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REVIEW

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Mesenchymal stem cell-based therapy for autoimmune-related fibrotic skin diseases—systemic sclerosis and sclerodermatous graft-versus-host disease

Han Yang[1†], Sousan Cheong[1†], Yunfan He[1*] and Feng Lu[1*]

Abstract

Background Systemic sclerosis (SSc) and sclerodermatous graft-versus-host disease (Scl-GVHD)—characterized by similar developmental fibrosis, vascular abnormalities, and innate and adaptive immune response, resulting in severe skin fibrosis at the late stage—are chronic autoimmune diseases of connective tissue. The significant immune system dysfunction, distinguishing autoimmune-related fibrosis from mere skin fibrosis, should be a particular focus of treating autoimmune-related fibrosis. Recent research shows that innovative mesenchymal stem cell (MSC)-based therapy, with the capacities of immune regulation, inflammation suppression, oxidation inhibition, and fibrosis restraint, shows great promise in overcoming the disease.

Main body This review of recent studies aims to summarize the therapeutic effect and theoretical mechanisms of MSC-based therapy in treating autoimmune-related fibrotic skin diseases, SSc and Scl-GVHD, providing novel insights and references for further clinical applications. It is noteworthy that the efficacy of MSCs is not reliant on their migration into the skin. Working on the immune system, MSCs can inhibit the chemotaxis and infiltration of immune cells to the skin by down-regulating the expression of skin chemokines and chemokine receptors and reducing the inflammatory and pro-fibrotic mediators. Furthermore, to reduce levels of oxidative stress, MSCs may improve vascular abnormalities, and enhance the antioxidant defenses through inducible nitric oxide synthase, thioredoxin 1, as well as other mediators. The oxidative stress environment does not weaken MSCs and may even strengthen certain functions. Regarding fibrosis, MSCs primarily target the transforming growth factor-β signaling pathway to inhibit fibroblast activation. Here, miRNAs may play a critical role in ECM remodeling. Clinical studies have demonstrated the safety of these approaches, though outcomes have varied, possibly owing to the heterogeneity of MSCs, the disorders themselves, and other factors. Nevertheless, the research clearly reveals the immense potential of MSCs in treating autoimmune-related fibrotic skin diseases.

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Conclusion The application of MSCs presents a promising approach for treating autoimmune-related fibrotic skin diseases: SSc and Scl-GVHD. Therapies involving MSCs and MSC extracellular vesicles have been found to operate through three primary mechanisms: rebalancing the immune and inflammatory disorders, resisting oxidant stress, and inhibiting overactivated fibrosis (including fibroblast activation and ECM remodeling). However, the effectiveness of these interventions requires further validation through extensive clinical investigations, particularly randomized control trials and phase III/IV clinical trials. Additionally, the hypothetical mechanism underlying these therapies could be elucidated through further research.

Keywords Mesenchymal stem cells, Autoimmune-related fibrotic skin diseases, Systemic sclerosis, Sclerodermatous graft-versus-host disease, Chronic graft-versus-host disease, MSC-based therapy

Background

SSc is a multifaceted and multisystem disease, characterized by microvascular damage, innate and adaptive immune dysregulation, and widespread fibrosis affecting the skin and various organs [1, 2]. The majority of hypotheses regarding SSc pathogenesis focus on the interplay between early immunological events and vascular alterations. This interplay results in the emergence of activated fibrogenic fibroblasts, generally recognized as the pivotal effector cells in the disease [3, 4]. Chronic GVHD (cGVHD) is a morbidity and mortality complication disease following allogeneic hematopoietic stem cell transplantation [5], and it shares clinical characteristics akin to autoimmune diseases [6]. Experimental researches support a three-phase pathophysiological model of cGVHD to simplify its intricate pathogenesis: initial inflammation driven and sustained by the innate immune system, with substantial involvement from damaged endothelial cells; chronic inflammation and immune disorders related to Treg cell dysfunction after early uncontrollable inflammation; and scarring and fibrosis in the late stage promoted by dysregulated immunity and aberrant tissue repair [7].The prevailing pathological alterations observed in cGVHD are Scl-GVHD, characterized by a significant rise in collagen deposition, primarily manifesting as lichen planus-like lesions, sclerotic skin manifestations, and poikilodermatous skin changes [8, 9].

Scl-GVHD and SSc share similarities in developmental fibrosis, vascular abnormalities, and innate and adaptive immune response disorders [10, 11]. As a result of the severe skin fibrosis that manifests in both SSc and Scl-GVHD at the late stage, these diseases are classified into the same group of chronic autoimmune connective tissue diseases [12]. Many immune effector cells (T cells, B cells, macrophages, and others) and myofibroblasts participate in the disease process [13–15]. The primary factors that trigger the initiation and progression of skin fibrosis include dysfunctional immune response, oxidative stress caused by hypoxia originating from vascular lesions, and subsequent fibroblast disorders [16, 17]. The significant immune system dysfunction observed in the skin of these two diseases, distinguishing autoimmune-related skin fibrosis from mere skin fibrosis, explain why SSc and Scl-GVHD collectively referred to as autoimmune-related fibrotic skin diseases in this study. In the skin tissue, it has been reported that autoimmune responses facilitated the proliferation and penetration of T cells, particularly T helper (Th)17 and Th2 cells, B cells, monocytes, or macrophages in the SSc and Scl-GVHD [18–20]. This process results in the secretion of enormous immune mediators and pro-fibrotic growth factors, such as interleukin (IL)-4, IL-6, IL-13, IL-17, TGF-β1, and connective tissue growth factors. This coordination promoted the proliferation and differentiation of fibroblasts, leading to the activation of α-smooth muscle actin $(\alpha\text{-SMA})^{+}$ myofibroblasts. Finally, the synthesis of extracellular matrix (ECM), including collagen I (Col-1), and collagen III (Col-3) was enhanced, resulting in fibrosis of both skin tissue and visceral organs [21–23]. In summary, as the key effector cells of fibrosis, fibroblasts are dependently regulated by immune cells in autoimmune-related fibrotic skin diseases to a large extent. Besides, oxidative stress is also a contributing factor to the development of skin fibrosis and is simultaneously modulated by the immune system. Therefore, considering the underlying mechanisms explicated above, treating autoimmune-related skin fibrosis should focus on the pathological complex of immune response—oxidative stress—fibrosis, emphasizing the contribution of the immune system.

The hypothesis regarding the pathological complex has been corroborated by the inefficacy of anti-fibrotic drugs alone in relation to SSc and Scl-GVHD [24]. The significant dysfunction of the immune system that distinguishes autoimmune-related skin fibrosis from purely fibrotic skin disease is crucial, and emphasis should be placed on treating both fibrosis and the autoimmune aspect. The clinical management of cGVHD is contingent on the severity of the disease.

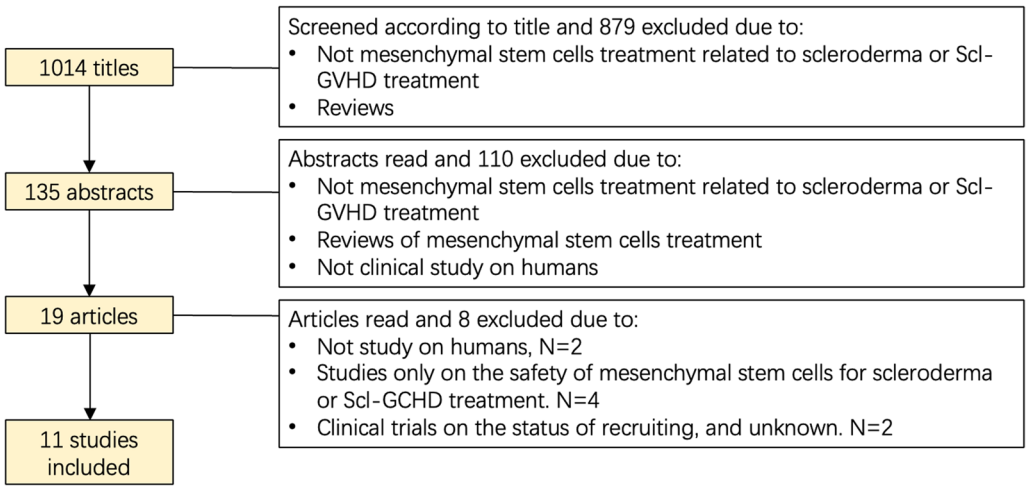

Fig. 1 Flowchart of exclusion process ending with 11 included studies

While mild manifestations may suffice with local treatment, moderate and severe forms invariably require systemic immunomodulatory or immunosuppressive therapies [25]. In the case of Scl-GVHD, topical glucocorticoids or calcineurin inhibitors could be additionally used as first-line therapy for drying and flaking skin [26] and ointments and creams are also recommended to relieve symptoms. Limited cutaneous SSc (lSSc) patients are frequently treated with topical corticosteroids and tacrolimus, as well as systemic methotrexate and mycophenolate mofetil [27]. For diffuse cutaneous SSc (dSSc), systematic methotrexate, mycophenolate mofetil, and cyclophosphamide are recommended routine treatments. In addition, immunosuppressive medicine such as rituximab may also be an alternative choice if the clinical therapeutic effect of routine treatments was poor [27]. However, to satisfy the demand for immune regulation and skin fibrosis improvement, traditional immune suppressive medicines may occasionally escalate the incidence rates and mortality rates associated with treatment, especially among steroid-refractory SSc and Scl-GVHD patients [24, 28]. Therefore, it is imperative to develop innovative treatments involving MSCs for autoimmune-related fibrotic skin diseases, encompassing immune regulation, inflammation suppression, oxidation inhibition, and fibrosis constriction [29]. This article presents a compelling rationale for applying MSCs in treating SSc and Scl-GVHD. MSCs have demonstrated the suitability and efficacy in overcoming these diseases in theory. Additionally, numerous clinical studies have exhibited positive long-term results with MSC-based therapies for autoimmune-related fibrotic skin diseases [30]. The diagram of article selection are shown in the Fig. 1 and the full text of 11 studies is retrieved for evaluation. This review aim to summarize the therapeutic effect and theoretical mechanisms of MSC-based therapy in treating autoimmune-related fibrotic skin diseases, SSc and Scl-GVHD, providing novel insights and references for further clinical applications. The discussion will focus on rebalancing immune and inflammatory disorders, enhancing antioxidant defenses, inhibiting overactivated fibrosis (including fibroblast activation and ECM remodeling), and managing the variability of MSCs in clinical and preclinical.

MSCs alleviate the autoimmune-related skin fibrosis by regulating the immune response

MSCs exert a regulatory effect on all participants in the immune system (Fig. 2). Particularly in SSc and Scl-GVHD, MSCs play an essential role in skin homeostasis by inhibiting the proliferation and recruitment of CD4+ T cells and macrophages, while promoting that of suppressor T cell—T regulatory (Treg) cells. Additionally, MSCs suppress the immune response of B cells. Thus, MSCs reduce the pro-inflammatory mediators secreted by CD4+ cells and macrophages, and suppress the expression of autoantibodies by B cells, while they increase anti-inflammatory mediators from Treg cells.

MSCs influence the migration of T cells and the release of inflammatory factors without needing to migrate into the skin

It is noteworthy that MSCs do not need to migrate into the skin to operate, and MSCs are eliminated in one week after intravenous infusion with a short duration in vivo [13, 31–33]. In contrast, their long-term efficacy is at least 6 weeks in animal models and 12 months

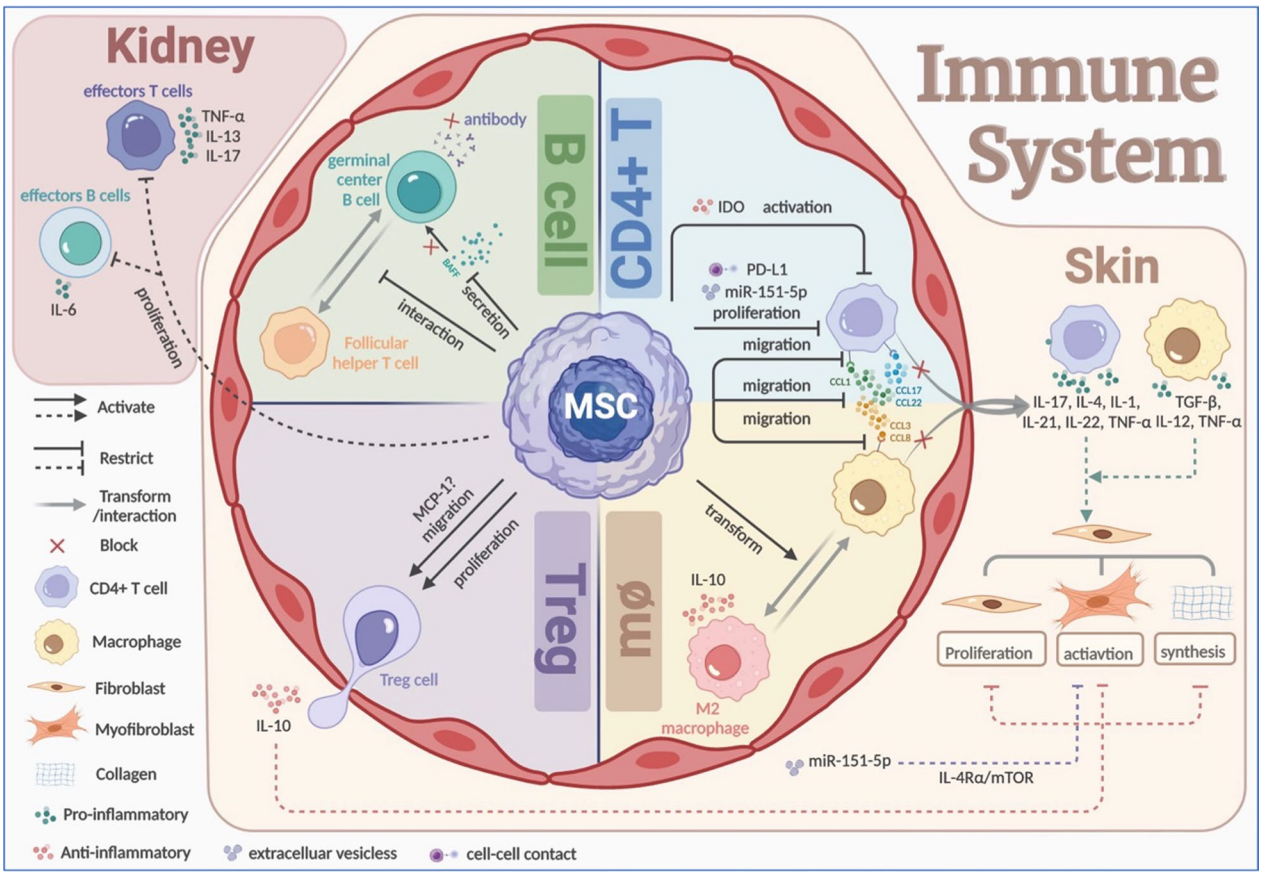

Fig. 2 Therapeutic value of MSCs to the pathogenic triad—the immune disorders. In skin, a lot of pro-inflammatory factors (IL-1, IL-4, IL-12, IL-17, IL-21, IL-22, TNF-α, TGF-β) from CD4+T cells and macrophages can trigger dermal fibrosis. To alleviate inflammation, MSCs inhibit the activation, proliferation, and migration by targeting chemokines and their ligands of CD4+T cells; inhibit the migration of macrophages while promoting the transformation to anti-inflammatory M2 phenotype; facilitate the migration and proliferation of Treg cells to secrete anti-inflammatory factors IL-10; and inhibit the activation of B cells by reducing BAFF and interaction between germinal center B cells and follicular helper T cells. In the kidney, MSCs inhibit the proliferation of effectors T and B cells. By Biorender (https://biorender.com/). *IL* interleukin, *TNF-α* tumor necrosis factor-α, *TGF-β* transforming growth factor-β, *MSCs* mesenchymal stem cells, *BAFF* B-cell activating factor of the TNF family

in the human body [33, 34]. This effect can even be observed long after elimination [31]. Except for intercellular contact, this phenomenon proves that most MSCs achieve long-term efficacy through paracrine signaling of cytokines, growth factors, and EVs [35]. Not only do MSCs not migrate to the skin, but they also hinder the chemotaxis and infiltration of immune cells to the cutaneous region by down-regulating the expression of cutaneous chemokines and chemokine receptors on immune cells. Among the chemokine ligands (CCL), CCL2, CCL3, and CCL5 are the most critical in fibrosis and inflammation of SSc and Scl-GVHD, serving as vital media for leukocytes to transport [36, 37]. Moreover, CCL17 and CCL22, as the ligands of chemokine receptor (CCR) 4, influence the severity of skin sclerosis and are also integral in recruiting the memory T cells [38, 39]. MSCs can reduce the expression of CCL1, CCL3, CCL8, CCL17, CCL22, and CCR4 on Th2, Th17, as well as Th22 cells, CCR8 on Th2 cells, and CCR1 on CD11β+ macrophages in autoimmune-related fibrotic skin to hinder the arrival of CD4+ T cells, including Th17 and Th2 cells, and CD11β+ macrophages, in particular [13, 40, 41]. Regardless, the infiltration of Th2 may be alleviated by miR-151-5p, a regulatory miRNA from MSC-EVs that can inhibit fibrotic disease [41]. As for CD8+ T cells, their reduction in the skin has been reported since using adipose-derived stem cells (ADSCs) [42]. No down-regulation of CD8+ T cell-related chemokine receptors such as CCR5 has been found. Nonetheless, the decrease of immune effector cells associated with SSc and Scl-GVHD in the skin will ultimately benefit skin fibrosis primarily through a consequent decrease in the secretion of pro-fibrotic factors. It is widely acknowledged that macrophages are a significant source of TGF-β, the most critical trigger for the activation of fibroblasts which leads to ECM

over-synthesis in the skin tissue and other organs [43]; T cells excrete a large number of specific cytokines, including IL-17 from Th17 cells, IL-2 from CD4+ T cells, and IL-4 from Th2 cells, as well as IL-1, IL-21, IL-22, tumor necrosis factor-α (TNF-α), and other pro-inflammatory mediators [41, 44]. Besides, Treg cells and their anti-inflammatory secretion such as IL-10 in the skin of cGVHD are instead promoted by MSCs, through a mechanism that cannot be explained by the decrease of CCR4 expression [44]. However, this phenomenon may be linked to the induced up-regulation of monocyte chemotactic protein 1 (MCP-1) toward Treg cells. In other words, MCP-1 from MSCs can recruit T cells and activate FAS pathway-mediated apoptosis of T cells, which transiently leads to high levels of TGF-β from macrophages and brings about the augmentation of Treg cells in mice with SSc [45].

MSCs suppress the immune response of B cells and impede the production of autoantibodies

Apart from infiltration accommodation, B cell response, including the interaction between follicular Th cells and germinal center B cells, as well as the ratio of B-cell activating factor of the TNF family (BAFF) to B cells, also impacts from the umbilical cord (UC)-MSC-EVs treatment, resulting in improvement of Scl-GVHD model [40]. Therefore, the levels or titer of anti-Scl-70 antibody and serum antinuclear antibody, associated with fibrosis development, are declining in SSc patients [33, 34].

MSCs regulate the proliferation of immune cells

With regard to immune cell proliferation, MSCs inhibit effectors T and B cells in the spleen, while inhibiting Treg cells until they migrate into the circulatory system [42]. The immunosuppressive effects of MSCs are selectively mediated through cell-to-cell contact of programmed death-ligand 1 (PD-L1) expression, leading to a decrease in both the number and function of mature Th17 cells in the serum [46]; the release of miR-151-5p by MSC-EVs weakens Th2 cell infiltration and reduces their numbers in the serum. However, there is no significant impact observed on the number of Th17 or Th1 cells in the serum. Furthermore, miR-151-5p directly targets IL-4 receptor α (IL-4Rα), thereby interrupting the IL-4Rα/mTOR pathway, which could impede the activation of resting fibroblasts by TGF-β [47].

In brief, MSCs function as a paracrine signaling and EV-based barrier, impeding the arrival of immune cells into the dermis and hindering the inflammatory and fibrotic responses of the immune system. MSCs thereby can attenuate the differentiation, generation, and extracellular matrix production of fibroblasts.

MSCs secrete anti-inflammatory mediators and possess plasticity and stable immunosuppressive abilities

In addition, MSCs can produce various anti-inflammatory mediators, especially indolemine 2,3-dioxygenase (IDO-2,3), IL-1Rα, tumor necrosis factor α stimulated gene 6 (TSG-6), and prostaglandin E2 (PGE-2) [35, 48]. IDO plays a critical role in inhibiting the tryptophan decomposition in T cells, thereby maintaining the adequate level of signal tryptophan. In the event of tryptophan deficiency, the mTOR pathway is activated, promoting aerobic glycolysis and subsequent T cell activation [49]. MSCs can promote the polarization of monocytes toward anti-inflammatory M2 macrophages, leading to an increase in IL-10 levels while simultaneously decreasing levels of TNF-α and IL-12 [50]. However, these inhibitory phenotypes may shift toward inflammation-supportive ones under certain circumstances, such as exposure to defective immune cells in vitro [51]. This plasticity of MSCs implies that their effects on disease should be explored based on specific pathophysiological backgrounds. Despite the cellular functional impairments of bone marrow-derived (BM) MSCs due to oxidative stress with SSc in vitro, such as cell lifespan, apoptosis, proliferation, and pro-angiogenesis capacity, many studies have repeatedly and consistently demonstrated that both SSc-derived and newly introduced MSCs can still sustain their immunosuppressive potential. This potential is evident in the consistent inhibition of CD4+ and CD8+ T cells and constant induction of functional Treg cells [52–56]. The resilience of MSCs in the unfavorable environment of SSc may be attributed to a higher level of IL-6. Studies have shown that even without IL-1Rα or IL-6, MSCs can still reduce skin thickness and collagen content in hypochlorite (HOCl)-induced SSc mice, indicating that IL-6 is not a crucial factor in the anti-fibrotic effect of healthy MSCs against SSc [57]. However, a higher level of IL-6 from SSc-MSCs can trigger and sustain the inhibition of T cells and induction of Treg cells by MSCs, while camouflaging the aging of MSCs [54].

To further enhance the function of MSCs, it is advisable to prime them with pro-inflammatory factors, such as interferon γ (IFN-γ), TNF-α, IL-1α, IL-1β, IL-17 [58]. This approach can prompt the immunomodulatory response from MSCs in advance, resulting in the up-regulation of anti-inflammatory secretion [IL-10, IDO, cyclooxygenase (COX)-2, PGE-2, TSG-6, CCL12, chemokine (C-X-C Motif) ligand 2 (CXCL2), CCL4], and direct immune cell behaviors [59–66], which can lead to significantly improved therapeutic outcomes for MSCs in treating immune-related disorders in GVHD models [66, 67]. Nevertheless, the immunomodulatory

potency of MSCs in clinics varies depending on the pathological background and tissue type, which partially dictates the suitability of tissue-derived MSCs for specific immune-related fibrotic diseases. For instance, in mice with asthma, BM-MSCs may be more effective than ADSCs due to their superior ability to reduce eosinophil infiltration and collagen deposition in the lungs, possibly owing to the increased polarization from monocytes to the M2 phenotype [68]. On the other hand, in mice with SSc, ADSCs are superior to BM-MSCs due to the noteworthy observation that ADSCs reduce the presence of Th17 cells in peripheral blood, which are closely associated with the progression of SSc. Additionally, ADSCs can drain away pro-inflammatory factors, such as TNF-α, IL-1β, IL-6, and IL-17, while simultaneously increasing Treg cells and IL-10 to confront SSc precisely [32].

MSCs alleviate the autoimmune-related skin fibrosis by resisting oxidant stress

MSCs improve vascular abnormalities to alleviate oxidative stress

The etiology of oxidative stress in SSc is hypoxia resulting from vascular abnormalities [15]. Despite the apparent tissue hypoxia observed in SSc, there is a lack of evidence supporting compensatory angiogenesis [53]. MSCs can promote angiogenesis and vasculogenesis in SSc by serving as an alternative source of endothelial progenitor cells (EPCs) and pericytes, up-regulating the expression of pro-angiogenic factors, and alleviating oxidative stress [1, 53, 69]. MSCs express specific characteristic proteins of mature endothelial cells such as von Willebrand factor (vWF), vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, vascular endothelial (VE)-cadherin, and vascular cell adhesion molecule 1 (VCAM1), which are considered supplementary sources of EPCs [53]. In the pathological microenvironment of SSc, TGF-β and platelet-derived growth factor receptor B (PDGFB) induce differentiation of SSc-MSCs into pericytes. These pericytes exhibit a more mature myofibroblast-like phenotype with high expression levels of α-SMA and smooth muscle 22 α (SM22α). When co-cultured with healthy vascular endothelial cells in vitro, this phenotype can reprogram the cells to promote angiogenesis behavior and improve formation of endothelial cell tubes [1]. In vitro overexpression experiments have demonstrated that SSc-MSCs overexpressing stromal cell-derived factor 1 (SDF-1) and VEGF produce potent pro-angiogenic effects. The blocking antibody experiments have also indicated that these cytokines derived from MSCs are responsible for this strong pro-angiogenic effects. The release of these factors in the local microenvironment can further stimulate their up-regulation and promote redistribution of CXC receptor 4 (CXCR4) and TGF-β receptor II (TGF-βRII) from the cell cytoplasm to the cell surface and focal adhesion contacts, respectively, which facilitate endothelial cell generation in the dermal microvasculature to promote angiogenesis [69].

MSCs enhance the antioxidant defenses to alleviate oxidative stress

MSCs can significantly enhance the antioxidant defenses and reduce levels of oxidative stress in patients with SSc (Fig. 3). Under treatment with MSCs, particularly advanced oxidation protein product (AOPP) levels in serum decreased. However, the levels of manganese superoxide dismutase (SOD) 2, a kind of antioxidant enzyme, and total antioxidant capacity (T-AOC) showed an increase, and these changes were found to be significantly associated with fibrotic flourishing [33]. iNOS is the key anti-fibrotic mechanism associated with MSCs against SSc, particularly in nitric oxide (NO)-related antioxidant stress function. Lacking iNOS in MSCs could not reduce AOPP regularly. Even if MSCs could induce more gluconic acid secretion and enhance the antioxidant capacity (AOC), the overall oxidative stress remained high after carefully considering both AOPP and AOC [70]. MSCs with iNOS can efficiently synthesize NO. Despite being a pro-oxidant in physiological conditions, NO has been proved to be an effective antioxidant in the case of specific pathological conditions, such as SSc, as demonstrated through various preclinical models; MSCs with iNOS can efficiently synthesize NO. Despite being a pro-oxidant in physiological conditions, NO has been proved to be an effective antioxidant in the case of specific pathological conditions such as SSc, as demonstrated through various preclinical models [71]. The presence of NO can impede the TGF-β pathway and the activation of myofibroblasts. At the same time, it promotes matrix metallopeptidase (MMP) and hepatocyte growth factor (HGF), degrades collagen fibers, and promotes ECM remodeling, thereby restraining fibrosis in various organs [72–74]. Nevertheless, whether iNOS exists or not does not significantly impact the regulation of tissue inhibitors of metalloproteinase (TIMP) 1 or the ratio of MMP1/TIMP by MSCs [70]. It is also worth noting that the absence of iNOS does not impair the function of MSCs, such as anti-fibrotic effects that depend on inflammation and immunomodulation. In HOCl mouse models, $iNOS^-$ MSCs showed no significant decline in secretion of high levels of inflammatory factors such as IL-1β and IL-6 compared to $iNOS^+$ MSCs [70]. Additionally, experiments in vitro have shown that BM-MSCs cultured under hypoxic conditions can resist

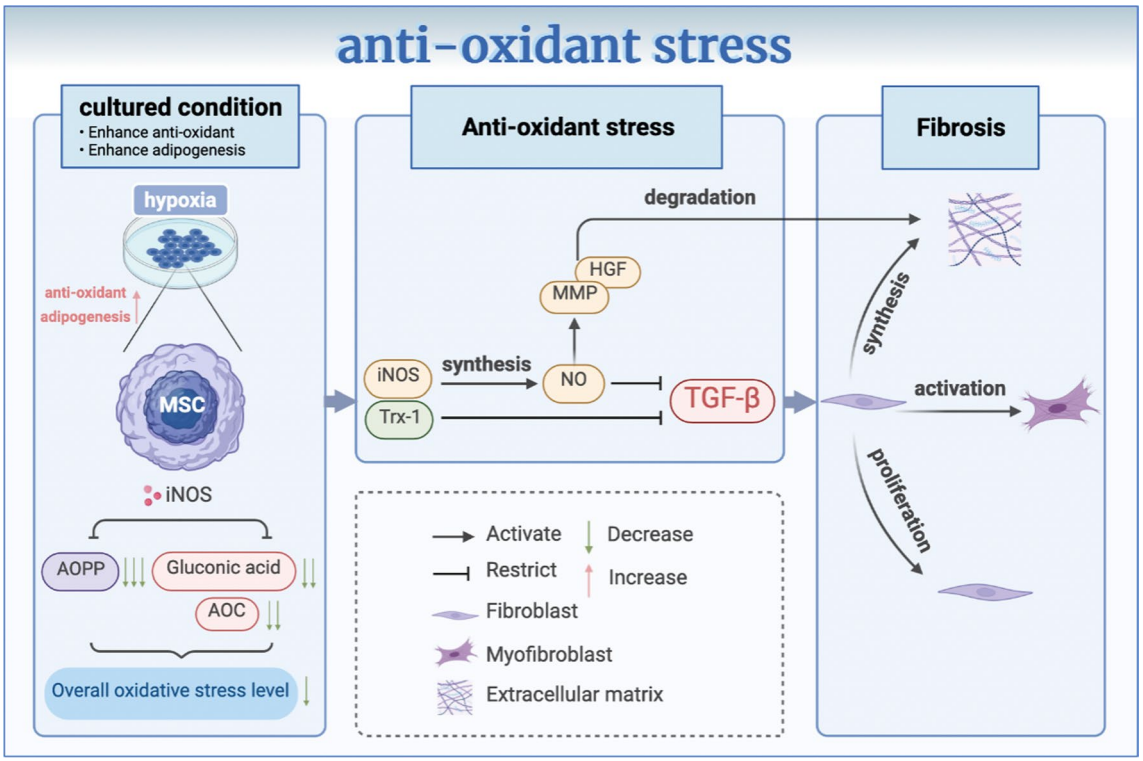

Fig. 3 Therapeutic value of MSCs to the pathogenic triad—the oxidant stress. The hypoxia cultured condition enhances the antioxidant and adipogenic capacity of MSCs. Secreted by MSCs, iNOS significantly drops AOPP and neutralize its suppression to gluconic acid and AOC, to regulate the overall oxidative stress level. iNOS helps to the synthesis of NO, increasing MMP and HGF for dermal ECM degradation and restraining TGF-β. MSCs also secrete Trx-1 to weaken TGF-β, which prevent fibroblasts from proliferating, activating and synthesizing ECM. By Biorender (https://biorender.com/). *AOPP* advanced oxidation protein product, *AOC* antioxidant capacity, *ECM* extracellular matrix, *iNOS* Inducible nitric oxide synthase, *MSCs* mesenchymal stem cells, *MMP* matrix metallopeptidase, *HGF* hepatocyte growth factor, *Trx-1* thioredoxin 1, *TGF-β* transforming growth factor-β

oxidative stress damage and inhibit the TGF-β pathway through the essential oxidoreductase Trx-1 [75]. Another experiment on hypoxia in mice with SSc suggested that ADSCs exposed to hypoxic conditions would mediate TGF-β, α-SMA, and hydroxyproline levels, resulting in a neater fiber arrangement and a thinner dermal thickness compared to the control group [76]. These findings suggest that the anti-fibrotic effect of MSCs cultured under hypoxic conditions may be enhanced and that the oxidative stress environment of SSc may not weaken MSCs, but rather strengthen their ability to inhibit the TGF-β signaling pathway. Moreover, AOPP, an oxidative stress marker of SSc [77], is a potential predictive indicator for MSC-based treatment of SSc. AOPP level is negatively correlated with the MSC proliferation rate and MSC proliferation rate is inversely correlated with the apoptosis rate. Therefore, the lower the AOPP level, the higher the MSC proliferation rate and the lower the MSC apoptosis rate can be. Besides, the immunosuppressive ability of MSCs remains stable despite exposure to an oxidative stress environment. Therefore, MSC infusion may be a promising therapeutic option for SSc patients with low oxidative stress [52]. Even in severe oxidative stress circumstances, the enhanced antioxidant defense capacity and adipogenic differentiation potential of MSCs may compensate for the shortage of the proliferation rate, thereby maintaining the overall function of MSCs [52]. In SSc mice treated with MSCs, it has been observed that the skin gradually regained its standard thickness, which can be attributed to increased adipogenic differentiation potential and elevated expression of fatty acid synthesis-related genes, both of which are stimulated by the oxidative stress environment in SSc condition [15, 52, 78]. These differentiated adipose cells share similar variability with healthy BM-MSCs [79].

MSCs alleviate the autoimmune-related skin fibrosis by miRNAs, inhibiting TGF-β pathway and supporting ECM remodeling

After inhibiting immunity and inflammation in the early stages of the disease, MSCs could alleviate skin fibrosis in the late stage by releasing miRNAs, blocking TGF-β

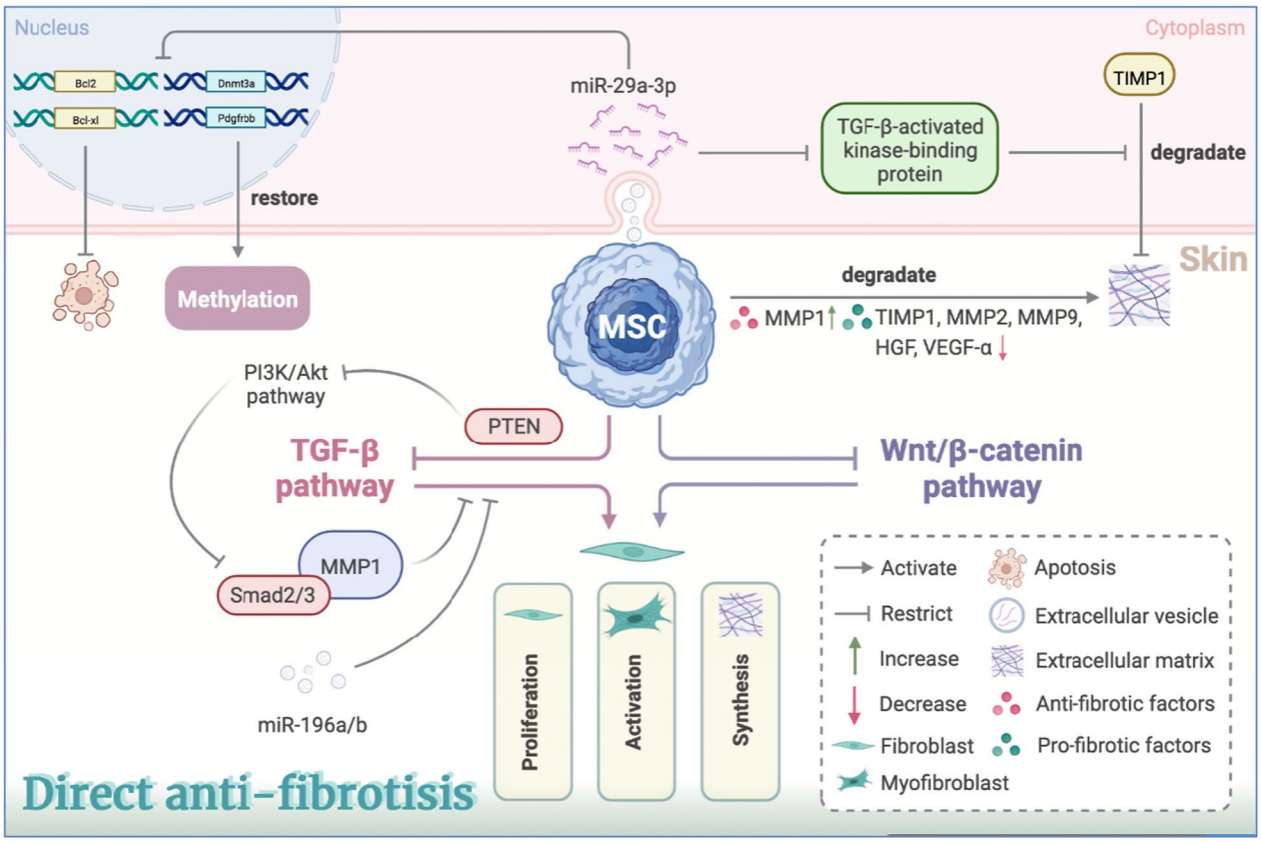

Fig. 4 Therapeutic value of MSCs to the pathogenic triad—fibrosis. MSCs release miR-29a-3p to attenuate the expression of anti-apoptotic genes (Bcl2, Bcl-xl), methylation-related genes (Dnmt3α), and PDGFRB, to promote fibroblast apoptosis and restore methylation. MSCs promote ECM degradation through up-regulating anti-fibrotic factors (MMP1) and down-regulating pro-fibrotic factors (TIMP1, MMP2, MMP9, HGF, VEGF-α), or inhibiting the suppression of ECM degradation with miR-29a-3p targeting at TGF-β-activated kinase-binding protein. To regulate fibroblast proliferation, activation, and ECM synthesis, MSCs block the Wnt/β-catenin pathway, and restore the expression of PTEN to restrain the PI3K/Akt-mediated Smad-2/3 and MMP1 superphosphorylation, to inhibit the TGF-β pathway. By Biorender (https://biorender.com/). *Dnmt3a* DNA methytransferase 3α, *PDGFRB* platelet-derived growth factor receptor B, *ECM* extracellular matrix, *MSCs* mesenchymal stem cells, *MMP* matrix metallopeptidase, *TIMP1* tissue inhibitor of metalloproteinases 1, *HGF* hepatocyte growth factor, *VEGF-a* vascular endothelial growth factor α, *TGF-β* transforming growth factor-β, *PTEN* Phosphatase and tensin homolog

signaling and, enhancing tissue remodeling (Fig. 4) [32, 42]. Among these, the inhibition of TGF-β signaling may be linked to phosphatase and tensin homolog (PTEN), a bispecific phosphatase with dual activity in lipid phosphatase and protein phosphatase. MSCs can block PI3K/Akt pathway by restoring PTEN expression, thereby eliminating the TGF-β-mediated superphosphorylation of Smad-2/3 and MMP1 to reduce fibroblast transdifferentiation in the skin of Scl-GVHD mice [13]. Moreover, since the anti-fibrotic effect of MSC-EVs is completely eliminated with the addition of the miR-29a-3p antagonist, miR-29a-3p may also play an essential role in anti-fibrosis [80]. It is acknowledged that miR-29a-3p is only down-regulated in the scleroderma spectrum disorders and has been shown to decrease the expression of anti-apoptosis genes such as B cell lymphoma (Bcl) 2 and Bcl-xl, methylation-related genes like DNA methytransferase 3α (Dnmt3α), and PDGFRB, eventually promoting fibroblast apoptosis and the restoration of abnormal methylation in SSc skin [80, 81]. Besides, miR-196a/b, including miR-196a and miR-196b-5p, which block the TGF-β-mediated synthesis of Col-1α2 in dermal fibroblasts of bleomycin-induced SSc mouse models, may be one of the mechanisms by which MSC-EVs inhibit skin fibrosis in SSc [82, 83]. It is illustrated that there is a more mature myofibroblast phenotype, overexpressing fibrotic markers such as α-SMA, SM22α, and TGFβR-II with BM-MSCs in the SSc compared to healthy individuals [34, 79]. Besides, CD248 overexpression in SSc-MSCs may be involved in TGF-β and PDGFB pathways, promoting pericell–mesenchymal transformation and skin fibrosis [84]. In addition to the mechanism mentioned above in fibroblast activation and proliferation, MSCs and MSC-EVs could interfere with the secretion of some enzymes, growth factors, and other proteins relevant to ECM remodeling,

to hinder or reverse skin fibrosis in autoimmune diseases directly. As a member of the miR-29a family, miR-29a-3p aims at down-regulating TGF-β-activated kinase-binding proteins, which act as modulators of TIMP1, thereby intervening in ECM deposition [85, 86]. In HOCl-induced mouse models of SSc, MSCs increase MMP1 while reducing the secretion of TIMP1 and other metalloproteinases such as MMP2 and MMP9, which show distinct biological characteristics from MMP1. This leads to the precipitation of collagen degradation and a reduction in the expression of fibrotic growth factors, HGF and VEGF-α, ultimately weakening the induction of dermal fibroblast collagen synthesis [33].

The variables of MSCs and interaction of MSCs and immunosuppressants for autoimmune-related fibrotic skin diseases

Regardless of the histocompatibility of MSCs, tissue sources, injection dose, infusion frequency, route of administration, and whether combined with other therapeutic modalities, a meta-analysis has shown that MSC-based therapy can remarkably alleviate cutaneous fibrosis and is generally safe [48, 87]. Nonetheless, there are concerns regarding the variability of MSCs that need to be addressed to stabilize the clinical effects, as their heterogeneity, which mainly includes preclinical variables during the production process of MSCs and clinical variables from the therapeutic course of MSCs, contributes significantly to the mixed clinical outcomes [88]. Regardless of the duration of treatment, the improvement of skin fibrosis after MSCs treatment was considered as the major progress in the majority of clinical and animal studies in Table 1 [10, 30, 32–34, 41, 42, 75, 78, 89–99]. In clinical studies, the improvements of skin fibrosis are primarily manifested as the reducing skin thickness, increasing skin elasticity, and shrinking lesion area [10, 30, 34, 78, 89, 90, 92–96]. Several clinical studies of SSc also reported significant improvements in vascularization, including the restoration of blood vessels in the hands and limbs and the alleviation of Raynaud's phenomenon [89–92]. The improvements of skin fibrosis shown in animal studies primarily include thinner skin thickness, increasing ECM remodeling, and less expression of fibrosis factors [32, 33, 41, 42, 75, 97–99]. Additionally, the restoration of inflammation levels is also an significant feature found in the majority of these studies [10, 32–34, 41, 93, 94, 97, 99].

The preclinical variables of MSCs

Heterogeneity and plasticity of MSCs arising from differences in production and processing include the source, culture conditions, and the number of passages [40, 100, 101]. Regarding the source of MSCs, ADSCs exhibit a more potent immunosuppressive ability for the maturation and differentiation of T cells, B cells, and monocytes than BM-MSCs, while ADSCs demonstrate high proliferation rates in vivo and in vitro [102–109]. ADSCs also possess a more substantial potential for adipogenesis differentiation that is not easily weakened or lost along with increasing passages and age of donor [24], possibly providing an advantage in restoring the subcutaneous fat layer of SSc simultaneously. A descriptive study by Maria et al. comparing the efficacy of human BM-MSCs with human ADSCs in the HOCl-induced SSc mouse model supported that ADSCs were significantly more efficient in alleviating skin fibrosis than BM-MSCs [32]. A total of 18 patients in two SSc clinical trials treated with ADSCs revealed significant improvements in skin elasticity, pigmentation, local skin lesion progression, subcutaneous fat thickness and function, edema, and hand movement [78, 89]. MSCs can be divided into two categories based on the donor source: healthy-originated allogeneic MSC (h-MSC) and SSc patient-originated autologous MSC (SSc-MSC). Compared to h-BM-MSCs, SSc-BM-MSCs have different phenotypes [1, 34]. Although immunosuppressive and hematopoietic functions of SSc-BM-MSCs avoid hefty clout, their cell lifespan and functional activities of proliferation, angiogenesis, and anti-fibrosis are inevitably impaired [53, 55, 56]. The same issue also applies to SSc-ADSCs. SSc does not modify the phenotype, morphology, differentiation, and adhesion capacity of autologous ADSCs. However, it weakens their proliferation rate, metabolic activity, migration, and invasion capacity [78, 110]. The miRNAs expression profile of both SSc-BM-MSCs and SSc-ADSCs has been found in the up-regulation of pathways, including senescence mechanisms and pro-fibrotic behaviors, and the down-regulation of pathways related to cell survival [111]. Recent clinical trials with h-MSCs have demonstrated that they could be an exciting alternative for treating SSc and Scl-GVHD [34, 90, 91]. Both autologous MSCs and allogeneic MSCs are considered to alleviate skin fibrosis in SSc clinically, but which one would be preferred still need further information [42, 112]. Additionally, the optimal culture conditions for MSCs are crucial for proliferation and functional properties. MSCs cultured in acidosis indicated that they produce more anti-inflammatory extracellular vesicles, leading to a more noticeable promotion effect on Treg cells than MSCs in standard conditions [113].

The clinical variables of MSCs

Meanwhile, proper prescription of injection dose, infusion frequency, administration time, and route of administration is also conducive to the therapeutic efficacy of MSCs and MSC-EVs in autoimmune-related fibrotic skin diseases [40], as evidenced by the dose and frequency

Table 1 Summary of clinical trials and preclinical studies of MSC for autoimmune-related fibrotic skin diseases

Clinical trials

Condition	Subject	Patients number (study type)	MSC Source and route of Injection	Frequency (time)	Dose (cells/kg)	Main results (follow-up period)	NCT number	References
SSc (Severe diffuse)	Human	1 (Case report)	Allo-BM IV	Single	1×10^6/kg	Reduction of ulceration and pain, improvement of hand vasculopathy	N/A	[91]
SSc	Human	5 (Phase 1)	Allo-BM IV	Single	$0.22–1.8\times10^6$/kg	Improvement of skin fibrosis and vasculopathy (6 M)	N/A	[90]
SSc (limb ischemia)	Human	1 (Case report)	Auto-BM IV	Triple (0, 1, 2 M)	$0.8–0.9\times10^6$/kg	Reduction of necrotic skin areas (0–1 M), epidermal thickness (2 M). Revascularization of extremities (2 M). Increase of angiogenic factors (2 M)	N/A	[92]
SSc	Human	14 (N/A)	Allo-UC + PE IV	Triple PE (1, 3, 5 D) + pulse cyclophosphamide + Single MSC (8 D)	1×10^6/kg	Improvement of mRSS. Reduction of inflammatory markers (12 M)	NCT00962923	[34]
SSc (Localized skin)	Human	6 (Case report)	Auto-AD IH	Single	$4–8\times10^6$	Disease stabilization for all patients and improvement of skin elasticity in 4/6 patients	N/A	[78]
SSc (Finger ulcers)	Human	12 (Phase 1)	Auto-SVF IH	Single	1.4×10^6	Improvement of pain, grasping capacity, finger edema, Raynaud's phenomenon, quality of life	NCT01813279	[89]
SSc (Severe diffuse)	Human	20 (Phase 1/2)	Allo-BM IV	Single	1×10^6/kg, or 3×10^6/kg	Improvement of skin fibrosis (1 Y). Increase of Breg cells ($CD24^{hi}CD27^{pos}CD38^{lo/neg}$ memory B) and IL-10	NCT02213705	[93, 94]
Scl-GVHD	Human	4 (Case report)	Allo-BM IV	4–8 (1–2 W interval)	$1.0–2.0\times10^7$	Improvement of skin stiffness, pigmentation and mRSS (4.6–23 M). Increase of Th1 cells, IFN-γ, IL-2, and decrease of Th2 cells, IL-10, IL-4 (2 W)	N/A	[10]
Scl-GVHD	Human	1 (Case report)	Allo-UC + rituximab IV	Twice (0, 3 W)	2×10^6/kg	Improvement of skin sclerosis in the abdomen and extremities (3 W). Disappearance of skin sclerosis, pigmentation, and other skin involvement (4 M)	N/A	[121]
cGVHD	Human	10 (Phase 1)	Allo-BM IV	Single	1×10^6/kg	Improved skin response in 1/5 patients with clinical improvement (2 W)	NCT01318330	[30]
cGVHD	Human	9 (Phase 2)	Allo-BM IV	≥ 6 (4–6 W interval)	2×10^6/kg	Improved quality of life, and reduced requirements of traditional immunosuppressive drugs (12 M). Almost complete disappearance of epidermal lesions in 6/9 patients (34–99 M)	NCT01522716	[95]

Table 1 (continued)

Animal Model	Subject	MSC source and route of Injection	Frequency (time)	Dose	Main results	Mechanisms	References
Bleomycin-induced skin fibrosis mouse	Animal	syngeneic BM IH	Daily (4 W)	1×10^6	Improvement remodeling matrix responsible for normal collagen arrangement in skin. Reduction of inflammation and α-SMA$^+$ myofibroblasts	Down-regulation of TGF-β, collagen I and HSP47 expression	[97]
HOCl-induced SSc mouse	Animal	Syngeneic/Allo-BM, or human ASCs & BM-MSCs IV	Single or twice (0, 21 D)	2.5×10^5	Reduction of fibrotic, inflammatory and oxidative markers in skin & lungs. Improvement of matrix remodeling	N/A	[33]
Type 1 tight skin (Tsk1) mouse	Animal	Allo-BM IV	8 W	1×10^5/kg	Improvement of osteopenia	Down-regulation of the IL-4R pathway by miR-151-5p in MSC-EV	[122]
Bleomycin-induced skin fibrosis mouse	Animal	Trx-1-overexpressing BM-MSCs IH	Daily (3 W)	1×10^6	Reduction of skin fibrosis and apoptosis, promotion of BM-MSC survival and differentiation into endothelial cells	TRX1-mediated inhibition of oxidative stress	[75]
Bleomycin-induced skin sclerosis mouse	Animal	human micro-fat + SVF IH	Single	0.5 ml micro-fat + 0.0114 ml SVF	Decrease in the established dermal fibrosis and increase in local vascularization	SVF cell pro-angiogenic properties, and the favorable conditions for grafting and survival offered by micro-fat	[98]
Bleomycin-induced skin sclerosis mouse	Animal	Human ADSC-assisted lipotransfer IH	Single	0.3 ml fat + 1×10^6 ADSCs	Improvement of the skin texture and collagen content. Reduced TGF-β1 and collagen III expression	N/A	[99]
Bleomycin-induced skin fibrosis mouse	Animal	Auto-AD IH	Single	2×10^6	Amelioration of dermal fibrosis Reduction of the skin thickness and the total content of hydroxyproline	Down-regulation of TGF-β1 and up-regulation of VEGF	[41]
Bleomycin-induced scleroderma and Scl-GVHD mouse	Animal	Allo-AD IV	Single	2×10^5	Attenuation of skin fibrosis	Suppression of infiltration of CD4+, CD8+T cells and macrophages into the dermis. Reduction of the messenger RNA expression of collagen and pro-fibrotic cytokines in the skin	[42]

Table 1 (continued)

Animal Model	Subject	MSC source and route of Injection	Frequency (time)	Dose	Main results	Mechanisms	References
Bleomycin-induced skin fibrosis mouse	Animal	Allo-AD IH	Single	2.5×10^4	Provision of dendritic cell-derived signals improved survival and effectiveness of therapeutically delivered ADSCs	LTβR-mediated activation of ADSCs in the late stage of fibrosis development	[123]
HOCl-induced diffuse SSc mouse	Animal	healthy murine and human ADSCs IV	Single	2.5×10^5	Decrease in skin fibrotic and pro-inflammatory markers	N/A	[32]

MSC Mesenchymal stem cell, *Ref.* reference, *SSc* systemic sclerosis, *Scl-GVHD* sclerodermatous graft-versus-host disease, *Allo* allogeneic, *Auto* autologous, *BM* bone marrow, *AD* adipose-derived, *UC* umbilical cord, *SVF* stromal vascular fraction, *IV* intravenous injection, *IH* hypodermic injection, *mRSS* modified Rodnan skin score, *PE* plasmapheresis, *N/A* not applicable, *IL* interleukin, *Th* T helper, *IFN-γ* interferon γ, *TGF-β* transforming growth factor-β, *α-SMA* α-smooth muscle actin, *HSP47* heat-shock protein 47, *IL-4R* IL-4 receptor, *MSC-EV* MSC extracellular vesicle, *Trx-1* thioredoxin 1, *VEGF* vascular endothelial growth factor, *LTβR* lymphotoxin B receptor, *HOCl* hypochlorite, *M* month, *W* week, *D* day

dependence of MSC efficacy demonstrated in both preclinical and clinical studies [33, 114]. Currently, the most common injection dose for treating SSc and Scl-GVHD with MSCs is 1×10^6/kg [4, 30, 34, 91]. However, it is worth noting that the relationship between doses and efficacy is not always linear, and the effective dosage range of MSCs should be determined based on clinical application [115]. An animal study has shown that the efficacy of MSC for skin fibrosis is inversely proportional to the dosage administered. In a study conducted on HOCl-induced SSc mice using three different doses of MSC (2.5×10^5, 5×10^5, and 1×10^6), MSCs administered at a dosage of 2.5×10^5 showed the most potent antifibrotic effects [33]. On the contrary, there are some significant issues in some research concerning MSCs, where the principal mechanism of anti-fibrosis, immunosuppressive potential, is affected by the dose. Such investigations indicated that the higher the dosage, the stronger the ability of MSCs to inhibit the proliferation, activation, and maturity of T and B cells [52, 116, 117]. The immune efficacy of MSCs will disappear if the infusion is below 10^4 [116]. Further research is necessary to establish a more precise dose gradient that can account for the formation of this apparent contradiction. Intravenous injection (IV) and hypodermic injection (IH) are the two most common routes for SSc administration. Considering the increased workload of managing extensive skin lesions of SSc and Scl-GVHD, IV is the main route compared to IH. Nevertheless, it is worth noting that MSCs tend to drain into lymphatic organs rather than entering the target organs such as skin through IV [118]. In contrast, IH can effectively reach skin lesions and has the potential to prolong the survival of MSCs. Consequently, IH may be an excellent alternative for lSSc, which involves relatively localized skin lesions and without the excessive difficulty of operation at the same time. Therefore, IV may be more suitable for dSSc, where IH is more challenging to administer. Additionally, early administration and multiple doses are recommended for a long-lasting outcome and the long-term success rate of MSC therapy. Early injection of MSC after allogeneic hematopoietic stem cell transplantation can reduce the severity of Scl-GVHD in several ways, manifested as decreasing skin scores, histopathological scores, skin thickness, skin fibrosis, as well as the mRNA expression level of Col-1 and Col-3 [13]. Since neither SSc nor Scl-GVHD is a rapidly curable disease and the efficacy of MSCs is not once and for all, repetitive intermittent infusions are required to maintain the therapeutic efficacy. In HOCl-induced mouse models of SSc, a single infusion of MSC on day 0 can restrain the progression within one week. However, reinfusion on day 21 can further consolidate and prolong the inhibition of skin thickening and fibrosis markers expression [33]. Likewise, early and multiple interventions have been shown to yield better long-term effects in most cases, including models of heart, liver fibrosis, and HOCl-induced pulmonary fibrosis [88]. Therefore, the administration intervals for Scl-GVHD are typically fixed at 1–2 weeks [10], with a recommended total duration of at least one year [119, 120].

The interaction between MSCs and immunosuppressants

The combination of MSC and immunosuppressants in the treatment of autoimmune-related fibrotic skin diseases has shown positive trends in several clinical studies [124]. In vitro studies or animal experiments have also demonstrated potential beneficial interactions between MSCs and immunosuppressants [125, 126]. MSCs mitigate the adverse effects of immunosuppressive drugs on T cell subsets [126–128], promoting the expression of anti-inflammatory Treg cells and inhibiting the expression of pro-inflammatory T cell subsets [129]. AD-MSCs enhance the immunosuppressive effect of cyclosporine A on T cells through the inhibition of jagged-1-mediated NF-kB signal [129] MSCs can counteract the up-regulatory impact of immunosuppressants, such as MMF and dexamethasone, on pro-inflammatory T cell subsets such as Th-17 cells. They can even attenuate the expression of inflammatory factors like IL-17. MSCs significantly enhance the down-regulatory impacts of immunosuppressants on IL-4 while collaborating with cyclosporine A and glucocorticoids to diminish the quantity of T-bet-positive cells [127]. Although immunosuppressants interfere with MSCs' function (proliferation, migration, etc.) [130–134], they barely affect the immunosuppressive properties and even prolong the duration of MSCs in vivo [126, 135, 136]. Both cyclosporine and dexamethasone are reported to enhance the promoting effect of MSC on Treg cell expression [126]. In addition, cyclophosphamide can improve the survival rate of MSCs [126], while dexamethasone extends the retention period of MSCs in vivo and mitigates apoptosis of MSCs [137–140]. Although further validations are required, the combination therapy involving MSCs still represents a promising method to reduce immunosuppressant doses while maintaining or potentially enhancing treatment outcomes [126, 127].

Conclusions

It has become increasingly evident that MSCs and MSC-EVs are advantageous in treating autoimmune-related fibrotic skin diseases (SSc and Scl-GVHD). These therapies have shown particular promise in three main areas: (1) rebalancing immune and inflammatory disorders, (2) enhancing antioxidant defenses, and (3) inhibiting overactivated fibrosis. The safety of MSC-based therapy in

clinics has been proved, and it is considered as a potentially effective option for treating SSc and Scl-GVHD. However, several questions remain unresolved. More evidence is needed to compare effectiveness of h-MSCs and SSc-MSCs, as well as MSCs combination therapy and immunosuppressant therapy alone. Further investigations are required to determine the optimal therapeutic dosage range and frequency and duration of infusions for individual patients. Another question, might be addressed by studying skin lesions, is whether generalized IV or localized IH is a more suitable treatment for the disease. Finally, randomized controlled trials that systematically assess the correlation between in vitro and in vivo mechanisms, may provide more definitive evidence on theoretical mechanisms underlying the efficacy of MSC-based therapy.

Abbreviations

SSc	Systemic sclerosis
Scl-GVHD	Sclerodermatous graft-versus-host disease
MSCs	Mesenchymal stem cells
iNOS	Inducible nitric oxide synthase
Trx-1	Thioredoxin 1
TGF-β	Transforming growth factor-β
EV	Extracellular vesicle
cGVHD	Chronic GVHD
Th	T helper
IL	Interleukin
α-SMA	α-Smooth muscle actin
ECM	Extracellular matrix
Col-1	Collagen I
Col-3	Collagen III
Treg	T regulatory
CCL	Chemokine ligand
CCR	Chemokine receptor
ADSCs	Adipose-derived stem cells
TNF-α	Tumor necrosis factor-α
MCP-1	Monocyte chemotactic protein 1
BAFF	B-cell activating factor of the TNF family
UC	Umbilical cord
PD-L1	Programmed death-ligand 1
IL-4Rα	IL-4 receptor α
IDO-2,3	Indolemine 2,3-dioxygenase
TSG-6	Tumor necrosis factor α stimulated gene 6
PGE-2	Prostaglandin E2
BM	Bone marrow-derived
HOCl	Hypochlorite
IFN-γ	Interferon γ
COX	Cyclooxygenase
CXCL2	Chemokine (C-X-C Motif) ligand 2
EPCs	Endothelial progenitor cells
vWF	von Willebrand factor
VEGFR	Vascular endothelial growth factor receptor
VE	Vascular endothelial
VCAM1	Vascular cell adhesion molecule 1
PDGFRB	Platelet-derived growth factor receptor B
SM22α	Smooth muscle 22 α
SDF-1	Stromal cell-derived factor 1
CXCR4	CXC receptor 4
TGFβR-II	TGF-β receptor II
AOPP	Advanced oxidation protein product
SOD	Superoxide dismutase
T-AOC	Total antioxidant capacity
NO	Nitric oxide
AOC	Antioxidant capacity
MMP	Matrix metallopeptidase
HGF	Hepatocyte growth factor
TIMP	Tissue inhibitors of metalloproteinase
PTEN	Phosphatase and tensin homolog
Bcl	B cell lymphoma
Dnmt3α	DNA methytransferase 3α
h-MSC	Healthy-originated allogeneic MSC
SSc-MSC	SSc patient-originated autologous MSC
IV	Intravenous injection
IH	Hypodermic injection
lSSc	Limited cutaneous SSc
dSSc	Diffuse cutaneous SSc
Ref.	Reference
Allo	Allogeneic
Auto	Autologous
AD	Adipose-derived
SVF	Stromal vascular fraction
mRSS	Modified Rodnan skin score
PE	Plasmapheresis
N/A	Not applicable
HSP47	Heat-shock protein 47
LTβR	Lymphotoxin B receptor
M	Month
W	Week
D	Day

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