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Mesenchymal stem cell-derived exosomes: The dawn of diabetic wound healing

Wu J *et al*. MSC-Exos for diabetic wounds

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Abstract

Chronic wound healing has long been an unmet medical need in the field of wound repair, with diabetes being one of the major etiologies. Diabetic chronic wounds (DCWs), especially diabetic foot ulcers, are one of the most threatening chronic complications of diabetes. Although the treatment strategies, drugs, and dressings for diabetic chronic wounds have made great progress, they remain ineffective in some patients with refractory wounds. Stem cell-based therapies have achieved specific efficacy in various fields, with mesenchymal stem cells (MSCs) being the most widely used. Although MSCs have achieved good feedback in preclinical studies and clinical trials in the treatment of cutaneous wounds or other situations, the potential safety concerns associated with allogeneic/autologous stem cells and unknown long-term health effects need further attention and supervision. Recent studies have reported that stem cells mainly exert their trauma repair effects through paracrine secretion, and exosomes play an important role in intercellular communication as their main bioactive component. MSC-derived exosomes inherit the powerful inflammation and immune modulation, angiogenesis, cell proliferation, and migration promotion, oxidative stress alleviation, collagen remodeling imbalances regulation of their parental cells, and can avoid the potential risks of direct stem cell transplantation to a large extent, thus demonstrating promising performance as novel "cell-free" therapies in chronic wounds.

This review aimed to elucidate the potential mechanism and update the progress of MSC-derived exosomes in diabetic chronic wound healing, thereby providing new therapeutic directions for diabetic chronic wounds that are difficult to be cured using conventional therapy.

Key Words: Diabetic wounds; Wound and injuries; Mesenchymal stem cells; Exosomes; Pre-conditioning; Preclinical translation

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Core Tip: Diabetic chronic wounds are one of the most serious chronic complications of diabetes, and the efficacy of stem cell therapy for refractory chronic wounds has been studied previously. Stem cell-derived exosomes are one of the important active components of stem cell paracrine secretion, which inherit the wound repair capacity of parental cells as parts of novel cell-free therapies in addition to cell-bases ones. Herein we discuss the mechanism and latest progress of mesenchymal stem cell-derived exosomes in promoting diabetic chronic wound healing.

INTRODUCTION

Wound healing after skin tissue injury relies on a dynamic chain of physiological reactions including hemostasis, inflammation, cell proliferation, and tissue remodeling[1]. Any step out of balance, such as excessive inflammation, impaired fibroblast migration and proliferation, abnormal collagen formation and deposition, and hindered re-epithelialization, ultimately leads to delayed wound healing and formation of chronic wounds. Chronic wounds are those that have failed to proceed through an orderly and timely reparative process to produce anatomical and functional integrity of the injured site[2]. They refer to wounds caused by multiple factors that have not healed or have not demonstrated a tendency to heal after a certain period clinically, with a chronic duration ranging from 4 to 12 wk[3,4]. Various pathological states result in chronic wound development, including diabetes, pressure injuries, infections, and arterial/venous insufficiency of which reports are similar in China and developed Western countries[4-6], which have the most complicated pathogenesis and therapeutic strategies being diabetic chronic wounds (DCWs).

Diabetes mellitus (DM) is a metabolic disease characterized by elevated blood glucose levels, of which DCWs are among the most threatening complications. The combination of a high-glucose environment and several biological factors, including ischemia and hypoxia, abnormal inflammatory response, excessive oxidative stress, and peripheral neuropathy, contributes to wound formation[7-9]. Such wounds have problems of protracted healing, long treatment time, difficulties in management, high cost, repeated attacks, and high disability/mortality rates, resulting in heavy physical, psychological and economic burdens[10,11]. The intervention of DCWs cannot be underestimated based on what is mentioned above. Hence, solving persistent inflammation, impaired cell proliferation and migration, decreased angiogenesis, and remodeling of the extracellular matrix (ECM) is important. Innovative wound repair methods, such as local negative pressure, growth factors, and autologous platelet-rich gels, have remarkable effects on healing DCWs[12-15]. However, more specific treatment options are required for refractory and contraindicated wounds.

With the rapid development of tissue engineering, cell therapies have gradually become widely used in various disciplines. Stem cells can be used in regenerative medicine and play an indispensable role in wound repair[16], of which mesenchymal stem cells (MSCs) are the most commonly used. MSCs have self-renewal abilities and multi-directional differentiation potential, participating in damage repair through intercellular communication and bioactive factor secretion, finally achieving the effect of promoting wound healing[17]. Clinical trials of MSCs for treating various types of cutaneous wounds are currently in full swing, and their efficacy and safety in promoting wound regeneration have been initially demonstrated. As clinical trials continue to progress, further attention and supervision need to be paid to their potential safety issues of proliferative lesion formation, abnormal organ reaction and unknown long-term health effects after transplantation[18-20].

Studies have revealed stem cells promote repair and regeneration mainly through paracrine signaling, whereas exosomes are one of their important paracrine active components[21]. MSC-derived exosomes (MSC-Exos) carry genetic information, functional RNAs, and proteins from parental cells, demonstrating wound healing effects *via* intercellular communication after these biologically active substances are acquired by recipient cells[22-24]. Thus, MSC-Exos have broad application prospects in diabetic wound repair[25]; however, they have not yet been carried out in clinical practice. The important role of MSC-Exos in all stages of diabetic wound healing and the preclinical application are highlighted in this review, to pave the way for their use as an effective tool in the management of these harmful diabetic complications.

DIABETIC CHRONIC WOUNDS: HEALING DISORDERS CAUSED BY VARIOUS MECHANISMS

DM is a metabolic disease characterized by elevated blood glucose levels, which poses a serious threat to human health. The continuous progression of hyperglycemic toxicity without effective control will affect macrovascular, microvascular, and peripheral nerves throughout the body and involve various organs such as the brain, eyes, heart, kidney, and skin, resulting in various diabetic chronic complications[26]. DCWs are one of the most common and threatening chronic complications, often accompanied by infection or deep-tissue destruction[27]. Protracted wounds are the most common cause of non-traumatic amputations. Diabetic foot ulcers (DFUs) are characterized by wounds on the feet, which are the most typical, and patients with DFUs have a 2.5 times higher risk of 5-year mortality than those with none[28]. The overall mortality of DFUs within 5 years is nearly 50%[29], and approximately 20% of moderate-to-severe DFUs will lead to amputation; the 5-year mortality rate after amputation exceeds 70%[30].

Impaired wound healing processes caused by hyperglycemia-induced disturbances in wound-linked cellular behaviors contribute to diabetic wound healing difficulties[7, 31]. Hyperglycemia, oxidative stress, and insulin resistance affect the function of vascular smooth muscle cells, endothelial cells, and platelets, which in turn may lead to abnormal coagulation processes and affect platelets of triggering for subsequent inflammatory and proliferative phases[32]. The hyperglycemic microenvironment can lead to dysfunction of immune and inflammatory cells and dysregulation of inflammatory factors. Perpetuated inflammatory states induced by increased mast cell degranulation[33], excessive extracellular traps produced by neutrophils[34], dysregulated and persistent M1 (pro-inflammatory) macrophage polarization[35], pro-inflammatory factors (IL-1β, TNF-α, and IL-6) overexpression, and anti-inflammatory factors (IL-10 and TGF-β) deficiency finally hinder wound healing[7]. The proliferative phase of diabetic wound healing is characterized by disturbed physiological functions of keratinocytes[36], fibroblasts[37], and endothelial cells[38], then the impaired re-epithelialization, granulation tissue formation, matrix deposition, and angiogenesis affect wound healing. Various factors also affect the function and activity of these cells during this phase, including decreased chemokines with pro-angiogenesis produced by macrophages, hemoglobin glycation, vascular stenosis, increased oxygen consumption affecting oxygen-dependent cellular behaviors, and impaired nerve fiber regeneration[7,31,39,40]. Remodeling of the ECM spans the entire injury response, and fibroblasts are the major cell type responsible for this phase[31]. Sequential changes in the ECM require a balance between collagen degradation and synthesis, achieved through temporal regulation of the dynamic changes in the ratio of matrix metalloproteinases (MMPs) to tissue inhibitors of metalloproteinases (TIMPs)[41,42]. Such changes in DCWs are unbalanced and lead to difficult wound healing and excessive scarring[41,43]. However, no clear demarcation exists between the various stages of wound healing, and functionally impaired cells can interact, eventually leading to poor diabetic wound healing, progressing to local infection, gangrene, and even amputation. Therefore, the most important aspect of effectively treating DCWs is to identify an appropriate approach that can comprehensively improve abnormalities in all phases of wound healing.

CURRENT STRATEGIES AND PROMISING DIRECTIONS FOR DIABETIC CHRONIC WOUNDS REPAIR

Traditional strategies for DCWs management include glycemic control, conventional dressings (*e.g.*, hydrocolloids, alginates, and silver ions, *etc.*), thorough debridement (*e.g.*, surgical, mechanical, ultrasonic waterjet, collagenase, and maggot, *etc.*), wound off-loading, autologous skin and skin substitute grafting, infection control, and revascularization, *etc.* These strategies are used to create the wound bed microenvironment suitable for repair through moisture balance maintenance, necrotic or inactivated tissues removal, systemic and local infections control, and local blood flow improvement[13,44-46]. Negative pressure wound therapy can also be used to achieve its role in improving wound exudate drainage, enhancing local perfusion, removing bacterial products, promoting granulation tissue growth, and facilitating wound healing[47]. However, these conventional treatments are often ineffective in many patients because of impaired cell function around the wound sites caused by underlying microenvironmental alterations[48]. Several innovative wound adjuvant therapies, including exogenous supplementation of growth factors[49], platelet-rich plasma[50], autologous platelet-rich gels[15, 51], and hyperbaric oxygen therapy[52] have been developed to promote the activity and function of damaged cells and offer the possibility of treating unselected refractory wounds. However, an updated systematic review has revealed that some measures had positive effects on accelerating wound healing, while others had limited impacts on diabetic ulcer healing[53]. However, the overall efficacy of various treatment modalities for DCWs remains unsatisfactory, and effective therapeutic strategies need to be continued.

STEM CELL-BASED THERAPIES BECOME HOT TOPICS, COMING EXOSOMES INTO BEING

Stem cells have the potential for self-renewal and multidirectional differentiation with great research and application value in life sciences, clinical trials and disease research.

Stem cell-based therapies are now approved by several countries, and have been widely used in various disciplines. MSCs are currently the main experimental cell sources and have shown their excellent therapeutic potential and value in clinical trials in the field of regenerative medicine[16,54].

MSCs provide assistance in all phases of wound healing by exerting their functions of regulating skin homeostasis and wound healing through migration into the skin damage site and interaction with skin cells and can influence the function of these cells by paracrine secretion of bioactive factors and differentiation into them[55,56]. As MSCs have exhibited wound healing in many preclinical studies as powerful tools for regulating inflammation, promoting cell proliferation and migration, angiogenesis, and collagen synthesis[57-60], the application of MSCs for DCWs contributes to progress toward clinical trials. Twenty-five clinical trials of MSCs for diabetic ulcers have been conducted or are recruiting subjects, which are recorded in the ClinicalTrials.gov database (clinicaltrials.gov).

Previous clinical studies have demonstrated that MSC transplantation in patients with DFUs is safe and feasible with the properties of improving microcirculation, wound healing, ulcer recurrence, and amputation[61-63]. However, stem cell therapies are still in their early clinical stage, further attention and supervision are required of declined performance during production and application as cellular senescence and loss of multipotency during *ex vivo* expansion and from variable donors[64,65], decreased survival rate caused by advanced glycosylation end products[66], potential safety issues as proliferative lesion formation and abnormal organ reaction[20], and unknown long-term health effects after transplantation. Basic and clinical researches related to allogeneic/autologous stem cells are subject to the International Society for Stem Cell Research Guidelines for Clinical Translation of Stem Cells and national ethical guidelines and related guidelines/regulations[20,67].

MSCs exert their repair and regenerative effects mainly through paracrine signaling, and exosomes are one of the important active components[21] that provide a more stable entity that minimizes the potential safety concerns for cell transplantation. MSC-Exos play an important role in intercellular communication by carrying various important functional substances of parental cells, being used of promoting wound healing[68,69]. Compared to direct cell transplantation, MSC-Exos avoid the immune rejection because of low immunogenicity; allow to cross various biological barriers and avoid the risk of embolism from intravenous injection based on their smaller sizes[70]; the dose and fraction can be adjusted artificially and genetic modifications are easier and safer[71]; avoid the problem of malignant transformation; and allow to repair diabetic complications through multiple actions[72]. They can also be used as ideal carriers for carrying and delivering therapeutic drugs, genes, enzymes, or RNAs[73], and their efficiency and targeted transport capacity can be tuned through pretreatment or engineering transformation[74], demonstrating their promising applications in the field of repair and regeneration.

STEM CELL-DERIVED EXOSOMES: NOVEL CELL-FREE STRATEGIES

Exosomes biology

The concept of "exosomes" was first proposed in 1981 by Trams *et al*[75], using to collectively refer to extracellular vesicles (EVs) that originated from the exudation of various cell line cultures. The currently defined exosomes were first discovered in sheep reticulocytes and considered cellular waste[76-78]. Of note, "EVs" is the preferred term by the International Society for Extracellular Vesicles (ISEV) to describe all nanoparticles with lipid bilayer structures released by cells[79].

Exosomes, the biological nanoscale spherical lipid bilayer vesicles[80], can be secreted by almost all cell types and are widely present in cell culture supernatants and many body fluids[81]. Their diameters range from 10 to 200 nm. In addition to exosomes, EVs also include microvesicles that are also called ectosomes with a diameter of 100-1000 nm, and apoptotic bodies larger than 1000 nm according to different sizes and biogenesis[82,83]. The types and functions of the bioactive substances carried by exosomes differ according to their cellular origins and adjacent cellular components[84]. The major substances include genetic information, RNA species (mRNA, tRNA, rRNA, miRNA, lncRNA, circRNA, *etc.*), proteins, lipids, cytokines, and growth factors[85,86]. Exosomal proteins include intrinsic components involved in exosome biogenesis, such as fusion-related proteins (GTPases, annexins, flotillin, and Rab proteins), heat shock proteins (HSP70 and HSP90), tetraspanins (CD63, CD81, CD82, and CD9), ESCRT complex, and specific functional proteins originating from parental cells[87]. Apart from serving as a medium for cellular communication, some proteins are also involved in the membrane composition and biosynthesis as identified biomarker proteins and can provide stability and permeability in concert with phospholipid bilayers.

Exosomes originate from endosomes during generation, circulation, degradation, and liberation[88]. Extracellular substances fuse with early sorting endosomes through plasma membrane invagination and endocytosis, and begin to accumulate bioactive substances. Eventually, they mature into late sorting endosomes, which invaginate to form intraluminal vesicles that can then generate multivesicular bodies (MVBs)[68,88]. MVBs can be absorbed by lysosomes comprising a degradative pathway, or they can undergo a specific exocytotic process whereby they fuse with the plasma membrane to release exosomes into the extracellular space[89]. After release, they act as mediators of intercellular and intra-organ communication to transfer the contained bioactive substances to recipient cells through direct fusion, endocytosis, and receptor-ligand binding to affect their functions[90,91], participating in the body's physiological and pathological state adjustment[92].

Isolation and characterization of exosomes

The extraction of exosomes is primarily based on their physicochemical properties. This process is difficult because of the heterogeneity of exosomes derived from different cell origins, the possible existence of subpopulations of exosomes with different functions and phenotypes even when extracted from a single cell line, and multiple EV subtypes with similar biophysical properties[93]. Therefore, different isolation methods should be targeted for different purposes[87]. Differential ultracentrifugation is the most widely used separation technique and is also known as the gold standard for isolation, while the main principle is to harvest the desired components based on size and density differences[94]. Polymer precipitation uses polyethylene glycol to harvest exosomes under centrifugal conditions by reducing their solubility[95]. Size-exclusion chromatography[96] and ultrafiltration[97] are both based on size differences between exosomes and other components, although they may adulterate other particles of similar size. Immunoaffinity capture is based on the specific binding of antibodies and ligands to isolate exosomes from a heterogeneous mixture[98]. Current isolation and purification techniques have varying effects and many problems such as low purity and recovery, structural damage, and time and cost consumption, making achieving efficient enrichment difficult, which has become a bottleneck of the translational applications of exosomes[87]. Hence, continuously exploring new isolation and purification techniques or combining multiple techniques is necessary to improve the isolation efficiency and thus obtain ideal exosomes.

Exosomes are mainly characterized by external characteristics (morphology and size detection) and the identification of surface markers[87]. As mentioned above, some protein components of exosomes serve as surface protein markers for identification. The ISEV has proposed the need to identify two types of proteins as follows: one is the biomarker proteins shared by exosomes to determine whether the extracted components are exosomes, and the other is cell-type-specific exosomal proteins that need to be identified to determine cellular origin[79]. Therefore, exosomes can be characterized by detecting their morphology using transmission electron microscopy, their size and concentration by dynamic light scattering, and nanoparticle tracking analysis technology, and their marker proteins by western blot, enzyme-linked immunoassay, and flow cytometry[87].

MSCs derived exosomes and biological functions

Stem cells have self-renewal abilities and multi-directional differentiation potential, while MSCs are one of the most frequently used and promising adult stem cells that can be derived from most adult tissues such as the bone marrow, adipose tissue, and umbilical cord[99,100]. Bone marrow-derived MSC-Exos (BMSC-Exos) are biologically stable, have low immunogenicity, and exhibit good proliferation and viability after transplantation. They are most commonly used in clinical trials and can play a prominent role in various disorders, especially bone-related diseases[101]. Umbilical cord-derived MSC-Exos (UCMSC-Exos) can be isolated non-invasively, with low immunogenicity and strong self-renewal and proliferation ability, although it has limitations in maintaining bioactive and clinical therapeutic transport[102]. Adipose-derived MSC-Exos (AMSC-Exos) have relatively abundant sources that can be easily obtained by painless minimally invasive surgery; they are also pluripotent, plastic, easy to store, and stable in blood or body fluids[103]. Exosomes of different origins share most of their bioactive factors and are generally similar in their biological functions; however, their specific biological properties depend on the molecules that are specifically expressed[104].

MSC-Exos are involved in intercellular communication through the transfer of proteins, RNA, DNA, and bioactive lipids that can be delivered to target cells to regulate their activities and functions[68]. They are generally involved in the regulation of cell survival and differentiation, the immune system, and inflammation modulation, and are also capable of promoting angiogenesis and tissue remodeling[73]. Considering these multiple biological functions, several studies have also reported that the MSC-Exos play a therapeutic role in autoimmune diseases[105], ischemic injuries[106], and metabolic diseases[107], and are also related to dynamically modulating tumor biological functions[108] , promoting repair and regeneration of damaged osteochondral, neural, and tendon tissues, and facilitating wound healing[109-112]. Current studies also discovered that they can improve COVID-19-related cytokine storms and the deterioration of lung function due to severe pneumonia[113].

MESENCHYMAL STEM CELL-DERIVED EXOSOMES FOR REPAIRING DIABETIC WOUNDS

MSC-Exos play an important role in each phase of wound healing[81]. They can regulate diverse cell types related to wound repair by enhancing or suppressing certain bioactivities, achieving hemostasis, inflammatory regulation, cell migration to the wound site, cell proliferation, and differentiation to form granulation tissue, angiogenesis, and ECM reorganization[69]. They can also be expected to be therapeutic agents for different types of diabetes by alleviating autoimmune damages[114], attenuating insulin resistance, and improving β-cell exhaustion[115]. Additionally, they can be used to prevent and treat DM-related complications. Based on these potentials, MSC-Exos may be of considerable importance in DCW treatment.

Hemostasis

Tissue factor (TF) is an initiator of coagulation activation and was identified in the plasma membrane of exosomes[116]. TF can transfer to the platelets and initiate the extrinsic coagulation cascade, leading to the conversion of prothrombin to thrombin and fibrin clot formation[117]. Induced coagulation and stimulated thrombogenicity were observed using EVs carrying TF from the pericardial blood of patients who received cardiac surgery[116]. Rat BMSC-Exos were applied to the bleeding site in the hemorrhage liver model, which exhibited an inhibited amount of bleeding and shortened bleeding time, demonstrating their excellent hemostatic properties. However, no studies related to exosomes' promotion of coagulation in cutaneous wound healing have been conducted. Further studies are needed to demonstrate the potential role of exosomes in the hemostasis phase of wound healing.

Inflammation

Excessive inflammation is a major cause of persistent diabetic wounds. Abnormal macrophage polarization and cytokine overexpression lead to an uncontrolled and persistent inflammatory state and can cause secondary tissue damage[7]. MSCs-Exos can inhibit the differentiation, activation, and proliferation of T cells as well as reduce IFN-γ release[118]. They can reduce the concentration of the inflammatory cytokines, TNF-α, iNOS, IL-1β, and IL-6[119] and upregulate the expression of the anti-inflammatory cytokine IL-10[120,121]. MSCs-Exos can also induce M2 polarization of macrophages to promote wound healing by delivering exosome-derived miR-223 to target regulating the expression of pknox1 protein[122].

Such abilities can also be observed in diabetic wounds. Topical application of native AMSC-Exos to diabetic mice dorsal full-thickness skin wounds also downregulated inflammatory cytokines (IL-6, TNF-α, CD14, CD19, and CD68) expression and promoted wound healing[123]. Similar alleviated inflammatory effects achieved by regulating inflammatory factors could also be observed in the combination of intraperitoneal Nrf2 pharmaceutical activator and BMSC-Exos subcutaneous injection, demonstrating decreased inflammatory cytokines TNF-α and IL-1β and increased anti-inflammatory cytokines IL-4 and IL-10[124]. Intradermal injection of MSC-Exos derived from human menstrual blood could induce macrophage polarization from the M1 to M2 phenotype, while this capacity is better than that of menstrual blood-derived MSCs[125]. Significantly lower M1 polarized macrophages and higher M2 polarized macrophages were also observed in the diabetic mouse air pouch model and diabetic rat full-thickness skin wound model using BMSC-Exos, while melatonin-stimulated BMSC-Exos (MT-Exos) had stronger effects[121]. Immunomodulatory capacity was enhanced after preconditioning. Moreover, MT-Exos could improve wound healing by activating the PTEN/PI3K/AKT signaling pathway to promote macrophage M2 polarization, angiogenesis, and collagen synthesis; promote the resolution of persistent inflammation; and drive the transition from inflammation to proliferation[121]. HUCMSC-Exos pretreated with lipopolysaccharides have better regulatory properties for macrophage polarization and resolution of chronic inflammation by transferring miR-let7b, while the TLR4/NF-κB/STAT3/AKT pathway is important in regulating this mechanism to promote wound healing[126]. The use of engineered TNF-α/hypoxia-pretreated HUVMSC-Exos in infected DCWs also decreased proinflammatory cytokines (TNF-α, IL-1β, and IL-6), induced M2 macrophage polarization, reduced bacterial burden, and bacterial colonization at the wound sites. Reduced levels of oxidative biomarkers and increased levels of antioxidant mediators also demonstrated the ability of oxidative stress suppression[127]. The combination of BMSC-Exos and carboxyethyl chitosan-dialdehyde carboxymethyl cellulose hydrogel revealed skewed macrophage functional polarity from M1 toward an anti-inflammatory M2 phenotype, as well as enhanced antibacterial effects by significantly inhibiting bacterial growth[128].

Proliferation

Fibroblasts, keratinocytes, and endothelial cells participate in the proliferative phase. Unlike the dual regulatory effects on the tumor, MSC-Exos directly affect the proliferative phase of wound healing by stimulating the proliferation and differentiation of these cells, as well as promoting angiogenesis at injury sites[104]. Enhanced migratory and proliferative capacity and inhibited apoptosis of keratinocytes by activating the AKT/HIF-1α and Wnt/β-catenin pathways were observed with AMSC-Exos[129,130]. BMSC-Exos demonstrated the ability to promote fibroblast proliferation, migration, and secretion of growth factors and can induce tube formation in human umbilical vein cells (HUVECs)[131]. AMSC-Exos induced angiogenesis in both *in vivo* and *in vitro* experiments, and the promotion of angiogenesis in ECs was achieved by transferring miR-125a to inhibit DLL4 expression, accompanied by the downregulation of pro-angiogenic genes (Ang1 and Flk1), and upregulation of anti-angiogenic genes (Vash1 and TSP1)[132]. In addition to its pro-proliferative ability *in vitro*, the pro-healing effect of MSC-Exos has also been observed in acute non-diabetic wounds. MSC-Exos from human umbilical cord Wharton's jelly could regulate HaCaT cell function by suppressing AIF nucleus translocation and PARP-1 hyperactivation, thus attenuating full-thickness skin wounds by enhancing re-epithelialization and angiogenesis[133]. Fetal dermal-derived MSC-Exos accelerated wound closure in a mouse full-thickness skin wound model by activating the Notch signaling pathway to promote the motility and secretory capacity of fibroblasts[134].

Similarly, exosomes from MSCs improve proliferation and angiogenesis in diabetic wounds. AMSC-Exos accelerated cutaneous wound healing in diabetic mice with full-thickness skin wounds model by enhancing cell proliferation, inhibiting apoptosis, and promoting angiogenesis. They also repaired skin barrier functions, and produced large amounts, regular arrangement, and dense distribution of new collagen[123]. Shabbir *et al*[131] have also reported that these cells significantly increased their proliferation when treated with MSC-derived exosomes. Enhanced angiogenesis and fibroblasts proliferation, migration, and differentiation abilities were observed in diabetic wounds treated with human decidua derived MSC-Exos, as well as an improved fibroblast senescent state, reduced scar width, and larger and better-organized collagen deposition[135].

Various methods have been used to modify MSC-Exos to enhance fibroblast proliferation and angiogenesis. Co-culture of lncRNA H19-transfected BMSC-Exos with fibroblasts extracted from foot tissue of patients with DFUs revealed that overexpressed exosomes regulated the PTEN-mediated PI3K/AKT signaling pathway by competitively binding miR-152-3p to enhance proliferation and migration of fibroblasts and inhibit apoptosis and inflammation[136]. Injecting such exosomes into the peri-wound tissue of diabetic mice revealed the same changes in expression and accelerated wound healing[136]. Atorvastatin-pretreated BMSC-Exos promoted proliferation, migration of HUVECs, and vascular endothelial growth factor (VEGF) expression and accelerated wound healing in diabetic full-thickness skin injury rat models[137]. Pioglitazone-pretreated BMSC-Exos-treated full-thickness wounds in diabetic rats achieved faster-wound closure, with more adequate re-epithelialization and extensive collagen deposition, significantly enhanced wound perfusion, and had significantly upregulated levels of VEGF and CD31[138]. Subcutaneous injection ofmmu_circ_0000250-modified AMSC-Exos *via* miR-128-3p/SIRT1-mediated autophagy promoted wound healing in diabetic mice, and increased capillary and granulation tissue production was detected owing to promoted proliferation and migration and reduced apoptosis of endothelial cells[139].

Biological scaffolds can improve the survival of exosomes in the inflammatory environment of diabetic wounds and maintain their sustained release. UCMSC-Exos combined with the Pluronic F127 hydrogel revealed promoted chronic wound healing in diabetic mice. The elevated number of blood vessels and microvascular density, enhanced regeneration of granulation tissue, and cell proliferation were also observed, with the significant formation of new hair follicles in the center of the wounds, sufficient subepidermal collagen deposition, and orderly arrangement of collagen fibers[140]. Similar changes were observed in the wounds of diabetic mice using engineered bioactive self-healing antimicrobial exosome hydrogels (FHE@exo), and the elevated number of dermal appendages and differentiation and re-epithelialization of the epidermis were also observed[141]. The combination of human gingival tissue-derived MSC-Exos (GMSC-Exos) and a chitosan/silk hydrogel sponge promoted re-epithelialization, angiogenesis, and collagen deposition, while the increased nerve fiber density also reflected enhanced neuronal ingrowth in the proliferative stage[142].

Matrix remodeling

In the final stage of wound healing, the production and remodeling of the ECM are key factors in determining the time of wound healing and degree of scarring. Recently, some studies have reported on the effects of exosomes on matrix remodeling. BMSC-Exos have been demonstrated to restore normal skin morphology in rats with full-thickness skin injury[143], while these capacities relied on the downregulation of TGF-β1 and upregulation of TGF-β3 by inhibiting the TGF-β/Smad signaling pathway. UCMSC-Exos had large amounts of miR-21, miR-23a, miR-125b, and miR-145, while it inhibited the differentiation and excessive aggregation of myofibroblasts and exerted an anti-scarring effect *via* the TGF-β2/Smad2 pathway *in vivo*[144]. UCMSC-Exos can also promote the phosphorylation of YAP, a key site of the Hippo pathway, to negatively regulate the Wnt4/β-catenin pathway to balance tissue regeneration and repair, with excessive cell proliferation and collagen deposition in the remodeling stage[145]. It was noted that intravenous injection of ADSC-Exos could increase the ratio of type III collagen to type I and TGF-β3 to TGF-β1, prevent fibroblast-to-myofibroblast differentiation, and reduce scarring at incisions in the full-thickness skin injury models[146]. They could also induce the ERK/MAPK pathway in fibroblasts to increase the expression of MMP3, thereby increasing MMP3/TIMP1 to regulate ECM remodeling[146].

In contrast to the promoted cell proliferation and abundant granulation tissue in the early stage of healing, proliferative activities were reduced during the late repair stage to prohibit tissue hyperplasia when using FHE@exo, suggesting entry into the remodeling phase that prevents excessive tissue proliferation to promote wound healing[141]. The application of GMSC-Exos with chitosan/silk hydrogel sponge on the wounds of diabetic rats revealed more collagen deposition and thick wavy collagen fibers that were arranged in an orderly fashion, which is similar to that in normal skin, implying enhanced ECM remodeling[142]. These were also observed in the local transplantation of HUCMSC-Exos with polyvinyl alcohol/alginate nano hydrogel and of miR-126-3p overexpressed synovial-derived MSC-Exos with hydroxyapatite/chitosan composite hydrogel[147,148]. Altogether, these studies indicate that MSC-Exos play a pivotal role in the ECM remodeling phase of wound healing.

The various stages of wound healing are closely interwoven. MSC-Exos inherit the genetic information of their parental cells and can transfer the therapeutic bioactive substances to target cells to participate in intercellular communication, resulting in the regulation of target cell function and promotion of wound healing[81,149]. We analyzed the current preclinical application of MSC-Exos in diabetic wound models, and the cell source, administration method, dose, frequency, animal type, wound diameter, efficacy, and possible molecular mechanisms are summarized in Table 1. Additionally, MSC-Exos were not only responsible for a specific stage but also promote microenvironment changes in the wounds at each stage to exert a pro-healing effect. Although the biological functions of promoting diabetic wound healing are generally similar, certain differences exist in the regulated signaling pathways of different cell-derived exosomes or receiving different preconditioning, according to previous studies. The regulatory mechanisms most frequently studied in diabetic wound models and may potentially confirmed in DCWs, as well as the microenvironmental changes in inflammatory and proliferative stages of wound healing after using MSC-Exos, are depicted in Figure 1.

CURRENT STATUS AND PROSPECTS OF CLINICAL APPLICATIONS OF EXOSOMES IN DIABETIC CHRONIC WOUNDS

Preclinical studies have demonstrated the ability of MSC-Exos to promote diabetic wound healing. No evident pathological abnormalities in the heart, liver, spleen, lung, and kidneys sampled after exosome treatment were observed, and biomarkers reflecting liver and kidney function blood biochemistry were also within normal limits[127]. Meanwhile, no erythema, edema, or irritation was observed in the wound area after exosome treatment[137], confirming the superior biosafety of exosome therapy.

We also searched for applications of exosomes secreted by stem cells from other sources in diabetic wounds and summarized them in Suppl Table S1. Noteworthy, the types of animals used for modeling were limited to mice and rats. Most of the studies involved acute diabetic wounds, that is, exosomes were administered immediately after successful modeling of full-thickness skin wounds. Only one study introduced *Staphylococcus aureus* to establish infected chronic wounds after the establishment of full-thickness cutaneous wounds and confirmed that exosomes were effective in treating infectious DCWs[127]. The efficacy and safety of MSC-Exos need to be further confirmed in larger animal models and DCW models. Because the islet morphology, structure and function, blood biochemical indices, and skin structure of minipigs are more similar to those of the human body, they are ideal animal models for studying diabetic wounds[159]. Our team has established a chronic skin ulcer model in diabetic miniature pigs in the early stage[160] and is researching on exosome products to explore the optimal administration methods and dosages and to verify their therapeutic effects.

According to the search results in ClinicalTrials.gov, no clinical trials of MSC-Exos and exosomes from other sources for diabetic cutaneous wound healing have been registered. Therefore, we expanded the scope of clinical trials to search for exosomes derived from any sources and exosome-enriched stem cell-conditioned medium in various wound types (Table 2). None of the included four registered clinical trials had related results published, while they were all non-randomized one-arm pilot studies. Thus, more high-quality randomized controlled trials are required to further confirm these research results. Of note, the application of cell-free therapies in clinical patients requires special attention to security, although no adverse reactions of exosomes have been reported in preclinical studies. Moreover, ADSC-Exos has been confirmed to not induce any irritation or toxicity in skin sensitization, irritation, or oral toxicity tests[161]; therefore, they can be considered in clinical practice to promote wound healing in combination with basic wound care measures. Nevertheless, toxicological analysis of different tissue-derived MSCs-Exos and more evidence of short and long-term health safety assessments are required to confirm their safety.

Exosome research is still in its infancy, and the realization of the transformation from preclinical research to clinical application still has great exploration value. The problems of optimal preparation, extraction, isolation, and storage of exosomes on a large scale and their production efficiency have not yet been determined; preparation and identification of components due to different source cells and the high heterogeneity of exosome components have not yet been solved; specific regulatory mechanisms in DCWs have not yet been fully elucidated; efficacy and safety of different cell sources and/or administrations have not been proven, and reasonable and effective methods of fusing exosomes with other biomaterials have not yet been implemented, all these issues are barriers that limit the clinical application of exosomes.

Thus, efficient, stable, safe, and mass-producible stem cells and related products for the treatment of diabetic wounds are yet to be explored and developed. More research is required in future clinical trials and routine practice to determine the most effective cell sources for diabetic wounds; to establish optimal large-scale culture conditions of MSCs; to solve the preparation problem of huge heterogeneity of exosome components; to explore standardized isolation, quality control, purification, and characterization techniques of MSC-Exos; and to determine the best approach for long-term storage[162]. Researchers also need to fully understand the abilities, loss, distribution, diffusion efficiency, and clearance efficiency of exosomes after transporting them to target areas. Physical, chemical, or biological methods for preconditioning, genetic engineering, and transfection are used to specifically enhance a certain therapeutic potential to achieve relatively better wound healing than native exosomes, thus becoming new treatment directions[163]. Additionally, combining exosomes with biomaterials is possible to create bioactive dressings to enhance or combine repair ability, provide local microenvironment stability, and achieve sustained release of exosomes[74]. Additionally, starting clinical trials as soon as possible is necessary to verify the optimal dosages, administration methods, and efficacy evaluation of MSC-Exos in clinical patients, looking forward to its broad application prospects in promoting DCW healing in clinical practices[162].

CONCLUSION

DCWs, which are one of the most common chronic refractory wounds, pose a heavy burden to patients, families, and society. Current studies have suggested that MSC-Exos can play an important role in various aspects of wound healing and hold sufficient promise for promoting diabetic wound healing. However, recent clinical applications of MSC-Exos in DCW repair are still limited. Moreover, clinical translational issues, such as exosome production, isolation, purification, and storage processes, the most effective route of administration and dose, and efficacy evaluation remain. Accurate and efficient exosome products need to be established, and experiments in animals that have a greater resemblance to human skin tissues and clinical trials need to be initiated as soon as possible to validate the optimal dosage and administration, and efficacy evaluation for using MSC-Exos to provide safety assurance for further clinical applications. Modification of MSC-Exos and integration with biomaterials to improve their efficacy and reduce their elimination rate may be a promising direction. We look forward to the clinical application of MSC-Exos for diabetic wound healing.

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