

Advances in the Role of Stem Cell-Derived Exosomes in Diabetic Foot Wound Healing

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Abstract: Chronic hyperglycemia over a long period can lead to diabetes-related complications, of which diabetic foot ulcers continue to have a huge economic and social impact worldwide. Mesenchymal stem cell-derived exosomes (MSC-Exos) have demonstrated positive efficacy in the preclinical research and clinical trial phases of diabetic foot ulcer (DFU) treatment. In this review, we provide a brief overview of the properties of MSC-derived exosomes and their biological functions, summarize the therapeutic efficacy of Exos in the treatment of diabetic foot ulcers and its mechanism of action, and discuss innovative technologies including hydrogel scaffolds and 3D bioprinting to enhance the effectiveness of MSC - Exos in the treatment of diabetic foot ulcers. This paper also explores the application of innovative technologies such as hydrogel scaffolds and 3D bioprinting in enhancing the efficacy of MSC-Exos in the treatment of diabetic foot ulcers and highlights the key challenges faced in translating these advanced technologies from the laboratory to the clinic.

Keywords: stem cell-derived exosomes, chronic wounds, diabetic foot ulcers, tissue engineering, translational research

Introduction

Diabetes is a chronic metabolic disorder characterized by elevated blood glucose levels.^{1–3} When blood glucose is not effectively controlled for a long period, it can lead to a variety of complications, among which DFU is one of the serious and common complications.^{4–6} Hyperglycemia contributes to DFUs through several mechanisms: first, long-term hyperglycemia induces neuropathy, leading to loss of protective sensation in the foot, making patients insensitive to trauma or pressure, and thus susceptible to foot injuries; second, hyperglycemia also leads to vasculopathy, which reduces the blood supply to the foot and affects wound healing. In addition, hyperglycemia also weakens immune function and increases the risk of infection, further aggravating ulcer formation and development.^{7–9} These factors work together to greatly affect the quality of life of patients. About 6.3% of the world's diabetic population suffers from DFU, and more than half of all diabetic patients are at risk of DFU. According to statistics, the global healthcare expenditure on DFU treatment reaches up to \$40 billion per year, putting enormous economic pressure on national healthcare systems.^{10,11} Currently, the treatment of DFU relies on traditional approaches such as glycemic control, anti-infective therapy, topical care, and surgery.^{12,13} However, these treatment modalities often have limited effectiveness, and there is an urgent need to develop and explore safe and effective therapeutic strategies.

MSC treatment of DFU has achieved significant results in preclinical studies and clinical trials, but has not been widely used in routine clinical treatment.^{14–16} Numerous studies have shown that stem cells promote the healing process of DFU through multiple mechanisms, including promoting wound healing, enhancing angiogenesis, and inhibiting inflammation.^{17,18} However, the exact mechanism of stem cell therapy for DFU has not been fully clarified. It has been found that the therapeutic effect of stem cells is not only through their differentiation potential but also through their paracrine effects. Paracrine action refers to the secretion of bioactive factors by stem cells, such as cytokines, microRNA exosomes, etc. These released substances can promote tissue repair and regeneration by regulating the local

microenvironment.^{19–21} Among the substances released by stem cells, exosomes, as a key component, play an important role in promoting cell migration, proliferation, and differentiation.²²

In recent years, Mesenchymal Stem Cell-derived Exosomes (MSC-Exos) have become an important research direction for DFU therapy due to their great potential in tissue repair and regeneration.^{23–25} It has been shown that exosomes deliver biological signals and regulate cellular functions through interactions with target cells, which in turn promote wound healing.^{26–28} Therefore, MSC-Exos is considered a promising treatment for DFU.

This review focuses on the role and mechanism of exosomes from different sources of stem cells in improving diabetic wound healing and enhancing the effectiveness of stem cell exosomes in treating DFUs from the perspective of tissue engineering to provide more promising candidates and ideas for the treatment of diabetic wound healing.

Biological Properties of Stem Cell Exosomes

Sources and Mechanisms of Secretion

Exosomes are nanovesicles with a diameter of about 30–150 nm.^{29–31} It was first discovered in 1983 when Harding et al³² were studying erythrocytes and stumbled upon the discovery that the cells secreted tiny vesicles, which were not simply cellular waste products, but were formed by periplasmic ectasia and had specific biological functions. It was not until 1996 that the concept of exosomes was widely recognized and clarified by the scientific community. Exosomes contain many biologically active substances, such as proteins, RNA, lipids, etc, which can regulate target cells through intercellular transduction.^{33,34} In addition, a distinctive feature of stem cell exosomes is their ability to carry biomolecules from source stem cells and deliver these substances to target cells, thus exerting a variety of biological effects, such as promoting tissue repair, anti-inflammation, and immune modulation.³⁵ The formation of exosomes begins with the endocytosis of cell membranes to form endosomes, which contain many extracellular substances inside. During maturation, endosomes are transformed into multivesicular bodies, in which small endosomes are encapsulated within large vesicles. The multivesicular body has multiple small vesicle-like vesicles, which contain many exosomes that will be secreted. When the multivesicular body matures, it fuses with the cell membrane and releases the inner vesicles outside the cell, ie, exosomes^{36–39} (see Figure 1). After formation, exosomes can be taken up by target cells and can participate in intercellular communication through receptor-ligand interaction, direct membrane fusion, and endocytosis.⁴⁰

In characterizing and analyzing MSC-Exos, we usually use the following techniques: transmission electron microscopy (TEM) for observing the morphological features of exosomes and confirming their typical cup structure;

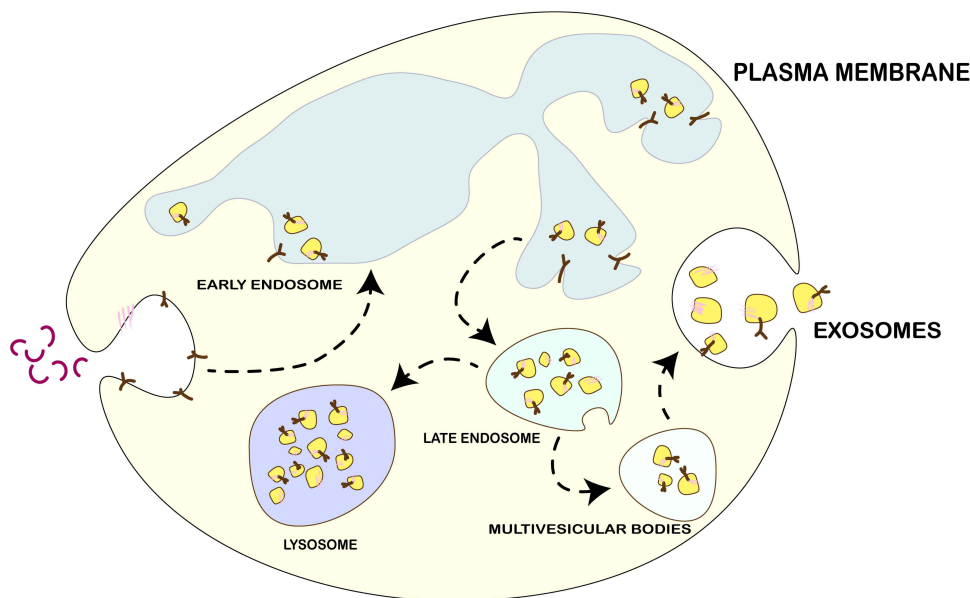


Figure 1 Biogenesis of exosomes.

nanoparticle tracking analysis (NTA) for determining the size distribution and concentration of exosomes; and protein blotting (Western blotting) for confirming the identity and purity of exosome-specific proteins by identifying them to confirm their identity and purity.^{41,42}

Biological Functions

Stem cell exosomes are involved in intercellular communication and signaling regulation.⁴³ Stem cell exosomes can regulate the function of target cells by carrying bioinformatic substances that transmit information between cells. They also selectively deliver signaling molecules to target cells by binding to specific receptors.^{44,45} In addition, RNA molecules in exosomes can be transcribed and expressed in target cells, thereby altering cellular biological behaviors such as proliferation, migration, and differentiation.^{20,46,47} Stem cell exosomes can also promote tissue repair and regeneration.^{22,48,49} They can promote cell proliferation, migration, and tissue repair, especially in the healing process of chronic wounds such as diabetic wounds. Secondly, stem cell exosomes promote neoangiogenesis and improve the repair and regeneration of ischemic tissues by regulating endothelial cell proliferation, migration, and lumen formation.^{50–52} In addition, stem cell exosomes have anti-inflammatory effects, which can reduce the local inflammatory response, regulate the function of immune cells, inhibit the secretion of pro-inflammatory cytokines, and avoid excessive inflammatory response at the wound.^{53,54} In addition, engineered stem cell exosomes can be used for drug delivery and gene therapy.^{55,56} Exosomes can carry small-molecule drugs, and their natural biocompatibility and targeting properties make them ideal drug carriers. In addition, stem cell exosomes repair or replace specific genes by loading molecules such as mRNA, siRNA, shRNA, etc, to treat diseases associated with genetic defects.⁵⁷ In addition, stem cell exosomes have antioxidant effects.⁵⁸ Exosomes released from stem cells are enriched with a variety of antioxidant enzymes, including superoxide dismutase, catalase, etc, which can scavenge reactive oxygen species, thus reducing cellular damage caused by oxidative stress.^{59,60}

Mechanisms of Stem Cell Exosomes in the Treatment of Diabetic Foot Wounds

Inflammation Regulation

Excessive inflammatory response of the wound is a major cause of DFU, and abnormal macrophage polarization and cytokine overexpression can lead to a persistent inflammatory state of the wound and may also trigger secondary peripheral tissue injury.^{8,61} Therefore, regulation of wound inflammation is one of the important targets for DFU therapy. In recent years, more and more studies have proven that many MSC-Exos can reduce the inflammatory response and promote wound healing.^{62,63} MSC-Exos as a potential therapeutic tool provides new hope for the clinical treatment of DFU.

Inhibition of Inflammatory Factors

MSC-Exos can regulate the expression of inflammatory factors by modulating the local immune response of the wound, thus inhibiting excessive inflammatory response. Yan et al⁶⁴ showed that under hyperglycemic conditions, exosomes released from human umbilical cord mesenchymal stem cells significantly reduced the expression of inflammatory factors such as IL-6, IL-1 β , and TNF- α , thus avoiding excessive inflammatory response. In addition, Wang et al⁶⁵ found that adipocyte-derived MSC-Exos could attenuate the inflammatory response by inhibiting the release of IL-27. Taken together, these studies suggest that exosomes isolated from multiple stem cell types can promote wound healing by regulating inflammatory mediators that play a key role in different stages of wound healing.

Macrophage Polarization Induction

MSC-Exos also regulates the phagocyte polarization state and promotes the conversion of M1-type macrophages to M2-type. Macrophages consist of two polarization states, M1 macrophages and M2 macrophages.⁶⁶ M1 macrophages are generally found in the early stage of the inflammatory response and play a pro-inflammatory role.⁶⁷ M2 macrophages, on the other hand, are generally found in the later stages of the inflammatory response and play an anti-inflammatory and pro-wound healing role.⁶⁷ However, in DFU wounds, hyperglycemia continues to stimulate macrophages to secrete large

amounts of pro-inflammatory factors, which leads to the persistence of the M1 phenotype in macrophages at the site of rupture, preventing further wound healing.^{68,69} Therefore, promoting the conversion of M1-type macrophages to M2-type may be an effective option for the treatment of DFU wounds.

Zhu et al⁷⁰ showed that adipose-derived MSC-Exos polarized macrophages to the M2 phenotype, which enhanced angiogenesis. He et al⁷¹ showed that bone marrow-derived MSC-Exos induced macrophage conversion to the M2 phenotype, attenuated inflammation, and promoted wound healing by targeting the PKNOX1 gene via transporter miR-223. Chamberlain et al⁷² found that bone marrow-derived MSC-Exos promoted macrophage conversion to M2 type and exerted inflammation modulation and accelerated tendon healing in a mouse tendon injury model. In addition, Li et al⁷³ showed that adipose-derived MSC-Exos inhibited the macrophage migration inhibitory factor, MIF, and promoted the conversion of M1-type macrophages to M2-type macrophages via miR-451a. Thus, MSC-Exos plays an important immunomodulatory role in diabetic wound healing by regulating the polarization state of macrophages and promoting the conversion of M1-type macrophages to M2-type.

Oxidative Stress Regulation

MSC-Exos reduces oxidative stress, relieves wound inflammation, and accelerates the healing process. Yan et al⁶⁴ showed that human umbilical cord-derived MSC-Exos inhibits the expression of two proteins, NOX1 and NOX, in human umbilical vein endothelial cells, which reduces oxidative stress. Xue et al⁷⁴ demonstrated that adipose-derived MSC-Exos promoted the expression of Nrf2 protein, which inhibited the expression of Nrf2 proteins in human keratinocytes, fibroblasts, and human umbilical vein endothelial cells, thereby reducing the expression of oxidative stress-related proteins and reducing oxidative stress. Zhang et al⁷⁵ showed that adipose-derived MSC-Exos could reduce ROS accumulation, attenuate oxidative stress induced by hyperglycemia, and mitigate inflammatory responses by modulating the SIRT3/SOD2 axis, thereby accelerating wound healing in a diabetes model. In addition, Ren et al⁷⁶ found that adipose-derived MSC-Exos could reduce oxidative stress by releasing eHSP90 protein, and it could lead to accelerated diabetic wound healing.

MSC-Exos has multiple mechanisms in the inflammatory regulation of DFU, including inflammatory factor inhibition, macrophage polarization induction, and oxidative stress regulation. Under the combined effect of these mechanisms, inflammatory overreaction can be avoided and wound healing can be promoted, as well as providing new ideas for the treatment of DFU.

Promote Cell Proliferation, Migration, and Angiogenesis

Promoting cell proliferation and migration, and angiogenesis is crucial in the comprehensive treatment of DFU wounds. Diabetic foot wounds are often associated with chronic inflammation, inadequate blood supply, and impaired cellular function; therefore, promoting the proliferation and migration of fibroblasts and other cells from diabetic patients can help accelerate the healing process.^{77,78} Cell proliferation and migration can promote wound epithelialization, collagen synthesis, and tissue repair, and reduce wound exposure time, thus reducing the risk of infection and complications.^{79,80} Meanwhile, angiogenesis is a key component in wound healing because DFU wounds often lack sufficient oxygen and nutrients due to impaired microcirculation.^{81–83} Therefore, by promoting new angiogenesis, the local blood supply can be improved to provide the necessary nutrients and oxygen for wound repair, thus accelerating healing and reducing the risk of amputation.

Li et al⁸⁴ found that the proliferation and migration of fibroblasts play key roles in wound repair, and MSC-Exos plays a crucial role in stimulating these cellular activities. Li et al⁸⁵ observed by wound scratch assay that adipose-derived MSC-Exos could be taken up by fibroblasts and significantly promoted cell migration in a dose-dependent manner after internalization. Specifically, the migration rate of MSC-Exos-treated fibroblasts increased by approximately 40% ($p < 0.01$) after 24 hours compared with the control group, suggesting a significant promoting effect of MSC-Exos. In addition, MSC-Exos promoted collagen synthesis and upregulated related gene expression. In a mouse skin incision model, adipose-derived MSC-Exos could be recruited to the wound and significantly accelerated skin wound healing. Xue et al⁷⁴ reported that administration of adipose-derived MSC-Exos to a diabetic rat model resulted in increased levels of angiogenic and growth factor expression in wound beds, and led to a significant reduction in the size of foot wound

ulcers in rats. Ma et al⁸⁶ showed that injection of adipose-derived MSC-Exos into rats with total skin defects was found to be taken up by fibroblasts and human umbilical vein endothelial cells, and could promote human venous endothelial cell production and fibroblast proliferation and migration.

Promoting Nerve Regeneration

Patients with diabetes are often associated with neuropathy.^{87,88} Neuropathy may result in sensory loss and neuropathic pain, which together may lead to uneven loading of the foot, increased pressure, and subcutaneous edema, which can increase the risk of falls and foot ulcers⁸⁹ In addition, the nervous system plays an important role in DFU wound healing.⁹⁰ In the treatment of DFU wounds, the promotion of nerve regeneration may favor the healing of ulcer wounds.

Fan et al⁹¹ developed an engineered MSC-Exos carrying miR-146, which was administered systemically to a diabetic mouse model and found to be therapeutically effective for nerve restoration, with significant increases and decreases in nerve conduction velocities as well as thermal and mechanical stimulation thresholds, respectively. Nakano et al⁹² found that in vivo injection of bone marrow-derived MSC-Exos repaired damaged neurons and glial cells. In addition, Singh et al⁹³ reported that bone marrow-derived MSC-Exos was fused with polypyrrole nanoparticles containing liposomes, which were injected into the muscles of rats with a diabetic neuropathy model, and found that nerve conduction velocity and compound muscle action potentials were normalized in the injected rats. In addition, Wang et al⁹⁴ developed a miR-218-carrying adipose-derived MSC-Exos, and treatment utilizing miR-218-carrying MSC-Exos in combination with engineered scaffolds promotes the regeneration of sciatic nerves in a sciatic nerve injury model.

The nervous system is critical for DFU healing, and promoting nerve regeneration facilitates diabetic wound healing. As all of the above studies have demonstrated, engineered MSC-Exos carrying specific miRNAs or in combination with other materials can significantly promote nerve repair and functional recovery in diabetic model animals, providing a new strategy for DFU treatment.

Other

Accumulation of advanced glycosylation end products (AGEs) in DFUs triggers oxidative stress and inflammatory responses, inhibits cell proliferation and migration, and thus impedes diabetic wound healing.^{95,96} Tang et al⁹⁷ treated rat chondrocytes with AGEs to induce cellular damage. Subsequent treatment of damaged chondrocytes with bone marrow-derived MSC-Exos revealed that their exosomes abrogated AGEs-mediated chondrocyte apoptosis. Therefore, treatment targeting AGEs is expected to promote wound repair and provide new ideas for DFU treatment. In addition, bacterial biofilms are widely present in DFUs, which are formed by the encapsulation of a polysaccharide matrix secreted by bacteria and are highly drug-resistant and immune-resistant, significantly increasing the difficulty of treatment. Bacteria in biofilms may release inflammatory factors that trigger chronic inflammation and inhibit cell proliferation and migration.^{98,99} At the same time, the presence of biofilm may also exacerbate local hypoxia, further affecting tissue repair. Therefore, the elimination of bacterial biofilm is a key aspect of DFU treatment. Bakadia et al¹⁰⁰ developed a novel double cross-linked hydrogel based on silk proteins, which contains MSC-Exos, and used it to treat diabetic wounds, and found that biofilm at the wounds became thinner after treatment. In summary, stem cell-derived exosomes can act through multiple mechanisms and therapeutic targets when treating DFU wounds (see [Table 1](#)).

Stem Cell Exosomes from Different Sources for the Treatment of Diabetic Foot Wounds

Umbilical cord mesenchymal stem cell-derived exosomes, bone marrow mesenchymal stem cell-derived exosomes, and adipose-derived mesenchymal stem cell-derived exosomes have many similarities in the treatment of DFU wounds, but the mechanism of action, therapeutic efficacy, and characteristics of the exosomes differ due to their different sources.^{101–104}

For this reason, according to the pathophysiological characteristics of DFU wounds, the selection of MSC-Exos from different sources can better meet the therapeutic needs.

Table 1 The Mechanism of Action and Experimental Model of Mesenchymal Stem Cell Exosomes in the Treatment of Diabetic Foot Ulcers

No.	Year	Exosomes Source	Disease Model	Function	References
1	2022	UCMSCs	Diabetic mouse wound model	Improve oxidative stress, promote angiogenesis, and accelerate wound healing.	[60]
2	2022	ADMSCs	Sepsis-induced Acute Lung Injury	Inhibits IL-27 secretion	[61]
3	2020	ADMSCs	Mouse matrix gel plug and hind limb ischemia model	Inducing macrophage polarization, promoting angiogenesis, and regulating immune responses.	[65]
4	2019	BMMSCs	Cutaneous Wound Healing Model	Promote macrophage polarization, accelerate wound healing, and regulate immune responses.	[66]
5	2019	BMMSCs	Achilles Tendon Transection Model	Promote macrophage induction to M2 type, promote angiogenesis, and regulate collagen tissue	[67]
6	2022	ADMSCs	Skull Defect Model	Regulate the M1/M2 polarization of macrophages to reduce the inflammatory response.	[68]
7	2018	ADMSCs	Diabetic Foot Ulcer Rat Model	Promotes angiogenesis, reduces oxidative stress and inflammation, reduces EPC aging, and accelerates wound healing	[69]
8	2022	ADMSCs	Chronic Diabetic Wounds	Improves oxidative stress, promotes angiogenesis, reduces inflammation, and accelerates wound healing	[70]
9	2022	ADMSCs	Chronic Diabetic Wounds	Promote cell proliferation and migration, enhance angiogenesis, alleviate oxidative stress, and accelerate wound healing.	[71]
10	2021	ADMSCs	Hypertrophic Scar	Inhibits fibroblast activity, reduces collagen deposition and promotes wound healing	[79]
11	2016	ADMSCs	Skin Wound Healing	Promotes cell migration and proliferation, promotes collagen synthesis and reduces scarring	[80]
12	2022	ADMSCs	Full-thickness skin defect wound healing model	Improves wound healing, collagen deposition and new blood vessel formation.	[81]
13	2022	BMMSCs	Diabetic peripheral neuropathy mouse model	Suppress inflammation, improve neurological function, and promote the remyelination of nerve fibers.	[86]
14	2016	BMMSCs	Diabetes-induced cognitive impairment mouse model	Repair damaged neurons and astrocytes, reducing oxidative stress injury.	[87]
15	2021	BMMSCs	A rat model of streptozotocin-induced diabetes was used	Promote nerve regeneration	[88]
16	2022	ADMSCs	Rat Sciatic Nerve Injury Model	Promote the regeneration of the sciatic nerve.	[89]
17	2021	BMMSCs	Osteoarthritis model	Inhibit chondrocyte apoptosis and reduce cell death induced by AGEs.	[92]
18	2023	BMMSCs	Streptozotocin-induced full-thickness skin wound model in diabetic rats	Reduce inflammation, promote angiogenesis, re-epithelialization, and collagen deposition.	[95]

AD-MSCs Exosomes

AD-MSCs exosomes are derived from adipose tissue, can be isolated and cultured from adipose tissue, and have strong regenerative and repairing ability, which has specific advantages in improving the tissue repair of DFU wounds.¹⁰⁵ AD-MSCs' exosomes have a wide range of clinical applications as a non-cellular therapy.

AD-MSCs' exosomes can promote DFU wound healing through anti-inflammation. It inhibits the release of pro-inflammatory factors such as IL-6, TNF- α , and IL-1 β in diabetic wounds.^{74,106,107} In addition, AD-MSCs' exosomes increase the release of anti-inflammatory cytokines such as IL-10.¹⁰⁸ AD-MSCs' exosomes are also enriched with specific miRNAs to control inflammation. Waters et al¹⁰⁹ found that AD-MSCs' exosomes enriched with miR-146a inhibited the NF- κ B signaling pathway, thereby decreasing pro-inflammatory factor release. AD-MSCs' exosomes

induced macrophage M2 polarization. Jiang et al¹¹⁰ showed that microRNA (miR)-30d-5p-enriched AD-MSCs exosomes inhibited macrophage M1 polarization. Wang et al¹¹¹ injected diabetic mice with exosomes of AD-MSCs and found that these exosomes induced macrophage M1 polarization via the JAK/STAT6 signaling pathway. STAT6 signaling pathway induced macrophage M2 phenotypic polarization and induced M2 macrophage proliferation, migration, and adhesion, promoting angiogenesis and hemotransfusion in the ischemic lower limbs of type 2 diabetic mice. AD-MSCs' exosomes also play an important role in regulating oxidative stress, as they can regulate reactive oxygen species (ROS) production and prevent excessive oxidative stress from stimulating wounds.^{112–114} Zhang et al¹¹⁵ showed that adipose tissue-derived MSC-Exos could reduce reactive oxygen species production in human umbilical vein endothelial cells by regulating SIRT3/SOD2 under high glucose conditions, thereby increasing the level of oxidative stress and promoting diabetic wound healing.

AD-MSCs' exosomes also induced cell proliferation and differentiation with angiogenesis. Huang et al¹¹⁶ showed that AD-MSCs' exosomes silencing NFIC were able to promote the proliferation and migration of human venous endothelial cells with vascular proliferation under high glucose conditions by regulating the miR-204-3p/HIPK2 signaling axis. Parvanian et al¹¹⁷ Waveform proteins were loaded into AD-MSCs exosomes, which were engineered to promote the proliferation and migration of fibroblasts as demonstrated by *in vivo* and *in vitro* experiments. Zhou et al¹¹⁸ injected model mice with AD-MSCs exosomes, which were found to promote wound healing, accelerate re-epithelialization, reduce the width of the scar, as well as promote vascular regeneration. In addition, Hsu et al¹¹⁹ found that AD-MSCs' exosomes stimulated resident monocytes/macrophages to secrete more TGF- β 1 and activated the TGF- β /Smad3 signaling pathway, which promoted more proliferation and activation of fibroblasts, and played a role in diabetic wound recovery.

AD-MSCs' exosomes demonstrated significant anti-inflammatory, immunomodulatory, and oxidative stress modulation, as well as cell proliferation and angiogenesis promotion abilities in DFU treatment. In addition, AD-MSCs' exosomes can be obtained by autologous harvesting, which is easier to obtain than exosomes from other stem cell sources. This autologous harvest not only reduces the risk of immune rejection but also lowers the cost of treatment. These features make it more promising for clinical application in DFU trauma.

BM-MSCs Exosomes

BM-MSCs exosomes are derived from bone marrow and are rich in a variety of stem cell growth factors and immunomodulatory factors, which have strong angiogenic and anti-inflammatory effects, as well as strong effects in immunomodulation, and are suitable for DFU wounds accompanied by chronic inflammation and immune abnormalities.

Exosomes from BM-MSCs accelerate the proliferation of diabetic wound cells and thus aid in wound healing. Pomatto et al¹²⁰ compared exosomes from bone marrow-derived MSCs with exosomes from bone marrow-derived MSCs and found that both ADSC- and BMSC-derived exosomes exerted beneficial effects on cells involved in cutaneous wound healing (eg, fibroblasts, keratinocytes, and endothelial cells). Hou et al¹²¹ reported that BM-MSCs' exosomes could enhance the migration and proliferation of human umbilical vein endothelial cells by activating the AKT signaling pathway. Chen et al¹²² showed that BM-MSCs' exosomes can regulate cell viability, proliferation, migration, and vascularization through the PI3K/Akt signaling pathway. In addition, Saccu et al¹²³ found that BM-MSCs' exosomes accelerate wound healing by regulating cell death, inflammatory response, and angiogenesis in injured tissues. In addition, Lu et al¹²⁴ showed that high levels of BM-MSCs' exosomal MiRNA-29a could be taken up by human umbilical vein endothelial cells and promote their proliferation, migration, and tube formation. BM-MSCs' exosomes also inhibited diabetic wound inflammatory response. Geng et al¹²⁵ prepared a carboxyethyl chitosan-dialdehyde carboxymethylcellulose hydrogel loaded with bone marrow-derived MSC-Exo for the treatment of diabetic wounds and was found to be effective in modulating the inflammatory microenvironment of wounds and promoting the conversion of M1-type macrophages to M2-type, in addition to promoting neovascularization. In addition, BM-MSCs' exosomes have been shown to affect dendritic cells, transforming them into immature and immunosuppressive regulatory dendritic cells. They can inhibit the activation and proliferation of autoreactive T cells by releasing IL-10, and play an immunomodulatory role.¹²⁶

According to previous studies, BM-MSCs' exosomes are able to enhance cell proliferation and migration and promote wound healing by activating signaling pathways such as AKT and PI3K/Akt. In addition, it can regulate the inflammatory microenvironment, promote the conversion of M1-type macrophages to M2-type, inhibit the inflammatory response, and play an immunomodulatory role. These properties give it great potential for application in DFU treatment.

Exosomes of UC-MSCs

UC-MSCs exosomes are derived from umbilical cords, which have strong immunomodulatory and regenerative abilities, and their lower immunogenicity avoids triggering a strong immune response during treatment, which is advantageous in the aspect of DFU wound treatment.

UC-MSCs' exosomes can regulate inflammation and thus promote diabetic wound healing. Yan et al⁶⁴ found that UC-MSCs exosomes could accelerate diabetic wound healing in an in vitro assay by modulating oxidative stress injury in endothelial cells. Xiang et al¹²⁷ injected UC-MSCs exosomes into diabetic rats by the tail vein and found that they could significantly reduce the production of pro-inflammatory cytokines (IL-6, IL-1 β , and TNF- α) in the blood of rats. UC-MSCs' exosomes were injected into the tail vein of diabetic rats and were found to significantly reduce the production of pro-inflammatory cytokines (IL-6, IL-1 β , and TNF- α) in the blood of rats. In addition, exosomes of UC-MSCs can promote cell proliferation, migration, and neovascularization, and enhance the regenerative ability of tissue cells. Liang et al¹²⁸ found that exosomes released from UC-MSCs treated with high glucose, and the circHIPK3 within the exosomes can significantly inhibit apoptosis, and promote cell proliferation, migration, and regeneration of blood vessels. Zhu et al¹²⁹ experiments showed that UC-MSCs exosomes promoted the growth and migration of dermal fibroblasts, and also significantly promoted cutaneous nerve repair, and played an important role in wound healing. These studies indicate that UC-MSCs' exosomes can effectively regulate inflammation, reduce the level of pro-inflammatory cytokines, promote cell proliferation, migration, and neovascularization, enhance tissue regeneration, and promote skin nerve repair (see Table 2). It significantly promotes diabetic wound healing and shows good therapeutic potential.

Table 2 Case Studies of Stem Cell Exosomes from Different Sources in the Treatment of Diabetic Foot Ulcers

No.	Year	Exosomes Source	Disease Model	Function	References
1	2019	ADMSCs	Chronic wound model in mice	Promote angiogenesis, anti-inflammation, and facilitate tissue regeneration.	[105]
2	2018	ADMSCs	Acute Ischemic Stroke Rat Model	Anti-inflammatory and neuroprotective effects	[74]
3	2022	ADMSCs	Ischemia model of lower limbs in type 2 diabetic mice	Inducing macrophage polarization and promoting angiogenesis and blood perfusion.	[106]
4	2022	ADMSCs	A mouse diabetic wound model	Improving oxidative stress and inflammation and promoting angiogenesis	[110]
5	2023	ADMSCs	Diabetic foot ulcer	Improvement of endothelial cell function	[111]
6	2020	ADMSCs	Diabetic wound model	Promote wound healing and regulate autophagy.	[112]
7	2021	ADMSCs	Full-thickness skin defect model in mice	Promote skin wound healing, accelerate re-epithelialization, reduce scar formation, enhance angiogenesis, and increase collagen synthesis.	[113]
8	2022	ADMSCs	Diabetic mouse full-thickness skin wound healing model	Increases collagen synthesis and promotes skin wound healing in diabetic mice	[114]
9	2021	BMMSCs	Diabetic mouse full-thickness skin wound healing model	Increase the number of blood vessels, enhance epithelial thickness, and promote re-epithelialization.	[115]
10	2013	BMMSCs	Diabetic mouse full-thickness skin wound healing model	Promote angiogenesis and wound healing.	[116]

(Continued)

Table 2 (Continued).

No.	Year	Exosomes Source	Disease Model	Function	References
11	2022	BMMSCs	Corneal injury model induced by alkali burn in mice	Promote corneal repair, enhance epithelial cell survival, and facilitate wound closure.	[118]
12	2020	BMMSCs	Osteoporosis model	Promote angiogenesis and osteogenesis.	[119]
13	2022	BMMSCs	Type 1 diabetes rat model	Promote angiogenesis, regulate inflammation, and accelerate wound healing.	[120]
14	2020	UCMSCs	STZ-induced type 1 diabetes rat model	Reduce inflammation, promote angiogenesis, and alleviate renal fibrosis.	[122]
15	2023	UCMSCs	Type 2 diabetes model	Promote cell proliferation, migration, and tube formation, and inhibit cell apoptosis.	[123]
16	2022	UCMSCs	Full-thickness skin defect mouse model	Promote the proliferation and migration of fibroblasts, enhance the secretion of nerve growth factor, and accelerate wound healing.	[124]

Stem Cell Exosome Composite Bioscaffold Material for the Treatment of Diabetic Foot Wounds

Exosomes released by stem cells contain a variety of bioactive substances inside, such as proteins and RNA, which can play an important role in DFU wound repair. However, the half-life of exosomes in wounds is too short, which seriously hampers their repair efficacy. For this reason, researchers have turned their attention to composite bioscaffold materials. The slow release of exosomes through the scaffold material allows it to act on the wound continuously and stably and forms a support structure at the wound to provide physical support for the exosomes. In DFU wound treatment, combining MSC-Exos with the scaffold material complex can play a synergistic role in accelerating DFU wound healing.

Hydrogel Scaffolds

The composition and structure of hydrogels are similar to the natural extracellular matrix and are biocompatible. In addition, hydrogels have slow-release properties, as they release exosomes slowly, allowing for a sustained and stable effect on the wound. Because of these properties, many scientists have developed composite scaffolds based on hydrogels.

Shi et al¹³⁰ developed and prepared a multifunctional hydrogel based on gallic acid-conjugated chitosan and partially oxidized hyaluronic acid, with which they piggybacked MSC-Exos of hypoxic bone marrow origin. The composite scaffolds constructed by them were found to improve the stability of the exosomes, enable stable and sustained release of the exosomes, and increase the efficiency of the exosomes' uptake by target cells. Han et al¹³¹ developed A composite hydrogel of filipin and filaggrin proteins to harbor human umbilical cord-derived MSC-Exos, which showed good wound healing promotion effects. Peng et al¹³² developed a multifunctional hydrogel scaffold combining chitosan-grafted dihydrocaffeic acid, benzaldehyde-capped Pluronic[®]F127, tannins, and adipose-derived MSC-Exos. Derived MSC-Exos to form a hydrogel network, this composite hydrogel scaffold significantly accelerated diabetic wound healing. In addition, Wu et al¹³³ constructed a composite excipient of chitosan hydrogel and adipose-derived MSC-Exos and demonstrated that exosomes could be slowly released from the dressing with the degradation of chitosan hydrogel and accelerated skin wound healing. These findings suggest that the hydrogel scaffold improves exosome stability, enhances target cell uptake efficiency, and significantly accelerates diabetic wound healing. Hydrogel encapsulation enhances exosome stabilization and retention at the wound site through physical and chemical methods. Physical methods include adsorption of exosomes into the hydrogel through non-covalent interactions, while chemical methods stabilize the binding of exosomes to the hydrogel matrix through covalent cross-linking or self-assembling peptide cross-linking. In addition, the tissue adhesion and shape adaptation properties of hydrogels can further improve exosome retention at the

wound site and promote wound healing. Moreover, its low immunogenicity and easy preparation make it show a broad application prospect in DFU treatment, and it is expected to become an effective new treatment.

3D Bioprinted Scaffolds

3D bioprinting is an advanced biotechnology that combines biomaterials, biomolecules, and living cells to print biomedical structures that create three-dimensional structures of tissues and organs by depositing biomaterials layer by layer.^{134–136} The use of 3D bioprinting technology enables personalization and precise construction of scaffolds according to the shape, depth, and size of DFU trauma, which is conducive to precise treatment.¹³⁷ 3D bioprinting technology offers higher precision and complex structure building capabilities compared to traditional scaffold manufacturing techniques, enabling personalization while operating under cell-friendly conditions to improve cell activity and biocompatibility. In addition, its rapid prototyping and high throughput characteristics give it an advantage in mass production.¹³⁸ With the deepening of related research, 3D bio-printed scaffolds are expected to become an effective solution for DFU trauma treatment.

Ferroni et al¹³⁹ developed a bioscaffold for carrying the release of MSC-Exos by 3D printing using methacrylate hyaluronic acid bio-ink. The biocomposite scaffold was experimentally found to sustain the release of MSC-Exos and to promote DFU wound healing. Hu et al¹⁴⁰ Utilized extrusion-based 3D printing technology and combined decellularized small intestinal submucosa, mesoporous bioactive glass, and exosomes to create a 3D scaffold dressing. It was found that this composite scaffold dressing could sustain the release of biologically active exosomes and that the scaffold could accelerate wound healing by promoting angiogenesis in diabetic wounds. In addition, Wu et al¹⁴¹ constructed a hydrogel scaffold containing adipose-derived MSC-Exos and nitric oxide using 3D bioprinting, and this composite scaffold could effectively promote the migration and angiogenesis of human umbilical vein endothelial cells.

The above studies indicate that 3D bioprinting technology combined with stem cell-derived exosome scaffolds can effectively carry and release exosomes to promote DFU wound healing and angiogenesis, which has a large clinical application prospect. Such composite scaffolds provide an innovative model for DFU treatment.

Discussion and Conclusion

MSC-Exos are nanovesicles with diverse biological functions that exhibit important roles in the treatment of DFU. They accelerate the repair process of diabetic wounds through various mechanisms such as modulating the local inflammatory response of wounds, enhancing neoangiogenesis, and promoting cell proliferation. However, despite the promising efficacy of MSC-Exos in laboratory studies, its translation into clinical care still faces many challenges, mainly in terms of regulatory barriers and the need for standardized isolation protocols. On the regulatory side, the lack of uniform standards for the production of MSC-Exos, the imperfect safety assessment, and the fact that global regulators have yet to develop specific guidelines increase the difficulty of clinical application. On the technical side, existing isolation methods are inefficient and poorly scalable, making it difficult to meet clinical needs. Therefore, the development of efficient, reproducible, and scalable separation techniques and the establishment of a standardized production process are key to achieving clinical translation of MSC-Exos. In addition, the delivery route, stability, and targeting of exosomes need to be studied in depth to ensure their safety and efficacy in clinical applications. Currently, clinical trials of exosomes are still in the preliminary stage, and more clinical data are needed to support their therapeutic efficacy and safety in the future.

To further enhance the therapeutic efficacy of MSC-Exos in DFU, many innovative technologies have emerged, such as hydrogel scaffolds and 3D printing technology. Hydrogel scaffolds can provide a favorable microenvironment for the release of exosomes, thus enhancing the therapeutic effect, while 3D printing technology can be used to precisely control the delivery and distribution of exosomes, further enhancing their effectiveness in DFU treatment. The integration of these technologies is expected to provide more possibilities for personalized treatment in the future.

Although MSC-Exos shows promising prospects in DFU therapy, there are still many challenges in its technological translation and clinical application. First, the preparation process and quality control of exosomes should be strengthened to ensure their efficiency and consistency in the production process. Second, a safer and more effective delivery system should be explored to improve the targeting and stability of exosomes. Finally, interdisciplinary cooperation should be strengthened, such as the combination of biomaterials, nanotechnology, and clinical medicine, which will pave the way for the clinical application of MSC-Exos.

In summary, MSC-Exos shows a large clinical application prospect in the treatment of DFU. With continuous technological advances and intensive research, MSC-Exos have been shown to have great therapeutic potential, promising to change the existing treatment landscape 490-49.

Acknowledgments

The authors gratefully acknowledge the support from the Shenzhen Platform of Trauma Rescue and Regenerative Medicine, the Bao'an District Clinical Medical Research Center for Trauma, and the High-quality Development Research Project of Shenzhen Bao'an Public Hospital. We also thank all team members for their dedication and contributions to this work, and look forward to continued collaboration in future research.

Funding

This project was supported by the Sanming Project of medicine in Shenzhen (No. SZSM202106019 and 202208).

Disclosure

The authors report no conflict of interest in this work.

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