as TGF-β2. Moreover, BMSC-CM exhibited inhibitory effects on ECM synthesis in fibroblasts. A recent study showed that the BMSCs incorporated Arg-

Gly-Asp (RGD) modified hydroxybutyl chitosan (HBC) (HBC-RGD) hydrogel inhibited the keloid fibroblasts proliferation and suppressed the nodular collagenous fibers in keloid tissue. This finding suggested that BMSCs/HBC-RGD hydrogel was potential for future applications in keloid therapy with subcutaneous in-situ injection. However, the widespread use of MSCs for keloid treatment is still an area of active research. Several factors, including the optimal source of MSCs, delivery methods, dosage, and long-term safety, need further investigation.

Interferons refer to a group of cytokines that have the potential to treat keloids by reducing the synthesis of collagen type I and III and increasing collagenase activity.[159] Among the three subtypes (α, β and γ) of interferon, INF-α (specifically IFN-α2b), and INF-γ have been found to be very effective in keloid treatment because they can reduce the expression of collagen and other ECM and increase collagenase activity.[160,161] However, there is a lack of consensus on the specific regimen. Common complications of interferon injection therapy include flu-like symptoms, headaches, fever, myalgia and fatigue (Table 3).[156,162] Further research is needed to establish standardized regimens and to better understand the long-term efficacy and safety of interferon therapy for keloid scars.

Future Directions

Keloid scars, often refractory to conventional therapies, necessitate innovative approaches for improved outcomes. Targeted therapies, ranging from small molecules to biologics, hold promise for disrupting keloid pathogenesis at the molecular level. Keloids are characterized by excessive fibroblast activity and collagen production. Future treatments may focus on regulating fibroblast proliferation and function. Three main types of noncoding RNAs (ncRNAs), including miRNA, lncRNA, and circRNA, have been identified as regulators of fibroblast proliferation, migration, invasion, apoptosis, and collagen synthesis through distinct pathways.[163] These ncRNAs play a crucial role in the keloidogenesis and development process, which will be potential diagnostic and therapeutic targets in the treatment of keloids. In addition, therapies targeting pivotal cytokines like TGF-β1 and epidermal growth factor, as well as interventions focused on key signaling pathways such as the PI3K/Akt/mTOR inhibitor CUDC-907[164] and mTOR kinase inhibitor OSI-027,[165] hold promise for the treatment of keloid scars.

Table 3 Emerging Biological Therapies Used in Clinical Studies

Study Type	N	Whether Hypertrophic or Other Scars were Included	Treatment	Outcome	Adverse Event	Potential Bias	First Author, Year
Retrospective study	40	No	Intralesional TA (20 mg/mL) for four sessions, 3 weeks apart, and intralesional PRP	Combining intralesional PRP with TA could yield cosmetically better outcomes in keloid treatment.	Not stated	Selection bias	Hewedy, 2022[137]
Pilot prospective Study	17	No	PRP was injected during resection and then 3 times with a 1-month interval.	Nine completely resolved keloid scars, 5 completely relapsed keloid scars, decreased pruritus severity score; improved Vancouver Scar Scale score	Not stated		Hersant, 2018[138]
Retrospective study	49	No	Extralesional surgical excision, PRP, plus SRT	94% success rate with 3 patients who reported recurrence	Not stated	Selection bias	Jones, 2017[139]
Retrospective study	50	No	Surgical excision, intraoperative cryosurgery, and PRP injections	74% of keloids were completely or significantly flattened	Transient pain and focal hypoesthesia	Selection bias	Azzam, 2018[140]

Abbreviations: N means the number of patients; TA, triamcinolone acetonide; PRP, platelet rich plasma; SRT, superficial radiation therapy.

Chronic inflammation is an important factor in the pathogenesis of keloids. Anti-inflammatory treatments targeting inflammatory cytokines and pathways involved in keloid formation, such as IL-6, IL-1, and TNF-α are under investigation. Combining anti-inflammatory drugs, such as corticosteroids, with other targeted therapies may enhance the therapeutic effect. In addition, epigenetic changes, such as DNA methylation and histone modifications, play an important role in the development of keloids. Developing drugs that can modify these epigenetic marks, such as histone deacetylase inhibitors (HDACi), thereby changing the expression of genes associated with fibrosis will be a new therapeutic approach. Furthermore, keloids usually have a greater blood supply than normal scars. Inhibiting angiogenesis can reduce the supply of nutrients and oxygen to scar tissues, thereby limiting the growth of keloid scars. Anti-VEGF drugs should be considered in the treatment of keloids.

The genetic basis of keloids remains complex and multifactorial.[2] Understanding the genetic landscape of keloids is crucial for targeted interventions. Various genes associated with collagen synthesis, inflammation, and wound healing play pivotal roles in keloid formation. The utilization of CRISPR and other gene-editing tools in manipulating genetic factors that contribute to keloid formation is a promising avenue of research. These advanced technologies offer precise control over specific genes, providing an opportunity to intervene in the complex genetic mechanisms underlying keloid development. However, challenges such as off-target effects and ethical concerns need careful consideration.

Another area of potential exploration is the use of tissue engineering and regenerative medicine for keloid treatment. Tissue engineering aims to repair or replace damaged tissues by combining cells, biomaterials, and growth factors. Stem cells can secrete a variety of growth factors and cytokines, regulate local immune responses, and promote normal wound healing. Advanced biomaterials like hydrogels and scaffolds provide an ideal environment for cell growth. These materials can be loaded with drugs or growth factors that are gradually released to inhibit the proliferation of scar tissue. Regenerative medicine focuses on leveraging the body's own repair mechanisms to restore tissue function. Using the patient's own healthy skin or other tissues to replace damaged parts can reduce rejection reactions while providing normal skin cells and structures. Additionally, by regulating the wound's microenvironment, such as oxygen concentration, pH value, and biomechanical properties, normal tissue regeneration can be promoted, and scar tissue proliferation can be inhibited.

In addition, the psychosocial impact of keloids is substantial. A holistic approach to keloid treatment must extend beyond physical interventions to encompass psychosocial support and patient education. By acknowledging the emotional impact of keloids and empowering individuals through education, healthcare providers can enhance treatment outcomes and contribute to a better overall quality of life for those affected by keloid scars.

Conclusion

This review delves into the intricate pathogenesis of keloids, exploring the molecular and cellular mechanisms underlying their formation. Conventional therapies are analyzed in-depth considering their efficacy and limitations, including surgical excision, pharmacotherapies, radiotherapy, cryotherapy, silicone-based product, pressure therapy, and light-based therapy. The emergence of novel therapeutic approaches is discussed, including pharmacotherapies, physical therapies, and biological therapies, shedding light on their potential in treating keloid scars. However, it is crucial to note that most investigations are either basic or retrospective studies with small sample sizes. Consequently, the insights gained from these studies may not robustly illuminate the true efficacy of emerging therapies for keloid scars. There is an urgent call for well-designed prospective clinical trials featuring larger cohorts. Such trials, characterized by rigorous methodologies, standardized outcome assessments, and extended follow-up periods, are essential for providing a comprehensive understanding of the true potential and limitations of emerging therapies in keloid scar treatment. We also contemplate future directions in the field, encompassing the application of targeted therapies, gene-editing tools, tissue engineering, and regenerative medicine, together with psychosocial support and patient education. By synthesizing current knowledge and highlighting ongoing advancements, this review aims to provide a comprehensive overview of keloid pathogenesis and therapeutic strategies, paving the way for innovative approaches in the management of this challenging dermatological condition.

Data Sharing Statement

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Ethical Approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the Special Health Project of Jilin Province (No. 2020SCZT087) and the Science and Technology Development Plan Project of Jilin Province (No. YDZJ202201ZYTS554).

Disclosure

All authors declare that they have no competing interests.

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