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Biological approaches for hypertrophic scars

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Abstract

Scar formation is usually the pathological consequence of skin trauma. And hypertrophic scars (HSs) frequently occur in people after being injured deeply. HSs are unusually considered as the result of tissue contraction and excessive extracellular matrix component deposition. Myofibroblasts, as the effector cells, mainly differentiated from fibroblasts, play the crucial role in the pathophysiology of HSs. A number of growth factors, inflammatory cytokines involved in the process of HS occurrence. Currently, with in-depth exploration and clinical research of HSs, various creative and effective treatments budded. In here, we summarize the progress in the molecular mechanism of HSs, and review the available biotherapeutic methods for their pathophysiological characteristics. Additionally, we further prospected that the comprehensive therapy may be more suitable for HS treatment.

KEYWORDS

wound healing, hypertrophic scar, prevention, biological strategies, MSC

1 | INTRODUCTION

As the largest organ in the human body, skin senses the stress and tension outside and protects the systems inside as a barrier. When injured, it is necessary to repair fast to maintain the cutaneous integrity and to recover its function. The wound healing process is complicated, and deep injury often leaves a scar in the repaired site.[1] Hypertrophic scars (HSs) as a kind of scar occur in 30% to 90% of patients suffered wound,[2] such as surgeries, burns, traumas, and so on. And it mainly results from aberrations of wound healing process.

HS protrudes the normal skin surface with irregular shapes, uneven surface, congestive appearance, and solid and firm textures.[3] Patients suffering from HSs often feel paresthetic including itchy and painful, which was more severe after increased ambient temperature, emotional arousal, or eating spicy food.[4] Therefore, many patients bear the double burden of psychology and physiology. In the clinical, the origin of HSs was mainly from the excessive proliferation of dermis. It develops within 1 to 3 months after deep skin injury.[5] During the normal healing process, the myofibroblasts undergo apoptosis in the remodelling stage and leave a rather acellular scar in the healed sites. While in HSs, the myofibroblasts persist and result in[6-8] excessive extracellular matrix (ECM) component deposition and tissue contraction which can lead to severe disfigured and malfunction. A great number of studies have

been proved that a variety of pro-fibrotic cytokines and chemokines, such as TGF-β1, TGF-β2, VEGF, FGF, and CTGF, are associated with the anomaly in HSs.[9-12]

Nevertheless, the exact mechanism and possible regulatory network still need to be exploration. Presently, several classical treatment methods have been developed. Because some treatment strategies have the feature with easy recurrence after treatment, or significant side effects, or poor efficacy, there is still a lack of effective treatment strategies.[13,14] Therefore, to better understand and study HS, we summarized the existing treatments based on the pathophysiological mechanism of HS and prospected the possible treatment principles of HS.

2 | PATHOPHYSIOLOGY OF HYPERTROPHIC SCARS

The wound healing process involves the following phases, inflammation phase (the first 2 to 3 days after injury), proliferation phase (4 days to 2 weeks including ECM formation, angiogenesis, and reepithelialisation), and maturation phase (several months even lasting to one year).[15] During proliferation phase, fibroblasts differentiate to myofibroblasts and express alpha-smooth muscle actin (α-SMA) which enables the wound to contract. HSs occurred within 1 month or so after wound injury,[16] and turned into flatter scar within 1 to 2 years. The pathological features of HS are that collagen-III bundles are oriented parallel to the epidermal surface with abundant nodules containing myofibroblasts expressing α-SMA and extracellular collagen filaments.[17] Besides, the occurrence of HSs is very complicated and often accompanied by the excessive inflammatory response, abnormal fibroblast-myofibroblast transformation, non-apoptosis of fibroblasts,[8] aberrant keratinocyte-fibroblast crosstalk, and disorder of ECM deposition.[18] Because of the complexity of the pathophysiology of HS, it may be difficult to get a good curative effect on a 'single point' treatment. The strategy of 'multi-point' combined comprehensive treatment may be a better strategy for the HS treatment.

3 | CURRENT TREATMENT FOR HSs

The clinic, effective therapy should be set individually by clinicians after talking with patients on their concerns, needs, expectations, alternative treatments, and their outcomes. Also, the goals of treatment were to reduce scar volume, minimize subjective symptoms, such as pain and pruritus, and improve aesthetic and functional appearance. Mature clinical measures include first-line therapy (silicone gel sheeting and topical onion extracts for small HSs) and second-line therapy.[19] The latter refers mainly to laser therapy as well as surgical excision in combination with intralesional corticosteroid injections postoperatively.[20]

Key Messages

- there are two major contributions to the field from this study: (a) current traditional treatment and biological therapy of hypertrophic scar (HS) were concluded and (b) the future trend of stem cells and combined therapy for HS was expected

4 | THE CLASSICAL THERAPY OF LASER AND SURGERY WITH CORTICOSTEROIDS

The prevention and treatment of scarring after trauma represent a daunting challenge for a dermatologist. Presently, clinicians accustomed to using the following modalities to treat HSs after injury. Silicone gel is commonly used in the prevention or treatment of HSs.[21] A recent study shows that the silicone gel reduces the expression of TGF-β1and platelet-derived growth factor 4 months after surgery for surgical scar,[22] although the use of silicone gel remains conflicting on account of the upregulation of the basic fibroblast growth factor (b-FGF) in the dermis of silicone gel sheet-treated scars.[23] Also, laser therapy is another common clinical mean for HSs treatment. It has been proved that long-pulsed Nd: YAG laser and pulsed dye laser play therapeutic roles in shallowing the colour, reducing the thickness and tension of HSs, and relieving symptoms such as pain and pruritus.[24] Surgical excision is also a highly recommended measure for surgeons. Surgery always combined with corticosteroid injection or radiotherapy in the clinic. Intralesional corticosteroids have shown to be useful in vivo by reducing the inflammatory process, decreasing collagen deposition, and fibroblasts proliferation.[25] It was demonstrated that triamcinolone acetonide alone reduced at least half of scar occurrences with a recurrence rate of 9% to 53%.[26] Also, there are other ways that have used in the prevention and treatment of HSs including 5-Fluorouracil, bleomycin, interferon, imiquimod, and methotrexate.[27] In spite of remitting the pathological scarring more or less in the short term by surgery above, it is easy to relapse as to the secondary injury to the wound. Besides, laser therapy combined with corticosteroids is at risk of leading to atrophy of the normal surrounding skin, fat and muscle, and even side effects such

as osteoporosis and pain at the injection site.[26] Therefore, these methods could not lay claim to an ideal standard.

5 | TRADITIONAL PLANT-BASED MEDICINE AND PRODUCTS

In recent years, traditional Chinese medicine (TCM) has been received more and more attention in the treatment of diseases. Some TCM, including extracts, plays a non-negligible role in promoting skin regeneration and resisting skin aging. Presently, many plants have been proved effective as the potential therapy for HSs treatment in vivo and/or in vitro.

Quercetin, a flavonoid, has been demonstrated to reduce the HSs formation. It plays various biological functions including anti-inflammatory, anti-oxidant, and antibacterial properties.[28,29] In vitro, quercetin has been shown to inhibit the collagen synthesis of myofibroblasts derived from keloids and HSs mainly through reducing their proliferation.[30,31] It was found that the Mederma, a derivative of quercetin improved and ordered collagen organization in the rabbit model, suggesting the potential effect on the treatment of HSs.[32] Quercetin is derived from vegetables like onions, and studies show that the onion extract has the properties of anti-inflammation and anti-proliferation on several cancer cells such as glioma and oophoroma A-2780 cells in vitro and vivo.[33-35] In addition, quercetin and onion extract have both been shown to up-regulate the expression of matrix metalloproteinase-1 (MMP-1) which plays an important role in ECM remodelling.[36] These results imply its effective prevention in fibrosis formation.

Onion extract, the main ingredient of onion. It could reduce the scar height and improve the appearance of the scar after Pfannenstiel's incision in the study of caesarean for Asian women.[37] In another study of some children undergoing a median sternotomy, the incidences of HSs were significantly decreased by the application of onion extract.[38] Furthermore, the combination of silicone derivative and onion extract relieved the itch and pain effectively more than the former alone, and the Vancouver Scar score was improved obviously.[39]

Resveratrol, a natural plant polyphenol and phytoestrogen derived from grape and peanuts,[40,41] is proved to have many beneficial functions, including anti-inflammatory and anti-oxidant properties.[42-44] In fibroblasts derived from HSs, resveratrol reduced their proliferation through cell cycle arrest at G1 and induce their apoptosis.[45] Besides, resveratrol has been shown to decrease the expression of collagen I and III, and reduce hydroxyproline levels. Meanwhile, resveratrol inhibited the proliferation and induced apoptosis of keloid derived fibroblasts. In an animal model, it was demonstrated that resveratrol decreased the expression of TGF-β and α-SMA in fibroblasts derived from scar, but has no effect on fibroblasts under physiological conditions.[46]

Epigallocatechin gallate (EGCG), as major catechin in green tea, has many biological properties in preventing fibrosis in various organs.[47] Connective tissue growth factor (CTGF) is an early response gene and belongs to a new family of cysteine-rich growth factors. It could promote the proliferation and migration of fibroblasts and plays a key role in tissue fibrosis.[48]

It has been shown that EGCG reduced the expression of CTGF and pro-fibrotic molecules such as TGF-β1.[49] Inhibition of TGF-β1 by EGCG could result in a reduction of ECM synthesis and HSs formation.[50] And EGCG relieved cardiac fibrosis through low expression of CTGF, suggesting the therapeutic potential on the prevention of multiple fibrotic diseases including scaring.[51]

Oleanolic acid (OA) is the compound of triterpenoid which has the properties of anti-inflammatory and anti-tumour effects.[52,53] It was found that OA reduced the expression of TGF-β1, induced the apoptosis of HS fibroblasts, decreased collagen synthesis, and alleviated deposition of collagen-I/III.[54,55] MMP-1 plays a crucial role in the degradation of collagen-I and III in scaring[56] and MMP-2 can degrade collagen-I.[57] Studies show that after OA treatment, the level of MMP-1 and MMP-2 was increased in the rabbit HSs model and the HS was suppressed significantly.[58,59] Additionally, compared with the higher collagen-III in normal skin, there is a high ratio of collagen-I to III in HSs, which could be reversed by OA.

Curcumin, as the antioxidant, has been proved to promote wound closure and promote wound healing in the rat model. After treating with curcumin, the wound shows increased maturation fibrin and collagen, thus to improve all the phases of wound repair.[60] Besides, it was reported that curcumin could induce apoptosis of several cells including fibroblasts after wound healing.[61] Furthermore, a high dose of curcumin could reduce and prevent scarring through reactive oxygen species-mediated heme oxygenase pathway.[62]

The TCM compound therapies including the above were commonly used in clinical, and the patients have relieved more or less to some extent. However, as the classical treatment, it still has the shortcomings of short curative effect, side effects, and recurrence of HS. Therefore, the development of other promising treatments with better effects and fewer side effects is urgent. Biotherapy has been favoured by clinicians and researchers in recent years. And biotherapy is used to treat various diseases by the way of biological macromolecules,[63] antibodies,[64] and even cellular methods.[65] Meanwhile, the strategy of biotherapy is also validated in the prevention and treating in HSs in vivo and in vitro.[66-68] Based on the unique physiological characteristics of HS, many targeted biological therapies have emerged.

6 | BIOTHERAPY FOR INFLAMMATION IN HSs

Wounds in early mammalian embryos evolved into scar-free wound healing compared with scar-forming wound healing in adults.[69] The development of HSs is associated with an excessive inflammatory response,[7,70] while the foetal wounds usually show fewer inflammatory cells, a shorter period of inflammation and less inflammatory factors.[71,72] Therefore, attempts to interfere with inflammation specific immune cells, or to block HS-related critical inflammatory signalling pathways, may effectively prevent the occurrence of HS.

Neutrophils are the most abundant inflammatory cells in the early stage of wound healing, which mainly play an anti-infection role in local sites, and the number of neutrophils has no significant influence on the wound healing rate.[73] Besides, neutrophils also play the role in recruiting other inflammatory cells, such as mononuclear derived macrophages which phagocytizes fibrin clots to remove tissue debris and dead cells.[74,75] Macrophages have been considered the indispensable immunological cells in wound repair, who involve in phagocytosis, antigen-presentation, and the secretion of cytokines and chemokines in wound sites.[76,77] Macrophages can be divided into M1 (classically activated) and M2 (alternatively activated) populations in the process of wound healing, and exhibit different functions.[78] This characteristic determines that macrophages play an important role not only in the inflammatory phase but also in the proliferation phase. Generally, macrophages with M1 phenotype have antimicrobial properties, and with the M2 phenotype possess the properties of stimulating the production of collagen, angiogenesis, reepithelialisation, regeneration of wounds, and the anti-fibrosis.[79,80] In the inflammation stage, M1 is required to defend against pathogens and clear senescent cells, and after that cells appear apoptosis. Minor macrophages undergo a transition from M1 to M2, modulating the wound healing. Experimental results showed that mice lacking macrophages showed delayed epithelial regeneration, collagen deposition and reduced angiogenesis.[76,81] However, M2 is an important source of TGF-β1 which plays multiple roles in different phases of wound healing. M2 persisted activation lead to excessive TGF-β1 production, which would further induce myofibroblast proliferation, abundant ECM deposition and the occurrence of fibrosis.[82] Therefore, the balance of M1 and M2 macrophage population is an important impact on the development of a scar. However, there are no studies aimed at mediating the different phenotypes of macrophages to achieve the anti-scar repair. Studies have shown that promoting M1 to M2 phenotype transition can promote chronic wound healing.[83]

Another strategy is targeting the regulation of inflammatory mediators. Therapies targeting inflammatory cytokines are used to lighten the HSs. Increased Th2 and Th3 response cytokines including interleukin-2 (IL-2), IL-4, and IL-10 have been found in circulating lymphocytes of fibrotic conditions.[84] Also, IL-4 and IL-13 have been proved to activate myofibroblasts through the IL-4R pathway.[85,86] And inhibitors of IL-4 could reduce dermal fibrosis in mice with scleroderma.[87] Besides, inhibition of IL4 and IL-10 simultaneously mediated pathway reduced fibrosis of multi-tissues.[88] Of course, the biological effects of different inflammatory factors are different. For example, proinflammatory cytokine IL-6 and IL-8 enhanced scarring and the anti-inflammatory cytokine IL-10 has the opposite effect.[89] Therefore, upregulating anti-inflammatory cytokine and reducing pro-inflammatory cytokine could inhibit HSs formation, as found in some TCM, such as bupleurum[90,91] and pirfenidone ointment.[92] Recently, a breakthrough study showed that adipocytes are regenerated from myofibroblasts by activating the adipocyte transcription factors during wound healing. The consequential effect was triggered by BMP signalling from the actively growing hair follicles, and the findings fortify the importance of BMPs in the transdifferentiation of myofibroblasts and adipocytes.[93] From another perspective, we should further pay attention to the temporal and spatial dynamic changes of BMP in the process of myofibroblasts-adipocytes transformation, to better regulate the number of myofibroblasts by BMP to reduce fibrosis.

Compared with acute inflammatory reactions, the pathological fibrosis representatively results from the chronic inflammatory reactions. Under chronic inflammatory condition, the injured area presents a complex traumatic microenvironment such as inflammation, tissue dissolution, and tissue repair.[86] It was reported that mitochondrial reactive oxygen species (ROS) participated in inflammatory reaction of wound healing. And fibroblast dysfunction is linked to the overproduction of free ROS.[94,95] Application of antioxidant or drugs with antioxidant properties could relieve the microenvironment of chronic inflammation, accelerate wound healing and alleviate scar formation on wounds.[96,97] Similarly, classical traditional medicine, arsenic trioxide, could effectively inhibit the formation of rabbit ear scars through the overexpression of antioxidant genes.[98]

7 | BIOTHERAPY TARGETING FIBROBLASTS AND MYOFIBROBLASTS IN HSS

In the proliferation stage, a great number of fibroblasts differentiate into myofibroblasts, which is an important

process in wound repair. Meanwhile, there are heterogeneous population cells of derived fibroblasts.[99] In the haemostatic phase of wound healing, collagen ECM replaced the provisional fibrin clot, and this change requires for fibroblastic cells with sufficient ability of migration from adjacent tissues and circulation to deposition of the ECM.[100] Firstly, the fibroblastic cells transform into a 'proto-myofibroblasts' phenotype[101] with low contractile capacity and high migration ability. Then, the proto-myofibroblasts evolve into mature myofibroblasts with contractile features and contribute to producing mechano-resistant scars. The two phenotypes of myofibroblasts not only enhance wound contraction[101] but also promote the formation of abnormal scarring.[102,103]

In the case of HSs, excessive fibroblasts are transformed into myofibroblasts in the proliferation phase. Massive and persistent myofibroblasts will lead to tissue deformation by contracture manifesting as HSs[104] and scleroderma[105] in the skin. Fibrillar collagen plays a crucial role in the elasticity and strength of the skin.[106] While in HSs, there is excess deposition of collagen-I and collagen-III,[107] especially the collagen-I which increases in both early and final remodelling stages of wound healing.[108] After repaired and regained tissue homeostasis, the myofibroblasts undergo apoptosis, leaving a rather acellular scar.[109] However, in HSs, myofibroblasts persist even in the final remodelling stage, resulting in bulky, contracted scar.[110] Therefore, myofibroblast has been considered the main mediator of non-healing wounds and excessive repair (HSs). Insufficient myofibroblasts are associated with chronic wounds, while excessive myofibroblasts are associated with scarring. Therefore, there are two available approaches to control the number of myofibroblasts in wound sits.

One way is to properly control the myofibroblast formation. Reducing the main derived fibroblast is an important way. Inhibitors of histone deacetylase have been reported play roles in regulation of fibrotic gene expression.[111] Suppressing histone deacetylase limits the proliferation of lung fibroblasts and inhibits fibrosis-related gene transcription, leading to the anti-fibrotic ending.[112] Trichostatin A, as the potent molecule, it could inhibit the proliferation of fibroblasts in vivo or in vitro.[113] And also, it could decrease the deposition of ECM in bleomycin-induced skin fibrosis of the mouse model.[114] TGF-β1 signalling pathway is the most important regulatory signal in fibroblast differentiation. It was found that TGF-β1 treatment could repress the expression of peroxisome proliferator-activated receptors in scleroderma, indicating the anti-fibrosis effect of TGF-β1 inhibitor.[115] Recently, the substance extracted from Chinese herb Arnebiae shikonin has been shown to attenuate the TGF-β1 expression and suppress myofibroblasts formation through modulating SMAD/ERK pathway.[116] The other way is to enhance the apoptosis of myofibroblasts or promote myofibroblast-to-non-fibroblastic cell conversion. As aspect to be insensitive to apoptotic signalling and expressing antiapoptotic-related molecules in myofibroblasts,[117] two kinases have been suggested to control myofibroblasts apoptosis, including phosphatidylinositol 3-kinase (PI3K)-AKT and focal adhesion kinase signalling.[118,119] Small molecule inhibitors targeting these protein kinases were prove to be effective anti-fibrotic therapeutic strategies in pulmonary fibrosis,[120] suggesting another promising strategy in skin fibrosis treatment.

8 | BIOTHERAPY TARGETING EPITHELIAL-MESENCHYMAL TRANSITION PROCESS IN HSS

Epithelial-mesenchymal transition (EMT) is involved in both embryonic development and wound repair. Response to skin injury, epidermal keratinocytes undergo EMT and became to motile cells with the mesenchymal phenotype to migrate across to wound bed.[121] The mesenchymal cells, especially contractile myofibroblast is necessary to restore tissue integrity in normal wound healing.[122] And in process of remodelling, myofibroblasts disappear once reepithelialisation completes.[68,123] But under pathological conditions, myofibroblasts persisted instead of undergoing dedifferentiation. Indeed, EMT is essential for proper reepithelialisation and ECM deposition, but the uncontrolled sustaining transition from epithelial cells to myofibroblasts might result in HSs. Therefore, targeting both fibroblasts and keratinocytes populations were the novel therapies for scarring.[124] It was shown that extracorporeal shock wave therapy was responsible for the anti-scarring by suppressing EMT in the post-burn scars.[125] As such, focus on the dysregulation of injury-triggered EMT is proved to contribute to HSs treatment. Keratin and vimentin are characteristic markers of epithelial cells and mesenchymal cells, respectively, and can serve as indicative markers of EMT processes.[126] Several studies proved that down-expression of vimentin and over-expression of Keratin can inhibit the process of EMT,[127-129] prompting another possible way to suppress scars.

Uncontrolled persist EMT and excessive proliferation of (myo)fibroblasts cause the deposition of ECM. ECM plays a critical role in wound healing and scar formation which was produced mainly by fibroblasts and myofibroblasts. The breakdown of fibrillar collagen type I, II, and III were mediated by MMP-1. Fibroblasts of HSs appear to have a low MMP-1 (collagenase) activity.[130] It was demonstrated that MMP-2 effect denatured collagen

in the late stage of wound healing, while MMP-9 was involved in the early stage of wound healing degrading collagen type IV and V, fibronectin, and elastin.[131,132] MMP transcription is induced partly by TGF-β and interleukin-I.[133] MMP expression is high in injuring skin compared with the intact skin.[134] Additionally, it was determined that myofibroblasts were resistant to breakdown by collagenase D and MMP-2. It was further found that fibroblasts derived from HSs over-expressed tissue transglutaminase which could inhibit the apoptosis of myofibroblasts.[135] It was reported that inhibiting molecular chaperone, FK506-binding protein 10 (FKBP10) could reduce ECM components and attenuate HS formation through TGF-β/Smad signalling pathway.[136] Y-box-binding protein (YB)-1, a suppressor of Collagen-1A1 resulted in repression of Collagen-1 and anti-fibrosis in cardiac, suggesting a novel therapeutic target for pathological scar point to ECM.[137]

9 | BIOTHERAPY AIMED AT MAIN CYTOKINES AND PROTEIN INVOLVED IN HSS

The wound repair process requires a variety of signal pathways to form a regulatory network that interacts with each other. The future of HSs management may lie in targeting specific molecular pathways. A large number of studies have confirmed inflammation and the abnormality of multiple signalling pathways during the healing of pathological scars, which leads to pathological repair.[138]

There are three isotypes of TGF-β, and all of them are associated with wound healing.[139,140] The HSs formation is associated with the overexpression of TGF-β1/2, and depressing the effect of TGF-β1/2 reduced fibrosis and scarring significantly wound model in vivo.[141] However, scarless healing is associated with high levels of TGF-β3.[142,143] In particular, scarless wound healing in foetal is always with the high ratio of TGF-β3/TGF-β1 which hint the ratio between different TGF-β types determines the effect of TGF-β signalling pathway.[144] TGF-β/Smad signalling has a pivotal role in scar healing through binding to dimeric TGF-β receptor complexes.[2,145] Upon activation, this receptor complex phosphorylated Smad2/3 proteins, which form corresponding dimmers with Smad4 and translocate into the nucleus to initiate downstream target genes including collagen-I and III.[146] The extent of wound fibrosis is related to the activity of TGF-β1 to a large extent.[147] In transgenic animals, it has been found that overexpression of the constitutively TGF-β1 receptor leads to spontaneous fibrosis of skin.[148] Activation of TGF-β1 assembles and TGF-β-receptor complex activated the Smad2/3 and JNK signalling in fibroblasts and exhibited the biological behaviour of myofibroblasts.[149] On the contrary, silencing TGF-β1 resulted in lower collagen synthesis and alleviative scarring which suggested it was a potential therapeutic target for limiting scar formation.[150] High levels of TGF-β1 may stimulate the activation of detrimental myofibroblasts, but blocking TGF-β1 completely shows spontaneous skin inflammation and defective vasculogenesis in TGF-β1 knockout mouse,[151] which indicated that maintaining a certain level of TGF-β1 in wounds was essential. What we need to do now is to pay attention to the expression level of TGF-β1 in scar-free repair wounds, and to the temporal and spatial dynamics of TGF-β1 to control the homeostasis of reepithelialisation, vascularization, and inflammation.[152,153] In fact, there are various means of regulating the TGF-β1 signalling pathway, including antibodies, antagonists, and even miRNA means.[154-158] However, using antagonists of TGF-β1 receptors or TGF-β1 specific antibodies could merely reach clinical request due to the safety accidents.[159,160] Hence, targeting to the modulation of TGF-β1 or its downstream pathway may be more feasible.

As to the downregulation of TGF-β signalling, blocking the downstream molecule, Smad3, has been attempted.[114] Smad3 shows a different effect on wound healing.[141] It was reported that Smad3 protein-induced HSs formation accordingly through activating the WNT pathway.[145] Studies showed that counteracting Smad3 signalling improved wound healing with inhibition of scarring. The rate of reepithelialisation is accelerated, but the area of the wounds and the number of myofibroblasts are significantly reduced in Smad3-null mice compared with wild-type mice after the exposure of irradiation.[141] It is thought to prevent Smad2/3-receptor interaction and phosphorylation after inhibiting fibrosis and preventing HSs formation.[161] A great body of studies has shown that the inhibitors of Smad3, for instance, halofuginone, quercetin, trichostatin A, and paclitaxel, could suppress the fibrosis of skin through inhibiting the phosphorylation of Smad2/3 and the formation of the Smad2/3/4 complex.[30,162,163]

Another way referring to the upregulation of the TGF-β family inhibitor, such as Smad7, has been tried.[164] Smad7, as a member of Smad protein, downregulated in HSs.[165] Studies have indicated that overexpression of Smad7 prevents the collagen gel contraction and inhibits collagen-I and α-SMA expression in fibroblasts derived from normal skin and scar.[166] Asiaticoside was isolated from the leaves of Centella Asiatic possessed inhibition properties to reduce scar formation through promoting the expression of Smad 7 instead of other members of the Smad family.[167]

The sequential transition of three post-traumatic repair phases mentioned above is pivotal in the HSs

formation. In the fibrotic and antifibrotic events of wound healing, the imbalance between profibrotic growth factors and antifibrotic factors results in abnormal deposition of ECM showing HSs.[168] To balance the two processes, an agent which binded to several targets is more refined. One typical example is decorin, a small leucine-rich proteoglycan,[169] which exists in the interstitial matrix of the dermis and combines with collagen fibrils preferentially,[170] and then setting their assembly.[171] And the normal scar is replaced by HSs with increased production of collagen-I/III, fibronectin, laminin, and decreased expression of hyaluronic acid and decorin.[15,172] Decorin, as a proteoglycan in the dermal ECM, regulates TGF-β1 to influence collagen fibrillogenesis and diminish scarring.[173] Studies showed decorin inhibited TGF-β induced contraction in HS-derived fibroblast-populated collagen lattice.[174] Therefore, balance is a very important point to adjust the outcome of wound healing, especially the balance between the pro- and anti-fibrotic processes in time and space.

10 | CONCLUSION AND PROSPECT

We summarized the feasibility of traditional laser, small molecule of TCM, and biotherapy in the clinical treatment of HSs. Systematically, biotherapy has its own characteristics compared with traditional therapy. We can conclude that biotherapy is based on one entry point, maybe a cell (inflammatory cell or fibroblasts), a factor (inflammatory factors or cytokines), or a response (transdifferentiation and dedifferentiation), and only one step change can significantly alter the formation and prognosis of HSs. So as to biotherapy, it is relatively more efficient than traditional treatments above.

About various schemes above, most treatments are carried out merely after scar formation has already taken place, targeting reversal fibrosis phenotype and restore normal ECM composition and structure. However, adjusting inflammatory response and proliferative phase in fibrosis pathological changes are relatively early. It prefers to prevention and early treatment, and is more attractive in anti-fibrosis strategies. So as far as current techniques are concerned, we could infer that early diagnosis and advanced prevention may be more advisable.

As we all know, prevention is the most significant section of the HSs therapy, including following Langer's lines that correspond to the direction of collagen fibres and paralleling to the orientation of underlying muscle fibres in elective surgery.[175] Generally speaking, scarring and other fibrotic diseases have a long process which is often ignored. Unfortunately, it was only when the fibrosis progresses to obvious clinical symptoms, such as function abnormalities, that would attract the attention of the patients.[176] And at this stage, fibrosis may be serious and current treatment could merely delay its process. Therefore, for most or large areas of scarring patients, the significance of prevention is greater than that of the treatment itself. Studies in vitro and in vivo have shown that there are many precautionary strategies against scarring.[177,178] Furthermore, the variation and outcome of the same measures in patients undergoing clinical trials are huge, and this leads to comparing problems. However, the same treatments are highly variable in the results obtained in different patients, which leads to comparing problems. Additionally, there remains no gold standard in the prevention and treatment of pathological scars due to the limitation of effective assess for anti-scarring therapeutics, HSs prevention, and scar models.[179] Because of this, there is a large amount of clinical data, and it is still difficult to compare the obtained data horizontally. Therefore, the prevention and clinical treatment of HSs still have a long way to go.

Additionally, although numerous scars are caused by local trauma,[180] many patients also manifest the formation of multiple scars, implying the systemic disease of HSs. In this case, we could hardly achieve desired outcome by altering separate genes. Starting from one entry point, and then covering whole body like a net to achieve earlier and extensive therapeutic effect needs to be further considered. Currently, HSs have been considered as an autoimmune disease.[181,182] Master cells (MCs), as an important of immune cells, participated in innate/acquired immunity and blood coagulation, which contributed to all three stages of wound healing.[164,165] In MC-deficient mice, it showed less scarring with more follicles than MC-sufficient mice after scald burns, and the significant difference was due to the activities of mouse mast cell proteases 4/5 (MCP-4/5).[166] In foetal mice, the wound was healed without scars at embryonic day 15 (E15), compared scar healing at embryonic day 18 (E18).[183,184] It was shown that there were few MCs in the dermis of mice on E15 detected with immunohistochemistry. Injection of the lysate of MCs into mice at E15 resulted in scar formation that was similar to which was observed in E18 embryos. On the contrary, wounds of MC-deficient mice revealed less scarring than MC-deficient embryos at the same time.[167] Therefore, it was suggested that inhibition of the mediators derived from activated MCs could prevent the formation of pathologic scarring. Regarding immune cells, it was reported that specialized dendritic cells, such as Langerhans cells (LCs), reside in epidermis play the key role in the forming of HSs.[185] In aberrant wound healing, LCs stimulated naive T cell responses, and identify the triggering

receptor expressed on myeloid (TREM)-1, a member of the Ig immunoregulatory receptor family, infiltrating hypoxic areas of active HSs, pointing to the pathogenic role in wound repair disorders.[186] Besides, it has been found that there is a correlation of NK cell, T-cell, and scarring.[187] For example, NK cells inhibit the progression of liver fibrosis through targeting and clearing the hepatic astrocytes directly which secrete ECM, suggesting an important role in antifibrosis.[188] Also, we mentioned in the previous section that macrophages of different phenotypes play different roles in the scar formation. These evidences suggest that immunomodulatory therapy is essential for HS.

In recent years, mesenchymal stem cells (MSCs) have been considered to possess the immunomodulatory capacity and play a therapeutic role in a variety of immune diseases.[189,190] In wound healing, stem cells could not only promote skin repair but also reduce scar formation and resist pathological scarring.[191] Several studies demonstrated that MSCs suppressed the formation of HSs in several ways. The first is its immunomodulatory effect.[192] MSCs prevented the formation of scar by regulated inflammation cells and pro-inflammatory mediators. The mechanism of modulating inflammatory reaction of MSC was mainly through reducing mast cell degranulation, suppressing T-cell proliferation, reducing NK cell function, activating macrophages, recruiting neutrophils, and antibacterial actions.[193-196] In atopic dermatitis, hMSCs were demonstrated the therapeutic functions in response to Th2 cytokines to mitigate dermatitis through suppressing MCs degranulation.[197] In vitro, MSC was able to diminish human keratocyte differentiation into α-SMA$^+$ limbal myofibroblast, and reduce the release of neutrophil extracellular traps, thus to promote corneal wound healing in an anti-inflammatory and antifibrotic way.[198]

Second, MSC can act on myofibroblasts, the main effector cells in HS formation. It was proved that bone marrow-derived MSCs inhibit myofibroblasts proliferation, migration, ECM synthesis, and scar formation through paracrine signalling.[199] Moreover, not only stem cells themselves, the conditioned medium of MSCs and exosomes can be used as the treatment of anti-scarring. The exosomes secreted by human adipose mesenchymal stem cells could benefit wound healing and promote scarless cutaneous repair by regulating ECM remodelling.[200] At the same time, MSC inhibited the bioactivities of fibroblasts in the HSs,[201] inhibited the proliferation and the differentiation of fibroblasts to myofibroblasts, and further suppressed the scar formation. Finally, as the multipotent cells, MSC could migrate to local trauma to prevent excessive matrix deposition by fibroblasts, forming new microenvironment to promote healing and alleviate scar.[202] More importantly, as a promising therapy, stem cells can be modified. And we could use physical chemistry and even genes to transform the stem cells into the therapeutic missiles we need to treat HSs. Therefore, MSC treatment may become a new generation of HS treatment strategies.

In sum, the occurrence of HSs is complex, and it is still a 'black box' that needs to be further explored, which further obstacle the development of effective therapeutic strategies. With a better understanding of pathophysiological mechanisms of HSs and the development of the high-throughput screening technologies, future studies in HSs will overcome current hurdles and develop promising treatments. And this may be solved with the joint efforts by multidisciplinary experts, including pathophysiologists, immunologists, pharmacologists, and so on. However, at present, due to the complexity of the development of HSs, a single treatment strategy is difficult to achieve the desired clinical effect and the simultaneous or sequential use of multiple methods, that is, the comprehensive treatment method may be preferable.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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