



Exosomes from adipose-derived stem cells: A potential therapeutic strategy for diabetic foot ulcers

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Abstract

Diabetic foot ulcers are among the most severe complications of the lower limb in patients with diabetes. As the immune resistance decreases due to the long-term exposure to hyperglycemic microenvironment, the wound often fails to heal, leading to a poor prognosis. Foot ulcers have a high risk of amputation and mortality rates making it a growing health concern. Recently, exosomes derived from adipose mesenchymal stem cells have been shown to promote tissue healing, making them a popular topic in cell-free therapies. This article focuses on the risk factors leading to the development of diabetic foot ulcers and the mechanisms of non-healing with the hope to provide new directions or targets for future diabetic foot ulcer treatment. Additionally, this article clarifies the potential mechanisms of action of exosomes from adipose-derived stem cells in promoting the healing of diabetic foot ulcers and discusses its clinical application and limitations. This review aims to provide effective scientific evidence for research on the mechanism and clinical application of exosomes from adipose-derived stem cells for the treatment of diabetic foot ulcers.

Key Words: Diabetic foot ulcers; Diabetic wounds; Exosomes; Mechanism; Healing

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Core Tip: This review critically analyzes the current state of research on the efficacy of exosomes from adipose-derived stem cells in promoting the healing of diabetic foot ulcers. It offers a comprehensive overview of the risk factors and refractory mechanisms of diabetic foot ulcers and explores the mechanism and application of exosomes derived from adipose stem cells to promote wound healing in patients with diabetes mellitus. This review aimed to provide scientific evidence to support the clinical application of exosomes from adipose-derived stem cells for the treatment of diabetic foot ulcers.

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INTRODUCTION

The skin, as the human body's most extensive organ, serves crucial functions in safeguarding against harsh external influences and warding off pathogens. Under normal physiological conditions, acute wound healing begins immediately after tissue damage, thereby restoring skin integrity. However, it is challenging to heal chronic refractory wounds, such as diabetic ulcers, radiation injuries, and extensive burns, without intervention. Currently, due to the increasing global prevalence of diabetes, the incidence of ulcers in the lower extremities, especially diabetic foot ulcers (DFUs) is continuously rising[1]. DFU is one of the most common serious complications of moderate-to-advanced diabetes. It is usually associated with diabetes-related peripheral neuropathy (DPN), peripheral artery disease (PAD), and other diseases[2]. Approximately 34% of the individuals with diabetes experience delayed healing of diabetic wounds or foot ulcers. Approximately 20% of these patients had to undergo amputation for DFU[3]. The findings of a significant 12-month study indicated that the mortality rate for patients with infectious DFU is as high as 15%, with approximately 17% of patients requiring amputation. The fatality rate for patients with DFUs reaches 70% within 5 years following amputation, and the risk of death from the disease is even greater than that of some malignant tumors[4]. DFU treatment involves many disciplines and requires a systematic and comprehensive treatment based on the control of blood glucose levels. Treatment options include local hypotension, surgical debridement, vascular reconstruction, skin grafting, and auxiliary antibacterial materials. However, these treatments have limitations and drawbacks such as long treatment periods, unclear effectiveness, and high cost, leading to significant physical and mental stress for patients; imposing a heavy burden on medical resources and the economy[5,6]. Therefore, an effective treatment of DFU wounds is deemed urgent. Mesenchymal stem cells (MSCs), a category of mature stem cells, possess the ability to regenerate and diversify into several cell types. They play a role in secreting growth factors, regulating immune and inflammatory responses, and promoting skin growth. This has made them a promising new approach for treating chronic wounds and has provided the field of regenerative medicine with new therapeutic possibilities[7,8]. MSCs are typically present in tissues like fat, bone marrow, and umbilical cord. However, stem cell applications face challenges such as low survival rates, limited homing capacity, tumor risk, immune rejection, and ethical limitations[9]. In recent years, many studies have evidenced that the key mechanism by which MSCs promote wound healing is paracrine, which, can express, synthesize, and secrete a variety of bioactive molecules and extracellular vesicles (EV) through paracrine effects, thus playing a role in tissue regeneration and repair, immune regulation, anti-apoptosis, and other effects[10-13]. Exosomes are a class of nanoscale vesicles released into the extracellular matrix (ECM) when the outer membrane of a multivesicular body fuses with the cell membrane. They mediate cellular communication through the circulatory system and are capable of eliciting inflammatory and metabolic responses. They also have the advantages of stable quality, easy preservation, and no risk of long-term adverse differentiation[14,15]. Exosomes maintain the biology of the original MSCs and exhibit similar therapeutic potential, while avoiding some of the drawbacks associated with stem cell therapy[15-17]. Exosomes from adipose-derived stem cells (ADSC-Exos) have the advantages of abundant sources, easy extraction, and minimal damage, and research in the field of soft tissue regeneration and wound repair has rapidly increased, making them a new hope for the treatment of DFU[18].

This review aimed to elucidate the predisposing factors and pathogenesis of DFU and provide new ideas for therapeutic targets. Simultaneously, we aimed to clarify the putative mechanism of action and therapeutic potential of ADSC-Exos treatment for DFU. To explore the progress and limitations of ADSC-Exos in preclinical studies on DFU treatment and to forecast future directions for cell-free therapies in refractory diabetic wound management, which offer novel treatment approaches.

RISK FACTORS FOR DFUs

DFU is a common complication of diabetes mellitus characterized by a complex etiology, long disease duration, difficulty in healing, susceptibility to infection, and poor prognosis. The interaction of multiple risk factors prevents normal healing of diabetic wounds, causing them to stagnate during the inflammatory stage and form chronic refractory wounds that do not heal for a long time. The most significant risk factors were DPN, PAD, and infection (Figure 1). Other risk factors include foot deformities, age, history of ulcers, uncontrolled hypercholesterolemia, hyperglycemia, plantar pressure

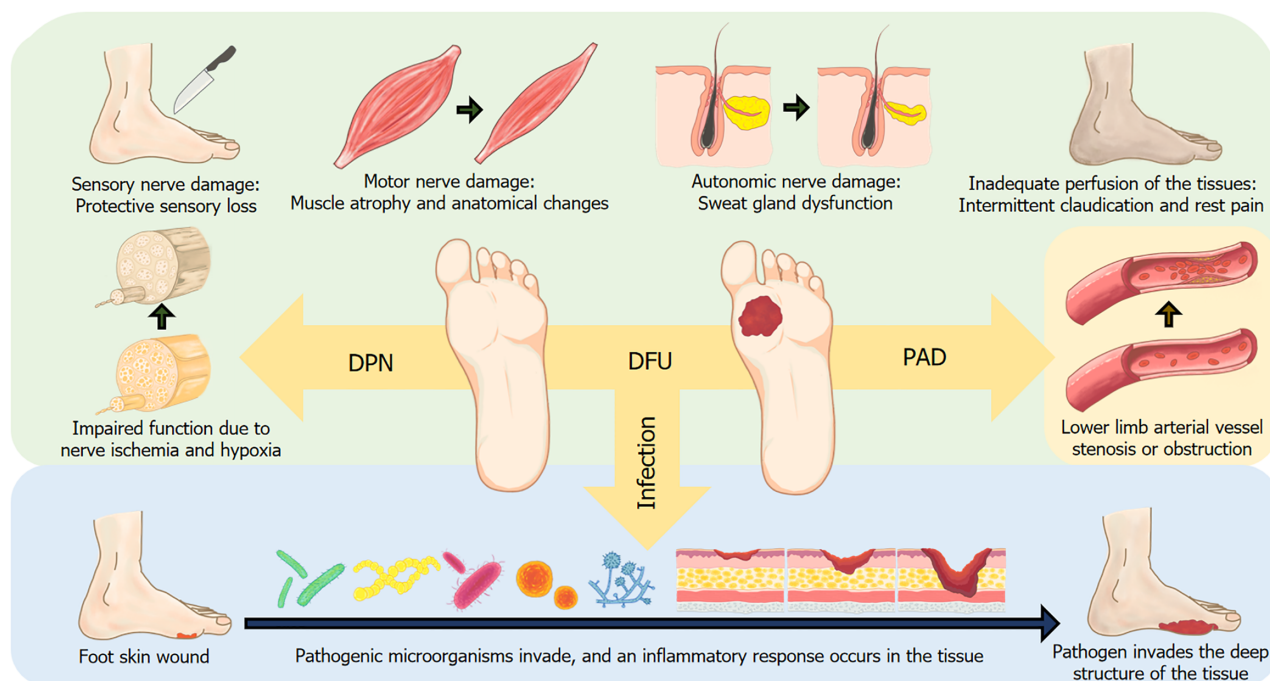


Figure 1 Risk factors for diabetic wound healing. The interaction of multiple risk factors prevents normal healing of diabetic wounds. The most important risk factors are diabetes-related peripheral neuropathy, peripheral artery disease, and infections. DPN: Diabetes-related peripheral neuropathy; DFU: Diabetic foot ulcer; PAD: Peripheral artery disease.

overload, obesity, and calluses[19-21].

DPN

DPN is a chronic microvascular complication of diabetes mellitus in which patients suffer from metabolic and microcirculatory disorders under the influence of a long-term hyperglycemic microenvironment. Eventually, this leads to impaired nerve function and reduced blood perfusion in the distal limbs due to nerve ischemia and hypoxia. DPN is a symmetrical psychiatric disease that causes accumulation of sensory, motor, and autonomic nerves, with the sensory nerves predominantly affected. When the sensory nerves are involved, patients may experience a loss of vibration sensation and superficial sensitivity, making it difficult to detect pain from wounds or mechanical stress. At the same time, atrophy of the anterior calf muscles occurs, resulting in increased pressure on the forefoot when the patient turns over, and ultimately, the formation of refractory ulcers in the case of persistent wound damage[21,22]. Damage to the motor nerves causes foot muscle atrophy and anatomical changes, leading to foot deformity. This factor causes patients to experience changes in gait and uneven foot pressure loads, increasing the risk of skin breakdown[23,24].

In addition, with the combined effect of sensory neuropathy, patient sensitivity to pain decreases, ultimately causing the continuous development of skin ulcers[23]. Autonomic neuropathy can lead to arteriovenous shunts in the subcutaneous vascular network, vasodilatory paralysis, and sweat gland dysfunction, which can lead to drying and keratinization of the skin of the foot, decreasing the skin's ability to protect itself and increasing the risk of breakage and infection[21,25].

PAD

PAD refers to lower-extremity arterial disease, which is not only a manifestation of systemic atherosclerosis but also an independent risk factor for DFU-related amputation[26]. This type of disease leads to narrowing or blockage of the arterial vessels of the lower extremities, resulting in inadequate perfusion of tissues, ischemia and hypoxia of the limbs, intermittent claudication, and pain at rest. Approximately one-third of patients presented with typical symptoms. In the case of continued progression of the disease, progressive dysfunction or disability may occur, leading to ischemic ulcers of the tissues or even amputation[22,27]. Owing to neuropathy, patients with diabetes have reduced sensitivity to PAD and may not experience the typical symptoms of the disease. Consequently, some patients may already have ischemic ulcers or gangrene when they seek medical attention[28]. The probability of healing and prognosis can be effectively assessed by determining the ischemic condition of a patient[3].

Infection

Immune dysfunction in hyperglycemia increases the likelihood of invasion by pathogenic microorganisms, causing an inflammatory response in the tissues. In addition, the risk of foot infections is increased by the combination of neuropathy and PAD, and signs of inflammation may be masked, which further slows the healing process and can have a serious impact on patient's prognosis[29]. Currently, DFU remains one of the leading causes of hospitalization and consultation for diabetes-related complications and is the most common precipitating event leading to lower-extremity amputation[1].

The foot is divided into separate but interconnected compartments, and compartment pressures are increased by the inflammatory response, causing ischemic necrosis and facilitating the spread and progression of the infection[1,30]. Suppose that an infection is not detected or controlled over time. In this case, the pathogen invades from the superficial tissues to deeper structures of the fascia, muscle, bone, and joints, resulting in osteomyelitis[31].

REFRACTORY MECHANISMS OF DFUS

Normal wound healing consists of four dynamic, consecutive, and overlapping phases: Hemostasis, inflammation, proliferation, and remodeling, all of which can lead to delayed or failed healing. The pathogenesis of DUF is complex and associated with a specific wound microenvironment, immune dysfunction, and signal transduction abnormalities. These factors affect the biochemical behavior of the cells involved in wound repair and the speed of healing, causing the wound to stagnate in the inflammatory phase and not move to the next stage, thus impeding tissue repair[32,33].

The formation of advanced glycation end products

Under the stimulation of a long-term hyperglycemic microenvironment, patients experience glucose metabolic dysfunction. In a non-enzymatic reaction, the carbonyl group forms a stable covalent bond with proteins, amino acids, and lipids, known as advanced glycation end products (AGEs). As disease progresses, AGEs accumulate in the body and cross-link with proteins. This inhibits the proliferation of human dermal fibroblasts and endothelial cell adhesion and migration. Additionally, it prevents normal protein folding, ultimately leading to decreased elasticity of the blood vessel wall, impaired cellular function, and delayed tissue repair[34,35]. At the same time, AGE binds to the receptor of AGEs (RAGE), generating a variety of signaling pathways and a variety of pro-fibrotic factors through cascade signaling, which ultimately leads to a series of pathological effects, such as the upregulation of various inflammatory cytokines, increase in the expression of inflammatory cytokines, generation of a large number of reactive oxygen species (ROS), and vascular sclerosis[36]. This affects the healing of diabetic wounds.

Sustained oxidative stress

Oxidative stress refers to an increase in the production of reactive molecules (*e.g.*, ROS) or the weakening of antioxidant scavenging defenses when the body is subjected to a harmful stimulus, causing an oxidative/antioxidative imbalance and leading to tissue damage. Under hyperglycemia, mitochondria produce large amounts of ROS. This leads to redox imbalance, increasing the level of oxidative stress and related products, simultaneously activating the polyol, hexosamine, diacylglycerol, and protein kinase C pathways; inducing the production of AGEs, and inhibiting wound healing[37-39]. AGEs bind to RAGE, leading to the release of superoxide anions and hydrogen peroxide. This increased production of superoxide and mitochondrial ROS further enhances RAGE expression, thus forming a vicious circle. In addition, high levels of ROS can damage proteoglycans in the ECM, inhibit collagen production, and regulate matrix metalloproteinase (MMP) expression; leading to disturbances in ECM homeostasis, stalled wound closure, and the inhibition of tissue remodeling and regeneration[40-42].

Excessive chronic inflammation

Inflammation plays a crucial role in initiating and maintaining wound healing. However, DFU wounds exhibit excessive inflammation, hindering the transition from the inflammatory to proliferative phases and impeding wound healing[32]. The key reason for this is the abnormal polarization of macrophages in DFU wounds, which hinders the transition from pro-inflammatory M1 macrophages to anti-inflammatory M2 macrophages. At the same time, M1 macrophages secrete numerous pro-inflammatory factors and exhibit decreased phagocytosis, leading to prolonged inflammation and reduced pathogen elimination capability[32,43]. In addition, M1 macrophages secrete excessive MMP and ROS, leading to high MMP expression, MMP/tissue inhibitor of metalloproteinase (TIMP) imbalance, and a vicious cycle of oxidative stress, thus delaying wound healing and inhibiting tissue remodeling[44,45].

Hypoxic environment of wounds

Hypoxia-inducible factor 1 (HIF-1) is a key regulator of hypoxic homeostasis. Its expression can be induced by a certain level of hypoxia to regulate pathological and physiological processes, such as glycolysis, erythropoiesis, angiogenesis, and inflammation, enabling the body to adapt to the hypoxic environment. During the inflammatory phase, HIF-1 can promote macrophage recruitment and differentiation[46]. During the proliferative phase, HIF-1 activates the transcription of various angiogenic factors, such as vascular endothelial growth factor (VEGF) and angiopoietin-2. DFU wounds experience long-term chronic hypoxia due to abnormal glucose metabolism and increased local oxygen consumption. This condition affects the stable expression of HIF-1, leading to the downregulation of HIF-1 signaling and target genes. The hypoxic response of cells is impaired, neovascularization and cell proliferation are hindered, and the healing ability is reduced[47]. Furthermore, downregulation of HIF-1/VEGF pathway expression, insufficient angiogenesis, and local ischemic wounds may be key factors causing vascular injury in DUF[48,49].

ECM and MMP

The ECM is an important mediator that provides structural support and facilitates cellular interactions, and maintaining ECM homeostasis is an important factor in wound healing. Fibroblasts are key cells in the production and reorganization of ECM. Due to the persistently high level of oxidative stress in DFU wounds, the formation of fibroblasts can be

hindered and fibroblast senescence can be accelerated, thereby impacting ECM synthesis[50,51]. As mentioned previously, high ROS levels can lead to abnormalities in ECM homeostasis, ultimately impairing wound healing. MMP are involved in the breakdown of collagen, fibronectin, and other protein components of ECM. The binding of MMP to TIMP can regulate its activity, and the right balance of MMP/TIMP can control the structural remodeling of the ECM and support tissue healing[52]. Under the effects of a hyperglycemic microenvironment, continuous oxidative stress, and inflammation, MMP-9 is overexpressed, TIMP-1 expression decreases, and the MMP/TIMP ratio increases. This impairs the balance of proteins in the ECM, causing excessive degradation of ECM in wounds, inhibiting the migration of keratinocytes, and impeding the remodeling of collagen[35,52]. As a result, wounds have difficulty closing and healing.

Others

In DFU wounds, bacteria in the skin colonize and exist in a biofilm state. Biofilms are highly resistant to antibiotics and microbicides, making diabetic wounds susceptible to multidrug resistance and infections, which affect the healing process. The diabetic state increases endothelial cell detachment and apoptosis and decreases endothelial nitric oxide synthase and bone marrow endothelial progenitor cells (EPCs), resulting in vascular integrity disorders and hindered neovascularization[53,54]. Growth factors play important roles in wound healing. The rapid degradation of endogenous growth factors such as platelet-derived growth factor, epidermal growth factor (EGF), and VEGF and the downregulation of their receptor levels in DFU wounds can lead to delayed wound healing[55,56]. In addition, diabetic patients experience long-term high blood glucose levels, which lead to immune dysfunction. This impairs the phagocytic function of immune cells, prevents granulation tissue formation, and increases the wound's susceptibility to infection[56,57].

Mechanisms underlying DFU wound formation are complex. It is related to the external environmental and internal body factors, and there is a certain correlation and interconnection between these factors. However, the existing research lacks a systematic and comprehensive understanding of the refractory mechanisms of DFU wounds. More in-depth exploration is required to identify new therapeutic targets and more effective therapeutic measures in the future.

MECHANISMS FOR PROMOTING DIABETIC WOUND HEALING

ADSC-Exos have been extensively studied in the field of regenerative medicine. They exhibit tissue regeneration capabilities similar to those of MSCs and, therefore, hold great potential for skin tissue regeneration and wound healing. Therefore, it is one of the most promising research areas in clinical medicine[58]. The complex pathological mechanisms underlying DFU wounds make them difficult to heal, cause great pain to patients, and impose a serious burden on healthcare resources. The mechanism by which ADSC-Exos promote diabetic wound healing exhibits highly complex characteristics. It is not a linear regulation through a single pathway, but involves multi-dimensional molecular networks (Table 1) and signaling pathways. Therefore, it is important to explore the mechanism and therapeutic potential of ADSC-Exos in promoting the healing of refractory diabetic wounds (Figure 2).

Regulation the wound inflammatory response

In the early stages of wound healing, the body releases numerous inflammatory cytokines due to inflammation. Under the action of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-12, tumor necrosis factor- α (TNF- α), *etc.*, the mature macrophages are polarized to the M1-type to remove pathogens and damaged tissues. Under the action of anti-inflammatory cytokines (IL-4, IL-13, *etc.*), macrophages are polarized from the M1-type to the M2-type, and the wound enters the proliferative phase. In DFU wounds, the failure of M1 macrophages to promptly transition to M2 macrophages results in a prolonged inflammatory phase, which is a key barrier to healing[32]. CircRps5 is a non-coding RNA carried by ADSC-Exos and is involved in a wide range of signaling pathways[59]. Yin and Shen[60] observed that circRps5 carried by ADSC-Exos corrected the unbalanced macrophage phenotype in wounds through miR-124-3p, induced M2 macrophage polarization, and accelerated wound healing by reducing persistent inflammatory responses. In the early inflammatory stage of wound healing, T cells can inhibit the production of interferon- γ . This inhibits the differentiation and aggregation of M1 macrophages, regulates inflammation, and promotes wound healing[61]. ADSC-Exos have been shown to possess an immunomodulatory effect on T cells, significantly reducing interferon- γ secretion and inhibiting excessive inflammatory responses[62]. Shi *et al*[63] found that circ-Snhg11 expression was enhanced in hypoxic ADSC-derived exosomes, which can inhibit endothelial cell damage and reduce hyperglycemia-induced secretion of inflammatory factors such as IL-6, IL-1 β , and TNF- α in diabetic wounds. These exosomes regulate wound inflammation by inducing M2 macrophage polarization through the miR-144-3p/HIF-1 α axis. In addition, exosomes can be used as carriers to deliver drugs to specific cells or regions, and icariin (ICA) has the regulation of macrophage polarization. The researchers introduced an ADSC-Exo-ICA delivery system, which solved the problems of poor penetration and low bioavailability of ICA and enhanced the modulating effect of ADSC-Exos and ICA on macrophage polarization; the anti-inflammatory effect was better than that of Exo or ICA alone[64]. ADSC-Exo-ICAs are considered to have potential therapeutic value in inflammatory diseases.

Promote neovascularization of the wound

Neovascularization is the biological process by which new blood vessels grow on top of existing vascular structures, and is a key step in wound healing and tissue repair. This new vascular network provides sufficient oxygen, cytokines, and nutrients to the wound, thereby promoting tissue regeneration[65]. However, various cells and cytokines that promote wound healing become dysfunctional in diabetic wounds, affecting neovascularization and healing[66]. EPCs are a group of naïve endothelial cells with migratory properties that can further proliferate and differentiate, and are involved in

Table 1 The cargo RNAs and functions of exosomes from adipose-derived stem cells in promoting diabetic wound healing[60,63,68,70,72,79,90,100,101]

Cargo	Target	Experimental model	Concentration	Function	Ref.
circRps5	miR-124-3p	C57BL/6 mice (8 weeks old, male)	2 mg/100 μ L PBS	Promote M2 macrophages polarization	Yin and Shen[60]
circ-Snhg11	miR-144-3p	C57BL/6 mice	100 μ L PBS containing 200 μ g ADSC-exosomes	Promote M2 macrophages polarization	Shi <i>et al</i> [63]
mmu_circ_0001052	miR-106a-5p	BALB/c mice (5 weeks old, male)	20 μ g/mL	Promote angiogenesis	Liang <i>et al</i> [68]
miR-146a-5p	JAZF1	HUVEC and C57/BL mice (8 weeks old, male)	50, 100 and 200 μ g/mL	Promote angiogenesis	Che <i>et al</i> [70]
circ-0001747	miR-199a-5p	BALB/C mice	Not clear	Promote wound healing and accelerate vascular regeneration	Wang <i>et al</i> [72]
miRNA-21-5p	HaCaT	HaCa and Sprague-Dawley rats (5 weeks old, male)	Not clear	Promote the proliferation and migration of keratinocytes	Lv <i>et al</i> [79]
miR-130b-5p	TGFBR3	C57BL/6 mice (8 weeks old, male)	1 μ g/ μ L in 100 μ L PBS	Promote collagen formation and angiogenesis, and activate the functions of fibroblasts and vascular endothelial cells	Yu <i>et al</i> [90]
miR-125a-3p	PTEN	HUVEC and C57BL/6 mice (6-8 weeks old)	25 μ g and 50 μ g/mL	Promote the proliferation, migration, and angiogenesis of human umbilical vein endothelial cells	Pi <i>et al</i> [100]
lncRNA H19	miR-19b	BALB/c mice (4 weeks old, male)	Exosomes isolated from 1×10^6 ADSCs suspended in 200 μ L PBS	Promote the proliferation, migration, and invasion of HSF cells	Qian <i>et al</i> [101]

lncRNA: Long noncoding RNA; JAZF1: Juxtaposed with another zinc finger gene 1; HaCaT: Human keratinocyte cell line; HUVEC: Human umbilical vein endothelial cells; PBS: Phosphate-buffered saline; ADSC: Adipose-derived stem cells; HSF: Human skin fibroblast.

angiogenesis in ischemic tissues and repair after vascular injury. Previous studies have shown that a hyperglycemic microenvironment can lead to premature senescence of EPCs and increase ROS levels and inflammation[67]. In the DFU rat model, ADSC-Exos increased the viability of EPCs, inhibited cellular senescence, and promoted the proliferation, migration, and tube-forming ability of EPCs, as well as angiogenesis. When nuclear factor erythroid 2-related factor 2 is overexpressed, this protective ability is enhanced through stromal cell-derived factor-1/chemokine receptor 7. It is mainly manifested by an increase in the levels of senescence marker protein 30 and VEGF, an increase in the phosphorylation of VEGF receptor 2 (VEGFR2), and a significant decrease in the levels of ROS and inflammatory cytokines, ultimately resulting in a reduction of the ulcer area and a delay in the progression of DFU[67]. Some studies have found that a hyperglycemic microenvironment induces the upregulation of miR-106a-5 expression and a decrease in fibroblast growth factor 4 (FGF4) in human umbilical vein endothelial cells (HUVECs) and wounds, accompanied by a reduction in proliferation, migration, and angiogenesis[68]. FGF4 regulates endothelial cell biology through the p38 mitogen-activated protein kinase (MAPK) pathway to promote wound epithelial regeneration[68,69]. Employing a mouse model of DFU, researchers found that mmu_circ_0001052 modified ADSCs-Exo significantly inhibited apoptosis and miR-106a-5p and activated the FGF4/p38MAPK pathway, which promotes angiogenesis in DFU and tissue healing[68]. In another study, juxtaposed with another zinc finger gene 1 (JAZF1), the direct downstream target of miR-146a-5p, was overexpressed in hyperglycemia, inhibiting the function of HUVECs and decreasing the level of the vascular marker protein VEGFA. However, ADSC-Exos upregulated the expression of VEGFA *via* the miR-146a-5p/JAZF1 axis and increased the proliferation, migration, and angiogenic capacity of HUVECs, promoting diabetic wound angiogenesis in a DFU rat model[70]. MiR-125b-mimics modified ADSCs-Exo increased the expression of cluster of differentiation 34, Ki-67, VEGF, and transforming growth factor (TGF)- β 1 and decreased the expression of *DLL-4*, Toll-like receptor 4, and IL-6 in the DFU rat model, meanwhile, it could regulate the function of HUVECs, inhibit apoptosis, and promote angiogenesis [71]. In addition, compared to normoxic treatment, the levels of VEGF, EGF, FGF, their receptors (VEGFR2 and VEGFR3), monocyte chemotactic protein (MCP)-2, and MCP-4 were significantly higher in hypoxia-treated ADSC-Exos (hypADSC-Exos), and hypADSC-Exos significantly improved neovascularization around the grafts. Wang *et al*[72] found that circ-0001747 derived from hypADSCs-exo enhances DFU wound healing by activating the miR-199a-5p/HIF-1 α signaling pathway, improves endothelial cell function, and restores the microenvironment required for endothelial cell recovery. Meanwhile, researchers found that hypADSC-Exos were more easily absorbed by HUVECs and had enhanced angiogenesis-stimulating activity, and that hypADSC-Exos improved angiogenesis by activating the protein kinase A signaling pathway and regulating VEGF/VEGFR signaling[73].

Promote cell proliferation and repair

Fibroblasts are the primary repair cells involved in wound healing. Through migration and proliferation, they secrete

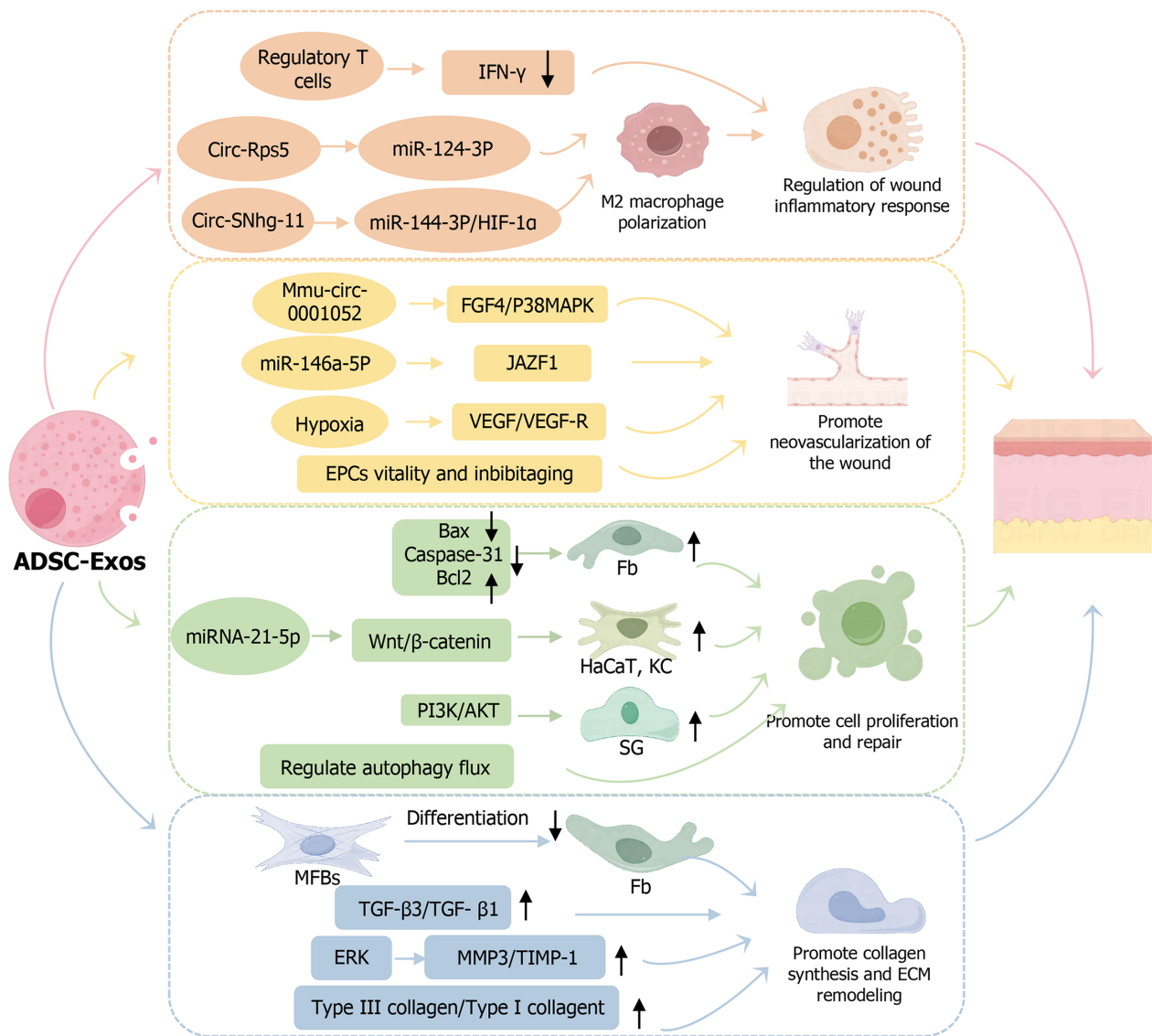


Figure 2 Mechanisms of exosomes from adipose-derived stem cells in promoting diabetic wound healing. The mechanisms by which exosomes from adipose-derived stem cells promote wound healing in refractory diabetes mellitus may include the regulation of inflammation, promotion of wound neovascularization, enhancement of cell proliferation and repair, and promotion of collagen synthesis and extracellular matrix remodeling. IFN: Interferon; HIF: Hypoxia-inducible factor; FGF4: Fibroblast growth factor 4; MAPK: Mitogen-activated protein kinase; JAZF1: Juxtaposed with another zinc finger gene 1; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; EPCs: Endothelial progenitor cells; Bcl-2: B-cell lymphoma-2; Fb: Fibroblast; HaCaT: Human keratinocyte cell line; KC: Keratinocytes; SG: Sebaceous gland; PI3K: Phosphatidylinositol 3-kinase; AKT: Protein kinase B; ADSC-Exos: Exosomes from adipose-derived stem cells; MFBS: Myofibroblasts; TGF: Transforming growth factor; ERK: Extracellular signal-regulated kinase; MMP: Matrix metalloproteinase; TIMP: Tissue inhibitor of metalloproteinase; ECM: Extracellular matrix.

large amounts of collagen fibers and ECM components to create conditions for epidermal cell coverage. Human dermal fibroblasts differentiate into myofibroblasts, thereby promoting wound contraction and healing[74]. However, in diabetic wounds, human dermal fibroblasts senesce at an accelerated rate and their ability to migrate, proliferate, and differentiate is reduced[75]. Yang *et al*[76] found that ADSC-Exos could reduce oxidative stress damage in fibroblasts in the hyperglycemic microenvironment by observing the flow cytometry results and expression of 8-oxo-2'-deoxyguanosine in fibroblasts. Meanwhile, researchers tested three apoptosis indicators (B-cell lymphoma-2, *Bax*, and caspase-3) and found that ADSC-Exos reversed apoptosis induced by hyperglycemia (downregulation of *Bax* and caspase-3 expression and upregulation of B-cell lymphoma-2 expression). Moreover, ADSC-Exos promote the migration and proliferation of fibroblasts, and collagen secretion and synthesis[76]. In another study, ADSC-Exos were found to be rich in microRNAs that could stimulate the proliferation of the epithelium and promote the regeneration of skin fibroblasts[77]. Ma *et al*[78] found that ADSC-Exos could promote the proliferation and migration of the human keratinocyte cell line, inhibit cell apoptosis through the Wnt/ β -catenin signaling pathway by the establishment of a model of skin injury, and ultimately play a positive role in the healing process of the wound. Keratinocytes, the main cells of the skin epithelium, are key defenses against foreign pathogens. Lv *et al*[79] enriched ADSC-Exos with miRNA-21-5p through artificial editing and found that ADSC-Exos promoted the proliferation and migration of keratinocytes in a hyperglycemic microenvironment and accelerated the healing of diabetic wounds. Sebaceous glands (SGs) secrete sebum that protects the skin from

oxidative damage. Sebocytes, the lipid cell type that primarily produces sebum in SGs, are crucial for the functional repair of the skin. Zhang *et al*[80] found that ADSC-Exos can regulate sterol regulatory-element binding protein-1 and perilipin-1 in SZ95 sebaceous cells through the phosphatidylinositol 3-kinase/protein kinase B pathway, enhancing the proliferation and migration of SG cells, inhibiting their apoptosis, and increasing the speed and quality of wound healing. Autophagy is a spontaneous process in which cells phagocytose, decompose, and eventually absorb foreign intruders, thereby forming an important part of lysosomal metabolism[81,82]. The regulation of normal cellular function is of great significance. Ren *et al*[81] established *in vivo* and *in vitro* diabetes models and found that a hyperglycemic microenvironment inhibits autophagy in epidermal cells, downregulates autophagy flux levels, and impairs some biological functions, such as epidermal cell proliferation or migration. ADSC-Exos upregulated autophagic flux and enhanced epidermal epithelialization in diabetic mouse models, thereby promoting wound regeneration. In addition, researchers have pointed out that ADSC-Exos may promote the survival and function of cells in the hyperglycemic microenvironment by activating the autophagy-nicotinamide phosphoribosyl transferase-nicotinamide adenine dinucleotide axis and participate in the specific regulation of autophagy in the wound[81].

Promote collagen synthesis and ECM remodeling

Collagen synthesis and ECM remodeling are key factors affecting the speed of wound healing and scar quality during wound healing. Scholars have explored how exosomes can promote wound healing, while also paying attention to the importance of improving scarring and the quality of healing. Hu *et al*[83] found that in the early stage of wound healing, ADSC-Exos promoted the expression of type I and III collagen and shortened the healing time, whereas in the late stage, ADSC-Exos inhibited the expression of collagen, thus inhibiting scar formation. Although scarring can restore the structural integrity of the tissue, it deprives it of its functionality. Pathological scars manifest as excessive proliferation of fibroblasts and excessive deposition of ECM, dominated by type I and III collagen. Wang *et al*[84] showed that ADSC-Exos could prevent fibroblasts from differentiating into myofibroblasts, and after ADSC-Exos treatment, the expression of α -smooth muscle actin decreased significantly and the number of myofibroblasts was reduced in the tissue slices. At the same time, ADSC-Exos regulated the ratios of type III/type I collagen, TGF- β 3/TGF- β 1, and MMP3/TIMP1 to promote the remodeling of ECM in the wound model of mice. Lv *et al*[79] found that miRNA-21-5p-enriched ADSC-Exos significantly increased collagen deposition in diabetic wounds after application to diabetic wounds using an artificial editing method, which is believed to promote diabetic wound healing by regulating inflammation, epithelialization, and tissue matrix remodeling.

APPLICATION AND CHALLENGE

Many studies have used ADSC-Exos subcutaneously or intravenously to treat wounds, and some results have been reported. Hu *et al*[83] found that in a mouse model, the healing rate of the intravenously injected exosome group was significantly higher than that of the locally injected exosome group. It is also possible to improve the ability of ADSC-Exos to promote wound healing by pretreating them with hypoxia[85]. Engineering methods are used to obtain ADSC-Exos with specific therapeutic effects by increasing their concentration and extending their action time[86]. Additionally, combining ADSC-Exos with other substances may improve their therapeutic effects. To better simulate the *in vivo* environment, Song *et al*[87] added ADSC-Exos into the ECM hydrogel of porcine myocardium to prepare an ADSC-Exo-loaded bio-ECM hydrogel, injected it into the wound of a mouse model, and found that ADSC-Exo-loaded bio-ECM hydrogel reduced the inflammatory response of the wound, promoted cell proliferation and migration, angiogenesis, and collagen production, and reshaped the skin structure. Wang *et al*[88] developed a polypeptide-based FHE hydrogel (F127/OHA-EPL) and found that it stimulated the release of AMSC-exos and had a synergistic effect on chronic wound healing and skin regeneration. In further studies, the FHE exosomes hydrogel was found to be more effective in promoting healing than exosomes or the FHE hydrogel alone. Shiekh *et al*[89] developed an oxygen-releasing antioxidant dressing named OxOBand that promotes diabetic wound healing by inhibiting oxidative stress, stimulating angiogenesis, and regulating collagen remodeling. Addition of ADSC-Exos enhanced the regenerative potential and healing of infected wounds. In addition, a study showed that ADSC-Exos with deletion of the transcription factor E2F1 (ADSC E2F1-/-Exos) could increase the expression and secretion of miR-130b-5p, promote the production of collagen and blood vessels, and promote the proliferation and migration of fibroblasts through the miR-130b-5p/TGFBR3 axis, thereby promoting wound healing[90].

A comprehensive search of the International Clinical Trials Registry Platform and ClinicalTrials.gov revealed limited human clinical trials evaluating the efficacy and safety of ADSC-Exos for treating DFUs. In 2024, a phase 2a multicenter, prospective, randomized controlled trial (No. NCT06319287) was initiated to evaluate the safety and efficacy of the topically applied purified exosome product-TISSEEL in DFUs. In a pilot study evaluating human adipose tissue-derived exosomes for the promotion of wound healing (No. NCT05475418), EV were mixed with a sterile hydrogel and applied directly to the wound surface, and the wound was covered with an inert protective dressing. To date, no such study has been published. A study on the safety and efficacy of human umbilical cord MSCs for treating DUFs is underway at the Qazvin University of Medical Sciences, spanning Clinical Trial Phases I and II (No. IRCT20240317061316N1). A double-blind, randomized, controlled phase I clinical trial evaluating the efficacy and safety of Wharton's jelly derived MSC exosomes for treating DUFs has been completed; however, no relevant trial results have been found (No. NCT06812637).

ADSC-Exos have a great potential clinical value in promoting wound healing. However, most existing studies are preclinical and have several technical problems and limitations. Owing to inherent limitations in cell sources and secretion efficiency, bottlenecks in culture systems and production technologies, and yield loss during extraction and

purification processes, the yield and purity of exosomes are not promising. The purity of exosomes is crucial for their therapeutic effects. High-purity exosomes exert their biological functions more effectively, reduce impurity interference, and improve therapeutic efficacy and safety. Ultracentrifugation is simple to perform and widely used, but its purity and yield are limited. The immunomagnetic bead method enables highly specific and targeted isolation of exosomes; however, its high cost and dependence on biomarkers limit its large-scale application. Density gradient centrifugation can remove most impurities, resulting in high purity; however, it has a low yield and complex operation. Size exclusion chromatography can separate exosomes with high purity and good activity; however, the number of uses of the purification column is limited, and repeated use affects purification. Compared with traditional technologies, microfluidic technology has obvious advantages, such as high efficiency, high purity, low sample demand, and low damage[91]. In addition, microfluidic chips can be mass-produced with low cost for single use, making them more suitable for comprehensive promotion in the future. However, the microfluidic exosome extraction system needs to further improve the sensitivity of biomarker discovery to promote the clinical translation of exosomes in liquid biopsy. To address the challenge of large-scale exosome production, Huang *et al*[92] designed a herringbone microfluidic bioreactor with cell microcarriers, using gelatin methacrylate (GelMA) porous particles as microcarriers for cell culture. By dynamically adjusting the perfusion rate of the culture medium, they increased the exosome yield by approximately 21 times. Meanwhile, they proposed to obtain hepatocyte growth factor (HGF)-overexpressing exosomes by culturing genetically engineered MSCs with overexpressed HGF in the microfluidic system[93]. Moreover, exosomes secreted by MSC^{HGF} exhibit good wound healing-promoting ability in mouse models.

To improve the yield and therapeutic potential of exosomes, various pretreatment methods for ADSCs, such as hypoxia, drugs, and mechanical stimulation, have been continuously emerging. Culturing ADSCs in a hypoxic environment can better simulate the physiological microenvironment and stimulate better secretion of exosomes without altering their characteristics. Existing knowledge indicated HypMSC-Exos demonstrates great therapeutic potential in promoting the repair and regeneration of blood vessels, skin, bones, nerves, and other tissue[94]. HypADSC-Exos also shown the ability to promote wound healing in mouse models[63]. Physical or chemical stimulation is also a commonly used pretreatment method to improve the quality of exosomes. Physical stimulation methods include extrusion, low-intensity pulsed ultrasound, *etc.*, while chemical stimulation methods include metformin, atorvastatin, *etc.* Chen *et al*[95] summarized this and believed that different physical or chemical pretreatments can enhance the regenerative or anti-inflammatory potential of MSC exosomes by regulating the secretion profile of MSCs. In the future, it is necessary to further optimize the pretreatment conditions (such as multi-factor combined stimulation) and combine three-dimensional (3D) culture or biomaterial scaffolds to improve the yield and function of exosomes. In the future, it is necessary to further optimize the pretreatment conditions (such as multi-factor combined stimulation) and combine 3D culture or biomaterial scaffolds to improve the yield and function of exosomes.

To promote wound healing with exosomes is a key challenge as they consistently maintain their effective therapeutic concentration and stability at the wound site. The development of engineered exosome delivery platforms seems to be expected to solve this problem. An ideal delivery platform needs to have controllable biodegradability, antibacterial properties, hemostatic ability, sustained release of bioactive molecules, and biocompatibility, *etc.*[96]. Yuan *et al*[97] developed a GelMA/poly (ethylene glycol) diacrylate (PEGDA) microneedle patch loaded with HUVEC-derived exosomes and tazarotene. They found through comparison that the GelMA/PEGDA@T + exos microneedles (MNs) patch group maintained better drug concentration and delivery rate than the GelMA/PEGDA MNs patch group, thereby more effectively promoting wound healing in diabetic rats.

Currently, the production of exosomes lacks good manufacturing practice (GMP)-compliant protocols, which hinders clinical approval. Issues such as raw material selection, cell expansion, product formulation, and the establishment of quality control parameters remain to be addressed[98]. To promote the clinical application of exosome therapy, the "MISEV2023 Position Paper" released by the International Society for EV has updated the naming conventions for EVs. It standardizes processes such as sample collection, isolation, and characterization, and also covers content including EV release, uptake, functional research, and *in vivo* analysis. By integrating expert feedback to form consensus, it aims to advance the standardization and reproducibility of research in the field of EVs[99]. This provides a reliable basis for transforming research-stage protocols into GMP-compliant ones.

DISCUSSION

DFU is a common, chronic, and serious complication of diabetes mellitus with high amputation and mortality rates, causing a huge burden on patients and society. DFU wounds differ from ordinary wounds in the process of healing and are characterized by a prolonged inflammatory period, limited proliferation period, irregular remodeling, *etc.* Several factors affect the development and healing of DFU. Only by good control of blood glucose, blood pressure, and blood lipids and by avoiding the occurrence of neuropathy, PAD, infection, and other related risk factors can we reduce the incidence or progression of DFU.

In recent years, new methods, technologies, and concepts have emerged for the treatment of diabetic feet. Among these, the research progress on ADSC-Exos in tissue repair and regeneration has been particularly rapid. As one of the most promising cell-free therapies for wound healing, ADSC-Exos have great potential for further development and application. As a natural carrier, ADSC-Exos have obvious biological characteristics, such as low immunogenicity, good tolerance, easy storage, and high safety. In addition, ADSC-Exos can pass through barriers that cannot be crossed by cells (*e.g.*, the blood-brain barrier), thus increasing the scope of their action. Researchers can also improve targeting by directional editing of its content or artificial modification of the molecular receptors on its surface.

Table 2 The impact of exosomes from different sources on wound healing[68,102-106]

Source	Cargo	Regulatory mechanism	Result	Ref.
ADSC	Mmu_circ_0001052	miR-106a-5p/FGF4/p38 MAPK	Promote angiogenesis in high-glucose-induced HUVECs and improve wound healing in DFU	Liang <i>et al</i> [68]
BMSC	circ-Snhg11	circ-Snhg11/miR-144-3p/ <i>SLC7A11</i>	Resulting in the inhibition of ferroptosis, restoration of EPC function, promoting angiogenesis and wound healing	Tang <i>et al</i> [102]
HUCMSC	Wnt-4	Wnt/ β -catenin	Promote tube formation of endothelial cells <i>in vitro</i> and angiogenesis	Zhang <i>et al</i> [103]
HFMSC	lncRNA H19	lncRNA H19/ <i>NLRP3</i>	Promote HaCaT proliferation, migration, and pyroptosis suppression <i>in vitro</i> and <i>in vivo</i>	Yang <i>et al</i> [104]
GMSC	<i>MALAT1</i>	Wnt/ β -catenin	GMSCs-exosomes can promote the proliferation, migration, and tube formation of HUVECs in a high glucose environment through a series of <i>in vitro</i> experiments	Liu <i>et al</i> [105]
USC	miR-486-5p	miR-486-5p/ <i>SERPINE1</i>	Hyp-USC-exos carrying miR-486-5p can inhibit the activity of <i>SERPINE1</i> in endothelial cells, promote angiogenesis, and accelerate the healing process	Fan <i>et al</i> [106]

ADSC: Adipose-derived stem cells; BMSC: Bone marrow mesenchymal stem cells; HUCMSC: Human umbilical cord mesenchymal stem cells; HFMSC: Human follicle mesenchymal stem cells; GMSC: Gingiva-derived mesenchymal stem cells; USC: Urine-derived stem cells; lncRNA: Long noncoding RNA; FGF4: Fibroblast growth factor 4; MAPK: Mitogen-activated protein kinase; HUVEC: Human umbilical vein endothelial cells; DFU: Diabetic foot ulcer; EPC: Endothelial progenitor cell; HaCaT: Human keratinocyte cell line; Hyp-USC-exos: Exosomes from hypoxic urine-derived stem cells.

In the treatment of DFU or the promotion of wound healing, ADSC-Exos can play an active role in all stages of the healing process by regulating the level of inflammatory factors and improving the microenvironment during the inflammatory phase; promoting cell proliferation, migration, and vascular regeneration during the proliferative phase; and regulating the ratio of collagen and ECM remodeling during the remodeling phase. In addition to ADSC-Exos, exosomes from other sources have also shown therapeutic potential in diabetic ulcer models (Table 2). Exosomes from different sources synergistically promote wound healing by regulating multiple pathways. The differences in their compositions and functions may be related to the various bioactive substances carried by exosomes and the characteristics of their source cells.

However, many questions regarding the use of ADSC-Exos in wounds remain unanswered. From a clinical perspective, these include the optimal concentration or dosage of ADSC-Exos, the need for repeated injections, the basis for the selection of therapeutic endpoints, the duration of the therapeutic effect in human wounds, the influence of the individual patient's condition on the therapeutic effect (fat mass, metabolic condition, underlying disease), and whether the above issues are the same for different wounds (diabetic wounds, burn wounds, radiated skin ulcers, *etc.*). In terms of technology, it is unclear whether the extraction and separation methods of ADSC-Exos affect the therapeutic effect, the type of pretreatment method that can maximize the impact of ADSC-Exos (drugs, hypoxia, gene modification, *etc.*), and how the choice of bioscaffolds affects different wounds.

Studies on ADSC-Exos' role in accelerating wound repair remain preliminary. Most current studies only focus on a single molecule or a certain link in a signaling pathway, lacking systematic research to reveal the synergistic effects or hierarchical relationships between various targets. In the future, basic research can be improved by constructing various *in vivo* or *in vitro* experimental models, and their mechanisms of action can be integrated. Its translation to clinical practice is limited by multiple factors such as technical standardization, safety verification, cost control, and disease complexity. The establishment of standardized procedures and preclinical safety evaluations can promote the practical application of exosome therapy. Large-scale application still needs to break through technical bottlenecks such as production, separation, loading, and regulation of *in vivo* behavior, while focusing on the research and development of equipment with high throughput, high efficiency, and high recovery rate. In addition, future efforts can focus on specific targeted modification of exosomes. This may improve the accuracy of diagnosis and treatment; or combine with biomaterials science to optimize the local release efficiency of exosomes, enhance the therapeutic effect, and truly strengthen the collaboration between basic research and clinical practice.

CONCLUSION

In summary, the composition and therapeutic efficacy of ADSC-Exos are highly dependent on the state of the ADSCs. However, whether used alone or in combination with bioengineering methods to enhance their biological activity; ADSC-Exos have already demonstrated significant therapeutic potential for promoting DFU healing. Thus, suggesting a promising new direction for the treatment of refractory wounds. Further research is needed on the effector molecules and mode of action of ADSC-Exos. The effects of ADSC-Exos pretreatment on the therapeutic effect, the extraction and

preparation of ADSC-Exos, and the optimal application pathway of ADSC-Exos to lay a solid theoretical foundation for eventual clinical translation. In addition, due to limitations in the methods of obtaining and researching ADSC-Exos, most research on their use in treating DFU remains at the animal model stage. Furthermore, most of the existing experiments use mouse-derived ADSC-Exos, which cannot exclude differences in outcomes compared to human-derived ADSC-Exos in wound healing. Challenges persist to exist; to stabilize, efficiently produce, and mass-produce ADSC-Exos for clinical use. Only through a better understanding of the pathogenesis, risk factors, and treatment of DFU can patients manage the disease correctly, maximize DFU regression, and improve cure rates. In the future, whether it is the study of DFU disease itself or the mechanism of improving wound healing with ADSC-Exos, as well as engineering strategies for ADSC-Exos, continuous exploration and innovation are required from scholars.

FOOTNOTES

Author contributions: Mao JX was responsible for data organization and manuscript drafting; Zhao MX undertook the manuscript editing and correction process; Chen S contributed to the revision of figures in the manuscript; Li JC, Wang H and Zhao MX were involved in establishing the conceptual framework and overall structure of the manuscript; All authors have read and approve the final manuscript.

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