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**Progress and expectation of stem cell therapy for diabetic wound healing**

Xu ZH *et al*. Diabetic wound and wound healing

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**Abstract**

Impaired wound healing presents great health risks to diabetics. Encouragingly, the current clinical successfully found out meaningful method to repair wound tissue, and stem cell therapy could be an effective method for diabetic wound healing with its ability to accelerate wound closure and avoid amputation. This minireview aims at introducing stem cell therapy for facilitating tissue repair in diabetic wounds, discussing the possible therapeutic mechanism and clinical application status and problems.

**Key Words:** Stem cell; Diabetic wound; Wound healing; Immunoregulation

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**Core Tip:** Diabetic wound is a common complication of diabetes and stem cell therapy is an effective treatment for diabetic wounds. It helps improve wounds mainly by regulating inflammation and blood circulation. At present, many kinds of stem cells have been used and studied, and good results have been achieved. However, there are still problems that need to be solved. Here we discuss the current role and progress of stem cells in the treatment of diabetic wounds.

**INTRODUCTION**

Diabetes with neurological abnormalities as well as peripheral artery disease of the lower extremities[1] can lead to diabetic wounds, particularly diabetic foot ulcers, which are considered one of the most serious complications. The international diabetes federation (IDF) reported that in 2021, there were nearly 536.6 million people living with diabetes[2], and the global diabetic foot ulcer prevalence was 6.3%[3]. Due to some risk factors, including poor glycemic control, peripheral neuropathy, peripheral vascular disease and immunosuppression[4], the progression of diabetic wounds can be accelerated, often resulting in complications demanding an amputation. At present, the treatment for diabetic wounds includes improving vascularization, debridement with pharmacological therapy, negative pressure wound therapy or using growth factors and skin substitutes, aiming at epithelial growth across the ulcer bed[4-7].

Stem cell therapies for wounds have vast prospects by using autologous or allogeneic stem cell transplantation for wound closure. It has been shown to help at all stages of wound healing and plays an important role in inflammation regulation, increasing both epithelialization and angiogenesis[8-11]. This minireview concentrates on the progress of stem cell therapy for facilitating tissue repair in diabetic wounds.

**POSSIBLE** **MECHANISM OF STEM CELL THERAPY**

Diabetes patients often suffer hyperglycemia, chronic inflammation, microvascular and macrovascular dysfunction, autonomic and sensory neuropathy, hypoxia and impaired neuropeptide signaling[12]. Necroptosis and apoptosis can be inreased by reactive oxygen species (ROS), advanced glycation end products and methylglyoxal, leading to diabetes complications[13]. Long term hyperglycemia leads to metabolic disorders because of the activation of additional polyol glucose metabolic pathway and the accumulation of toxic sorbitol in nerve tissue cells increases, leading to vascular damage[14,15]. With diabetic peripheral neuropathy as well as peripheral artery disease playing a central role, diabetes patients frequently suffer diabetic foot ulcer[16]. At present, stem cell therapies have been reported to contribute to diabetic wound healing in the following ways.

**POSSESSING THE FUNCTION OF ANGIOGENESIS**

First, stem cells help secrete vascular endothelial growth factor (VEGF), which promotes angiogenesis and the differentiation of endothelial progenitor cells into endothelial cells[17] and the extracellular matrix through the PI3K/threonine kinase (AKT) signaling pathway[18,19]. And they increase epithelialization, granulation tissue formation and capillary formation[20]. In a high glucose environment, stem cell-secreted exosomes contribute to angiopoiesis in endothelial progenitor cells, and overexpression of the transcription factor nuclear factor-E2-related factor 2 synergizes as a protective factor[21]. Moreover, including angiopoietin-1 (Ang-1), stromal cell-derived factor 1, inducible nitric oxide synthase (iNOS), epidermal growth factor (EGF), keratinocyte growth factor 2, erythropoietin, insulin-like growth factor 1 (IGF-1), basic fibroblast growth factor and placental growth factor, there are still many paracrine cytokines helping angiopoiesis, improving microcirculation in diabetic foot ulcer[22-24].

**MODULATING INFLAMMATION**

Stem cells are able to switch classically activated macrophages, which are called M1 macrophages and have proinflammatory effects, into optionally activated macrophages, which are called M2 macrophages and have anti-inflammatory effects[8,25-27]. In addition, it has been shown that together with exosomes, stem cells can decrease oxidative stress injuries of endothelial cells, providing immunomodulatory effects[28], and the level of Tregs is also upregulated at the same time[29,30]. Cytokines also play an important role in inflammation, and stem cells have the ability to lower the levels of proinflammatory cytokines, including interleukin-1 (IL-1), IL-6, IFN-β and TNF-α, while increasing the levels of anti-inflammatory cytokines, such as IL-10 and IL-4[31,32]. In a recent study mesenchymal stromal cells (MSCs) expressing IL-6, signaled by activating STAT-3 transcription factor, inhibited ROS by protecting neutrophils from apoptosis, preserving the excessive or inappropriate activation of the oxidative metabolism[33].

**IMPROVING THE REMODELING PHASE**

By cell differentiation, stem cells can translate into keratinocytes as well as endotheliocytes[34]. It has been reported that microvesicles from stem cells help to reprogram injured cells, thus achieving differentiation[35]. Recent studies have shown that stem cells might offer an important early signal to dermal fibroblast responses for their proliferation and migration[9,18]. Additionally, they lower the levels of matrix metalloproteinase-9 (MMP-9) to decrease proteolysis[36]. By reducing expression of phosphorylated focal adhesion kinase and increase the levels of MMP-2, EGF and IGF-1, MSCs improve the function of keratinocytes[37].

**REGULATION OF MICRORNAS**

MicroRNAs (miRNAs) have been discovered regulators of gene expression in the regulation of inflammation[38]. Generally, miRNAs promote wound healing by activating multiple pathways directly or indirectly. For example, after MSC treatment it is found that the increased levels of miR-146a result in attenuating expression of proinflammatory and inflammatory genes, including IL-1 receptor-associated kinase 1 (IRAK1), TNF receptor-associated factor 6 (TRAF6), and nuclear factor-κB (NF-κB)[39]. MSCs also enhance diabetic wound healing by improving collagen I content through increasing miR-29b expression[36]. A research has revealed that miR-21-5p promoted angiogenesis through upregulations of vascular endothelial growth factor receptor, activations of serine/ AKT and mitogen-activated protein kinase[40]. In addition, miR-126-3p from MSCs contributes to wound healing by increasing the formation of granulation tissue and angiogenesis[41]. MiRNA mediates the cell microenvironment, regulates the biological activity and phenotype of specific target cells, induces changes in the function of target cells, and leads to a series of biological reactions to play a variety of biological functions[42,43].

In conclusion, stem cells accelerate diabetic wound healing in many ways. Nevertheless, more connections between stem cells and diabetic wounds are under exploration.

**STEM CELL THERAPIES FOR DIABETIC WOUNDS IN CLINICAL WORK**

Over the past few years, it has been revealed that different types of stem cell therapies have been used in clinical work[44], as shown in Table 1. Although clinical data drew the conclusion that using stem cells benefits diabetic wounds, various types of stem cells with diversified methods still need to be identified. Attention should be given to adverse effects that have appeared in some research. For example, increased exudation from diabetic wounds may be associated with stem cells[45]. However, some clinical studies and analyses support its safety[46-48]. There are several types of cells used in clinical work. For example, adipose-derived mesenchymal stromal cells (ADMSCs) have been proven to be able to accelerate the time to wound closure[49] and the level of wound healing[50]. By intravascular and intralesional injection, umbilical cord mesenchymal stromal cells (UCMSCs) can not only improve the completion of wound closure[51] but also increase the number of vessels[52]. One case in which bone marrow mesenchymal stem cells (BMMSCs) were used for diabetic wound healing showed a good result in the next 10 years[53]. In addition, it has been revealed that BMMSC therapy might be better tolerated and more effective than bone marrow-derived mononuclear cells (BMMNCs) for increasing lower limb perfusion and promoting foot ulcer healing in diabetic patients with critical limb ischemia[54]. By treating with different doses of granulocyte colony stimulating factor (G-CSF), peripheral blood stem cells can be gained to promote the establishment of collateral circulation[55].

Although stem cell therapy has been shown to be a relatively safe treatment for diabetic wounds, unavoidable transplantation complications have appeared in diabetics, including febrile neutropenia, alopecia and gastrointestinal reaction[56]. A clinical trial reported one diabetes patient died of pseudomonas sepsis in the course of neutropenia after autologous hematopoietic stem cell transplantation[57]. Thus, complications as well as adverse events still can’t be ignored while the safety of stem cell transplantation has been reported in some studies[58].

**CONCLUSION**

Stem Cell therapy could be an effective treatment for diabetic wounds[59,60], which contains endless medical value together with a wide scientific perspective accelerating diabetic wound healing. Stem cells have also demonstrated their therapeutic potential in the field even if infection is present[61]. However, there are still problems that need to be solved.

First, the mechanisms of stem cell therapy are still considered as a vital part of the theoretical basis of clinical study. Although animal experiments and clinical trials provide us with great results, studies based on the molecular level should be carried out to gain more molecular mechanisms.

Second, the safety of treatment cannot be ignored, although only a few adverse events have been reported, which urges more clinical trials. At the same time, more specific therapeutic doses and administration routes should be revealed, which accounts for how to reduce side effects and adverse reactions. For example, on account of its differentiative capacity, surgical dressing with stem cells may have the ability to decrease bleeding as well as accelerate operative incision closure, since it has been reported that advanced dressings for the delivery of progenitor cells are at the point in research[62]. Moreover, considering patients with cancer who cannot receive stem cell treatment[63], alternative solutions need to be identified.

Third, it is still important for physicians to simplify the approach of gathering as well as preconditioning stem cells because preconditioning MSCs with pretreatment agents significantly hastened healing in delayed-healing wounds[64]. In addition, evidence has shown that the ability of stem cells in elderly people to proliferate and differentiate diminishes with age[65]. Therefore, the differences between autotransplantation and allotransplantation should be taken into consideration to improve the success rate of transplantation.

Last, the questions of ethics also matter. Promising and effective stem cell therapy has raised serious ethical problems[66]. Not only do social responsibility and moral constraints regularize approaches of treatment, but relevant laws and medical guidelines also need to be improved.

The answers to these questions will lead to better and more appropriate treatments for different patients.

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**Table 1 Recent clinical trials regarding stem cell therapies for diabetic wounds**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Type of stem cells** | **Number of cases** | **Mean age (year)** | **Methods of treatment** | **Possible mechanism** | **Outcome** | **Adverse events** | **Conciusion** |
| Uzun *et al*[49], 2021 | ADMSCs | 10 | 57.5 | Intralesional injection | The release of angiogenic cytokines, increasing epithelialization, granulation tissue formation, anti-inflammatory, and anti-apoptotic effects | Time to wound closure (d): ADMSCs group (*n* = 10): 31.0 ± 10.7; Control group (*n* = 10): 54.8 ± 15.0; *P* = 0.002 | No found | Allogeneic ADMSCs injection is a safe and effective method with a positive contribution to wound-healing time in the treatment of chronic diabetic foot ulcers |
| Suzdaltseva *et al*[51], 2020 | UCMSCs | 31 | 58.5 | Intralesional injection | The release of angiogenic cytokines, cell differentiation, and immunomodulation | Complete wound closure or significant improvement (% in group)a: UCMSCs group (*n* = 59): 22%; Placebo group (*n* = 49): 8.2%; *P* < 0.05 | No found | Locally delivered allogeneic UCMSCs can contribute to chronic wound repair and provide an additional support toward new therapeutic strategies |
| Moon *et al*[50], 2019 | ADMSCs | 30 | 59.9 | Topical | Synthesizing higher amounts of collagen, fibroblast growth factor, and vascular endothelial growth factor in vitro | Complete wound closure at Week 12 (% in group): ADMSCs group (*n* = 30): 82%; Control group (*n* = 29): 53%; *P* < 0.05 | No found | Allogeneic ADMSCs might be effective and safe to treat diabetic foot ulcers |
| Chen *et al*[53], 2018 | BMMSCs | 1 | 64 | Intramuscular injection | The release of angiogenic cytokines, differentiation and angiogen | No recurrence in the next 10-yr follow-up span | No found | Autologous BMMSC transplantation therapy may be an effective measure for recurrent bullosis diabeticorum |
| Qin *et al*[52], 2016 | UCMSCs | 28 | 75 | Intravascular and intralesional injection | The release of signalling or growth factors, and differentiation of injected precursor cells into functional tissue | Increased number of vessels: Experimental group (*n* = 28): 9.3 ± 2.7; Control group (*n* = 25): 5.9 ± 3.3; *P* < 0.05 | No found | UCMSC transplantation after angioplasty is a safe and effective clinical therapy for severe diabetic foot |
| Xu *et al*[55], 2016 | Peripheral blood stem cells | 63 | 69 | Intralesional injection | Angiogenesis and vascularization | CTA scoreb: Pre-transplantation (*n* = 63): 1.22 ± 0.15; Post-transplantation (*n* = 63): 2.35 ± 0.784; *P* < 0.01 | No found | Autologous peripheral blood stem cell transplantation can promote the establishment of collateral circulation in patients with diabetic foot |
| Lu *et al*[54], 2011 | BMMSCs | 18 | 63 | Intramuscular injection | The release of angiogenic cytokines, differentiation and angiogenesis | Angiographic score of MRA in limbs at 24 wkb: BMMSCs (*n* = 18): 1.9 ± 0.5; BMMNCs (*n* = 19): 1.5 ± 0.6; *P* = 0.018 | No found | BMMSCs therapy may be better tolerated and more effective than BMMNCs for increasing lower limb perfusion and promoting foot ulcer healing in diabetic patients with critical limb ischemia |

a108 patients, including 31 patients (28.7%) suffering from diabetic foot, were randomized to the umbilical cord mesenchymal stromal cell group and placebo group.

b0 points, no new collateral vessels; 1 point, little new collateral circulation; 2 points, moderate new collateral circulation; 3 points, abundant new collateral circulation.

ADMSCs: Adipose-derived mesenchymal stromal cells; UCMSCs: Umbilical cord mesenchymal stromal cells; BMMSCs: Bone marrow mesenchymal stem cells; CTA: Computed tomography angiography; MRA: Magnetic resonance angiography; BMMNCs: Bone marrow-derived mononuclear cells.



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