

REVIEW

Mesenchymal stem cell therapy for attenuation of scar formation during wound healing

Wesley M Jackson^{1,2}, Leon J Nesti^{1,3} and Rocky S Tuan^{4*}

Abstract

Scars are a consequence of cutaneous wound healing that can be both unsightly and detrimental to the function of the tissue. Scar tissue is generated by excessive deposition of extracellular matrix tissue by wound healing fibroblasts and myofibroblasts, and although it is inferior to the uninjured skin, it is able to restore integrity to the boundary between the body and its environment. Scarring is not a necessary process to repair the dermal tissues. Rather, scar tissue forms due to specific mechanisms that occur during the adult wound healing process and are modulated primarily by the inflammatory response at the site of injury. Adult tissue-derived mesenchymal stem cells, which participate in normal wound healing, are trophic mediators of tissue repair. These cells participate in attenuating inflammation in the wound and reprogramming the resident immune and wound healing cells to favor tissue regeneration and inhibit fibrotic tissue formation. As a result, these cells have been considered and tested as a likely candidate for a cellular therapy to promote scar-less wound healing. This review identifies specific mechanisms by which mesenchymal stem cells can limit tissue fibrosis and summarizes recent *in vivo* studies where these cells have been used successfully to limit scar formation.

Introduction

Adult human skin is limited in its ability to repair itself following injury that penetrates beyond the epidermis. The cutaneous wounding healing process results in the formation of a scar that is composed of excess extracellular matrix (ECM) in the place of the normal dermal tissue. Besides having a different visual appearance,

which can be undesirable, the tissue in the vicinity of the scar does not function like the surrounding skin, as it does not contain many of the structures that are native to the dermis, including sebaceous glands, hair follicles and sensory nerve receptors [1]. The scar tissue is also limited to approximately 80% of the tensile strength of the surrounding skin [2] and results in a weak point that is susceptible to re-injury. However, scar formation is not required for cutaneous healing, as wound healing occurs in the absence of scarring throughout most of fetal development (reviewed in [3]). There has been considerable scientific effort to understand the mechanism of cutaneous scar formation with the goal of developing potential therapies to promote scar-less wound healing.

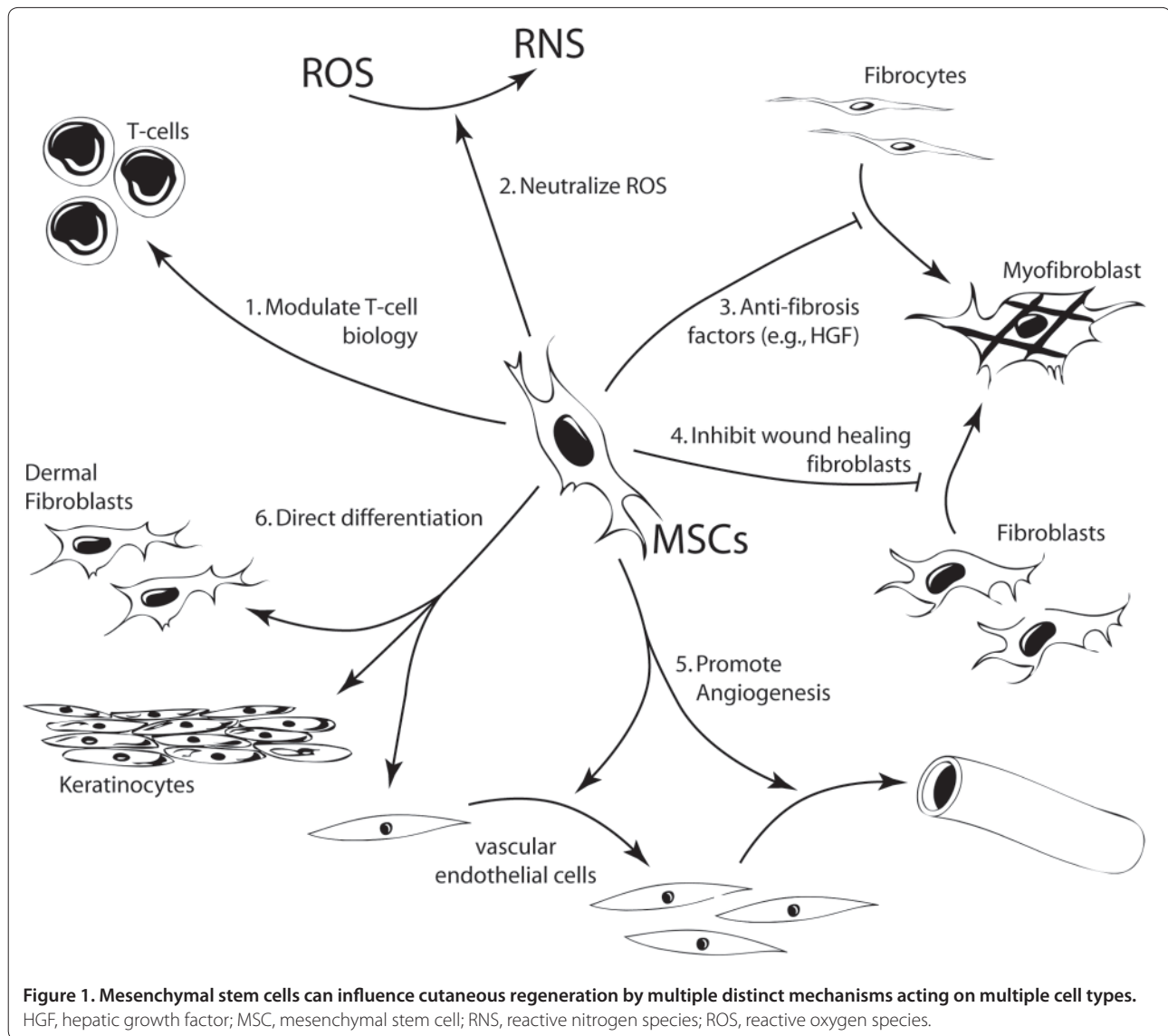
Despite the deleterious consequences of fibrosis and scar tissue formation, current treatments to promote scar-less wound healing are primarily limited to the standard principles of wound management. These include the use of topical antibiotics and sterile dressing in order to minimize the risk of infection to advance the wound healing process through the inflammatory phase and into the cellular proliferation and remodeling phases [1], where functional tissue regeneration can occur. Irrigation and debridement of the wound may be applied as necessary to remove foreign bodies and necrotic tissue that can promote tissue inflammation [4]. If the inflammatory phase is prolonged, the pro-inflammatory mediators will direct the wound healing cells, such as myofibroblasts and fibrocytes, in generating the non-functional, void-filling tissue that will result in the formation of a scar [5].

Mesenchymal stem cells (MSCs), which appear to be a native constituent of the wound bed [6], have emerged as an alternative to the standard pharmaceutical treatment modalities. These cells are important trophic mediators to promote tissue regeneration and can be readily derived from a variety of autologous or allogeneic adult tissues, as well as from commercial providers [7]. The versatility of these cells has made them an attractive candidate for clinical translation in a variety of therapeutic applications. In particular, MSCs may offer the means of recapitulating several mechanisms that are sufficient for inhibition of scar formation in skin wounds (Figure 1).

*Correspondence: rst13@pitt.edu

⁴Center for Cellular and Molecular Engineering, Department of Orthopaedic Surgery, University of Pittsburgh School of Medicine, 450 Technology Drive, Room 221, Pittsburgh, PA 15219, USA

Full list of author information is available at the end of the article



This review will provide an overview of current research into cutaneous wound healing with an emphasis on specific mechanisms by which MSCs may enhance functional tissue regeneration.

Anti-scarring mechanisms of mesenchymal stem cells

MSCs are a broadly generalized cell type that can be found in a variety of adult tissues throughout the body and exhibit specific characteristics when cultured *in vitro* [8]. In particular, MSCs must be capable of robust *ex vivo* expansion and maintain the ability to differentiate into osteoblasts, adipocytes and chondrocytes. Many recent studies have also demonstrated that MSCs exhibit a number of trophic functions to enhance tissue regeneration, such as promoting angiogenesis and modulating the

inflammatory response (reviewed in [9]). Originally harvested in the adherent fraction of cells in a bone marrow aspirate [10], MSCs have since been identified in a variety of other adult tissues, including adipose tissue [11,12], the marrow space of long bones [13,14], trabecular bone chips [15-17], periosteum [18,19], synovial fluid [20-22], periodontal ligament [23,24], palatine tonsil [25], parathyroid gland [26], fallopian tube [27] and traumatized muscle tissue [28,29]. MSCs have also been harvested from prenatal tissues that are lost as a result of development, such as umbilical cord [30,31], umbilical cord blood/Wharton's Jelly [32,33] and primary tooth dental pulp [34,35]. There is a growing body of evidence to suggest that a substantial fraction of the cells exhibiting the *in vitro* characteristics of MSCs arise from vascular pericytes *in vivo* [36], suggesting that there is a common

precursor cell type in a wide variety of adult and fetal tissues. Given their regenerative functions, availability and potential for cell banking [37], there is immense interest in developing cellular therapies based on auto-genous or allogeneic MSCs

The basic biology of wound healing has been extensively studied (reviewed in [1]), and MSCs are clearly capable of responding and modulating their function when exposed to the cells and biochemical factors that are characteristic of an injury environment. Human MSCs migrate preferentially to regions of inflammation [38] and express several chemokine receptors that are necessary to coordinate their homing ability [39]. Furthermore, MSCs have demonstrated chemotaxis toward a variety of wound healing cytokines *in vitro*, including platelet-derived growth factor, insulin-like growth factor-1, IL-8 and TNF α [40,41]. These data suggest that bone-marrow-derived MSCs or endogenous cells resembling MSCs, such as pericytes, are likely to migrate to and participate in the response to tissue injury.

There is ample evidence based on murine models of injury and disease to demonstrate that systemically administered allogeneic MSCs are capable of homing to and engrafting at the site of tissue damage [42,43]. Several recent studies have further quantified the extent of bone marrow-derived MSC involvement during wound healing. A chimeric mouse model was developed to evaluate MSCs by lethally irradiating female C57BL/6 mice, followed by replacement with fluorescently labeled MSCs from male BALB/c mice in the bone marrow [44]. These mice demonstrated gradual engraftment of the donor cells in the dermis as the bone marrow-derived MSCs participated in the process of dermal regeneration, and fluorescent cells in the regenerated tissue also exhibited markers of dermal fibroblasts. Furthermore, the number of green fluorescent protein-labeled cells in the dermis increased approximately 400% in regions that experienced cutaneous injury [45], suggesting that recruitment from the bone marrow occurred at the site of wound healing. As with other populations of marrow stromal cells, the mobilization of MSCs appears to be dependent on systemic levels of granulocyte-colony stimulating factor (G-CSF), and homing to the site of injury is dependent on local expression of stromal cell-derived factor (SDF)-1 [46]. Exogenous administration of either G-CSF or SDF-1 is sufficient to increase MSC recruitment to the site of injury and corresponds to enhanced wound healing at the sites of MSC recruitment.

One likely function of MSCs in the process of wound healing is to regulate the function of the leukocytes that have invaded the tissue in response to injury [47,48]. Once the MSCs enter the inflammatory environment, their immunomodulatory phenotype becomes activated by IFN γ , TNF α and IL-1 β [49]. The ability of MSCs to

regulate T-cell recruitment, proliferation and activity is well documented [49,50]. There is also evidence that MSCs are capable of suppressing the proliferation of B cells [51] and natural killer cells [52], thereby ameliorating the acute immune response to injury. By attenuating the function of these cell types, the MSCs would likely reduce the pro-fibrotic responses that can occur coincident with prolonged inflammation during wound healing [53,54]. However, a variety of other likely mechanisms by which MSCs could suppress fibrosis and the formation of scar tissue are discussed below.

Modulation of macrophage and T-cell function during wound healing

During the transition between the inflammatory and proliferation stages of wound healing, macrophages resident in the wound undergo a change in phenotype to an alternative activation (M2) state. IL-4 and IL-13 are the archetypical activators of the M2 phenotype [55], and there is evidence that IL-4 may be produced by mast cells that migrate from the margins into the wound bed during this stage of healing [56]. The precise alternative phenotype of the macrophages during cutaneous wound healing has not been fully defined, as the M1/M2 macrophage model varies somewhat between tissue types [57]. However, alternative macrophage activation is generally characterized by decreased expression of pro-inflammatory cytokines accompanied by an increase in anti-inflammatory signaling [57]. This shift in inflammatory modulation is accompanied by the expression of cytokines that promote tissue regeneration, such as heparin bound epidermal growth factor (HB-EGF), fibroblast growth factor (FGF)-2 and vascular endothelial growth factor (VEGF) [1]. HB-EGF signaling to keratinocytes provides additional stimulus to promote re-epithelialization and the formation of a new epidermal layer [58]. FGF-2 and VEGF promote the proliferation and migration of fibroblasts and endothelial cells into the fibrin clot [59].

The inflammatory environment of the wound activates the MSCs to initiate their immunomodulatory functions, including an increase in cyclooxygenase-2 activity and up-regulation of prostaglandin E₂ (PGE2) expression [60], which has multiple fibroregulatory effects on the wound. In particular, PGE2 plays a necessary role in the immunoregulatory mechanism of the MSCs to inhibit the expression of IL-2 [61] and attenuate mitogenesis and proliferation of T cells in the wound [62]. PGE2 is also a co-factor in the transition from T_H1 cells into T_H2 cells [63], corresponding to a decrease in the expression of INF γ and up-regulation of IL-4 by the effector T cells [64]. The decreasing ratio of INF γ relative to IL-4 in the wound promotes functions that are associated with the alternative activation of macrophages [65], which favor wound

healing over inflammation and promote the activity of mesenchymal cells during the proliferation stage (reviewed in [55]).

PGE2 expression results in other indirect fibroregulatory effects by interacting with immune cells that are resident in the wound. In response to PGE2, T cells [66] and macrophages [60] become reprogrammed and begin to express higher levels of IL-10, an important anti-inflammatory cytokine with multiple functions to limit or attenuate the inflammatory mechanism of immune cells [67]. IL-10 is a powerful inhibitor of neutrophil invasion into the wound and prevents further oxidative tissue damage from their release of reactive oxygen species (ROS) [68]. IL-10 may also have direct effects on fibrosis by down-regulating the expression of transforming growth factor (TGF) β 1 in macrophages and T cells [67], and reprogramming wound fibroblasts to favor ECM remodeling by up-regulating the expression of matrix metalloproteinases (MMPs) and down-regulating the expression of collagens [69]. IL-10 also prevents excessive collagen deposition by attenuating the expression of pro-inflammatory cytokines in the wound, such as IL-6 and IL-8 [70]. As a result of these mechanisms, expression of IL-10 contributes to a resolution of the inflammatory stage and acceleration of the wound into the proliferation stage [71]. The role of IL-10 in fibroregulation has been verified by demonstrating that scar-less wound healing can be abrogated in fetal mice by knocking out IL-10 [70], and then over-expression of IL-10 in post-natal skin generates a permissive environment where wound healing is more likely to occur with the absence of scar formation [72].

Neutralization of reactive oxygen species in the wound

MSCs substantially up-regulate the expression of inducible nitric oxide synthase in response to their interaction with T cells in a pro-inflammatory environment. Nitric oxide is complementary to PGE2 for the inhibition of T-cell proliferation [73], but there is evidence that it has other, more direct mechanisms to prevent the formation of scar tissue. ROS secreted by neutrophils, including superoxide, hydrogen peroxide and alkyl peroxides, are highly cytotoxic compounds used to achieve wound sterility, but these ROS are also intensifiers of collagen deposition [74]. Prolonged ROS exposure during wound healing leads to enhanced fibrogenesis and accumulation of fibrotic tissues through a mechanism involving membrane lipid oxidation and induction of TGF β 1 [75]. Nitric oxide produced by MSCs in the wound can scavenge ROS to produce reactive nitrogen species, such as peroxynitrite [76]. Although these reaction products are also oxidative and cytotoxic, they react more slowly than their associated ROS [77] and prevent oxidative damage to DNA and membrane lipids [76]. A recent study has

demonstrated that inducible nitric oxide synthase expression is sufficient to alter the ROS/RNS balance to prevent the formation of fibrotic tissues [78].

Mesenchymal stem cells produce anti-fibrotic factors

MSCs secrete a variety of cytokines and growth factors that have anti-fibrotic properties, including hepatocyte growth factor (HGF), IL-10 and adrenomedullin [79-81]. The anti-fibrotic properties of IL-10 have been described earlier in this paper. HGF has also been shown to attenuate fibrosis and scar formation through a variety of mechanisms. Fibroblasts respond to HGF by down-regulating their expression of TGF β 1 [82], collagen type I [83] and collagen type III [82], as HGF receptor binding antagonizes downstream signaling cascades [83] and promotes the nuclear exclusion of SMAD 3, the transcription factor associated with many pro-fibrotic genes [84]. HGF also stimulates the up-regulation of MMP-1, MMP-3 and MMP-13 expression in fibroblasts [85], thereby promoting the turnover of the ECM. In addition to fibroregulation of fibroblast function, HGF promotes keratinocyte migration, proliferation [86], and up-regulates their expression of VEGF-A [87]. Therefore, the expression of HGF contributes to the generation of a high-quality, well-vascularized granulation tissue and enhanced re-epithelialization of the wound [86].

There is also evidence for an additional anti-fibrotic mechanism of HGF by contributing to the inhibition of myofibroblast differentiation. Although contraction may facilitate re-epithelialization by narrowing the wound margin for alignment of ECM components [1], this process does not necessarily require fully differentiated myofibroblasts. Fetal wound healing occurs in the near absence of myofibroblasts [88]. Furthermore, during oral epithelial wound healing, which is characterized by high levels of HGF and keratinocyte growth factor, rapid wound contraction occurs in the absence of robust myofibroblast commitment and yields less scar tissue compared to cutaneous wound healing [89]. TGF β 1 is a potent driver of myofibroblast differentiation, and high levels of TGF β 1, which is often related to a prolonged acute inflammatory response, can lead to over-contraction, formation of tight collagen bundles and excessive matrix deposition with the visual appearance of a scar. In diseases caused by excessive fibrosis, HGF appears to resist the differentiation of fibroblasts into myofibroblasts [90], thereby limiting the pro-fibrotic functions that are characteristic of these cells.

Mesenchymal stem cells enhance dermal fibroblast function

During the proliferation stage of wound healing, dermal fibroblasts from the wound margin proliferate and migrate into the wound, generate granulation tissue, and

begin to remodel the wound matrix to generate new dermal tissue. However, there are additional sources of fibroblasts that may be recruited to participate in these wound repair processes, as is warranted by the extent of the injury. In response to elevated levels of TGF β 1, endothelial cells from damaged blood vessels may be encouraged to undergo epithelial-to-mesenchymal transition (EMT) and become wound healing myofibroblasts [91]. Fibrocytes may also be recruited into the wound due to prolonged inflammatory response or when the wound matrix cannot be rapidly converted into granulation tissue [92], and the fibrocytes rapidly differentiate into myofibroblasts in the presence of TGF β 1 and T cells [93]. Although these generic wound-healing fibroblasts may be needed to restore integrity of the skin after some types of injury, they produce excessive amounts of ECM compared to dermal fibroblasts, and they are more likely to yield a tissue with the visual appearance of a scar [94]. MSCs resident in the wound can inhibit EMT by producing HGF [95] and PGE2 [96], and they can resist myofibroblastic differentiation as described in the previous section. MSCs also produce paracrine factors that promote specific wound healing functions of dermal fibroblasts [97]. These combined mechanisms enable MSCs to regulate the cells populating the wound to favor resident wound healing cells to produce an ECM that more closely resembles the surrounding dermal tissue.

Mesenchymal stem cells promote angiogenesis and vascular stability

Angiogenesis is a necessary process during the proliferation phase of wound healing to provide the fibroblasts with sufficient nutrient supply for the production of a provisional granulation matrix [98]. Failure to generate an adequate microvascular network leads to deficiencies in wound closure and may develop into a chronic non-healing wound. Equally important is the need to stabilize the provisional vessels as the tissue remodels and to form a permanent vascular network. In addition to macrophages and fibroblasts, MSCs produce basic FGF and VEGF-A, which provide powerful mitogenic cues to promote proliferation, migration and differentiation of microvascular endothelial cells [99,100]. MSCs also express paracrine factors to promote vascular stability and vasoprotection [101,102], including adrenomedullin [103]. It has been hypothesized that these functions are unique to MSCs due to their possible perivascular origin, and they are able to exploit these functions to recreate their perivascular niche as the process of vasculature remodeling is concluded [104]. Enhancement of vascular formation by bone-marrow-derived MSCs has been demonstrated *in vitro* [105] and to facilitate the development of long-lasting functional vasculature as perivascular progenitor cells [106].

Mesenchymal stem cells differentiate into dermal cell types

MSCs are typically characterized based on their ability to differentiate into osteoblasts, adipocytes and chondrocytes *in vitro*. It is likely that MSCs in the wound environment may assume a phenotype that resembles that of the resident dermal fibroblasts or myoblasts, and this differentiation process has been recapitulated *in vitro* [107]. More interesting and relevant is recent evidence demonstrating that MSCs may trans-differentiate to epidermal cells, keratinocytes and microvascular endothelial cells under defined conditions *in vitro* [39,108,109]. Finally, MSCs may also trans-differentiate into keratinocytes under conditions that allow them to interact with native epidermal cells [110]. These studies suggest that MSCs could participate directly in the structural regeneration of dermal and epidermal tissues, thus representing an additional mechanism by which the MSCs may promote cutaneous wound healing.

Conclusions and future perspectives

In this review, we have highlighted many recent scientific findings that illustrate the cellular mechanism by which MSCs participate in and enhance the process of wound healing with the potential to minimize the formation of scar tissue. Although it is unlikely that MSCs can replicate the mechanisms of scar-less wound healing that occur in fetal dermal tissues, they may still re-initiate or promote some of the processes that characterize fetal wound healing. There is also emerging evidence that MSC phenotype can be polarized by inflammatory environments, and suggests a paradigm for MSC function mirroring similar behavior in T cells and macrophages [111]. These studies indicate that MSCs respond to inflammatory cytokines by modulating the expression levels of Toll-like receptors, thereby attenuating the immunosuppressive biochemical signaling that is typical of MSC populations [112]. A better understanding of how MSCs interact with and regulate the resident immune cells in the wound will facilitate their clinical translation for wound healing applications.

In a recent review [113], we have summarized the recent pre-clinical and clinical studies designed to evaluate MSCs as a cell therapy to improve wound healing, and a summary of these studies is provided in Table 1. Based on a variety of small and large animal studies, a growing body of evidence suggests that MSCs provide significant benefit during dermal wound healing, as they can (1) accelerate the rate of wound closure and re-epithelialization, (2) improve the quality and strength of the regenerated tissue, (3) recover wound healing pathologies that might otherwise result in a chronic, non-healing wound, and (4) minimize the visual appearance of scar tissue. In spite of these encouraging pre-clinical findings, there are currently only four active clinical trials

Table 1. *In vivo* outcomes of wound healing augmented by mesenchymal stem cell therapy

Experimental details	Accelerated wound closure	Improved tissue strength	Prevented chronic ulceration	Improved visual appearance	Reference
Murine MSC conditioned medium Topical delivery Splinted excisional wounds in mice	✓				[80]
Allogenic and syngenic murine MSCs Injection into the wound Excisional wounds in mice	✓				[43]
Murine MSCs Injection into the wound Excisional wounds in db/db mice	✓		✓		[116]
Rat ASCs Injection into the wound Excisional wounds in diabetic rats	✓		✓		[117]
Murine MSCs Injection into the wound margin Splinted excisional wounds in db/db mice	✓		✓	✓	[110]
Human MSCs Injection into wound Incisional wounds in rabbits		✓		✓	[118]
Human V53/2 MSC cell line Seeded on collagen scaffolds Splinted excisional wounds in mice	✓			✓	[119]
Human MSCs Incorporated in fibrin spray Chronic and acute wounds in humans	✓		✓	✓	[120]
Swine MSCs Injection into the wound Thermal wounds in mini pigs	✓			✓	[108]
Murine MSCs Systemic injection Excisional wounds in mice	✓				[39]
Rat MSCs Systemic injection Excisional wounds in rats	✓	✓			[121]

ASC, adipose-derived stem cell; MSC, mesenchymal stem cell.

pertaining to the treatment of dermal wounds with MSCs [114]. This is evidence of several substantial barriers that still exist that limit the clinical translation of MSCs, including a scalable cell-sourcing platform, a means of cell delivery (reviewed in [115]), and a predictable regulatory framework. In this review, we have brought attention to the promise of MSCs as a therapy to improve cutaneous wound healing and the need for new technologies to overcome these barriers and enable the clinical use of MSCs in wound healing applications.

Abbreviations

ECM, extracellular matrix; FGF, fibroblast growth factor; G-CSF, granulocyte-colony stimulating factor; HB-EGF, heparin bound epidermal growth factor; HGF, hepatocyte growth factor; IFN, interferon; IL, interleukin; MMP, matrix metalloproteinase; MSC, mesenchymal stem cell; PGE₂, prostaglandin E₂; RNS, reactive nitrogen species; ROS, reactive oxygen species; SDF, stromal cell-derived factor; TGF, transforming growth factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

Competing interests

The authors declare that they have no competing interests.

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Author details

¹Clinical and Experimental Orthopaedics Laboratory, Department of Surgery, Uniformed Services University, Bethesda, MD 20814, USA. ²The Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda, MD 20817, USA. ³Orthopaedic Research Group, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD 20892, USA. ⁴Center for Cellular and Molecular Engineering, Department of Orthopaedic Surgery, University of Pittsburgh School of Medicine, 450 Technology Drive, Room 221, Pittsburgh, PA 15219, USA.

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