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REVIEW

Diverse-Origin Exosomes Therapeutic Strategies for Diabetic Wound Healing

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Abstract: Diabetic wounds represent a pressing clinical challenge in the medical field. Compared to healthy individuals, patients with diabetes present with various complications, including abnormal blood sugar levels, microcirculation disorders, and impaired cellular function. Moreover, they are at a higher risk for skin damage and have a more difficult healing process. In recent years, exosome-based regenerative medicine has provided new strategies for diabetic wound treatment. The bioactive molecules contained in the exosomes, including functional proteins, bioactive lipids, and regulatory RNAs, allow them to suppress inflammation, enhance cell migration, and promote angiogenesis. As exosomes from different sources have different composition and function, the characteristics of their source must be considered when using them. Unlike traditional single source research, this review describes the mechanism of action of exosomes from different sources in diabetic wound-healing process, including mammalian cell-derived exosomes and plant-derived exosome-like nanoparticles. These findings not only provide a theoretical basis for the selection of exosome sources but also lay a foundation for the development of personalized, multimodal treatment plans.

Keywords: exosomes, diabetic wounds healing, mammalian-derived exosomes, plant-derived exosome-like nanoparticles, drug delivery, nanomedicine

Introduction

Diabetic wounds are a common complication of diabetes. Poor blood sugar control, microcirculation disorders, oxidative stress, and inflammation often result in delayed wound healing in diabetes. This can progress to severe ulcers or even require amputation, severely affecting the patient's quality of life.[1,2] Statistically, patients with diabetic foot ulcers (DFUs) have a 50% mortality rate over 5 years.[3,4] Regardless of the most advanced clinical interventions, approximately 10% of the patients with DFUs undergo amputation, and the mortality rate following such procedures can be as high as 80%.[5] Normal wound healing involves numerous factors, including cell proliferation and migration, angiogenesis, and extracellular matrix (ECM) deposition and remodeling.[6] However, in patients with diabetes, sustained high blood sugar levels lead to substantial challenges in the typical wound-healing process, interfering with wound repair.[7] Diabetic wound fails to enter the normal healing phase and instead falls into a chronic inflammatory state. This phase is characterized by excessive accumulation of M1 macrophages, leading to persistent inflammation. Moreover, there is a significant reduction in fibroblast proliferation, function, and differentiation into myofibroblasts, which further affects collagen synthesis and tissue remodeling.[8–10] Multiple methods including wound dressings, hyperbaric oxygen therapy (HBOT), growth factor therapy, and stem cell therapy are currently used in clinical practice.[11] For example, hydrogels can load active substances and its composition and structure can be adjusted to provide different functions such as antibacterial, antioxidant, or inflammatory factor expression regulation, effectively alleviating wound infection and inflammation.[12–14] However, these methods have substantial clinical limitations. First, traditional dressings have insufficient penetration

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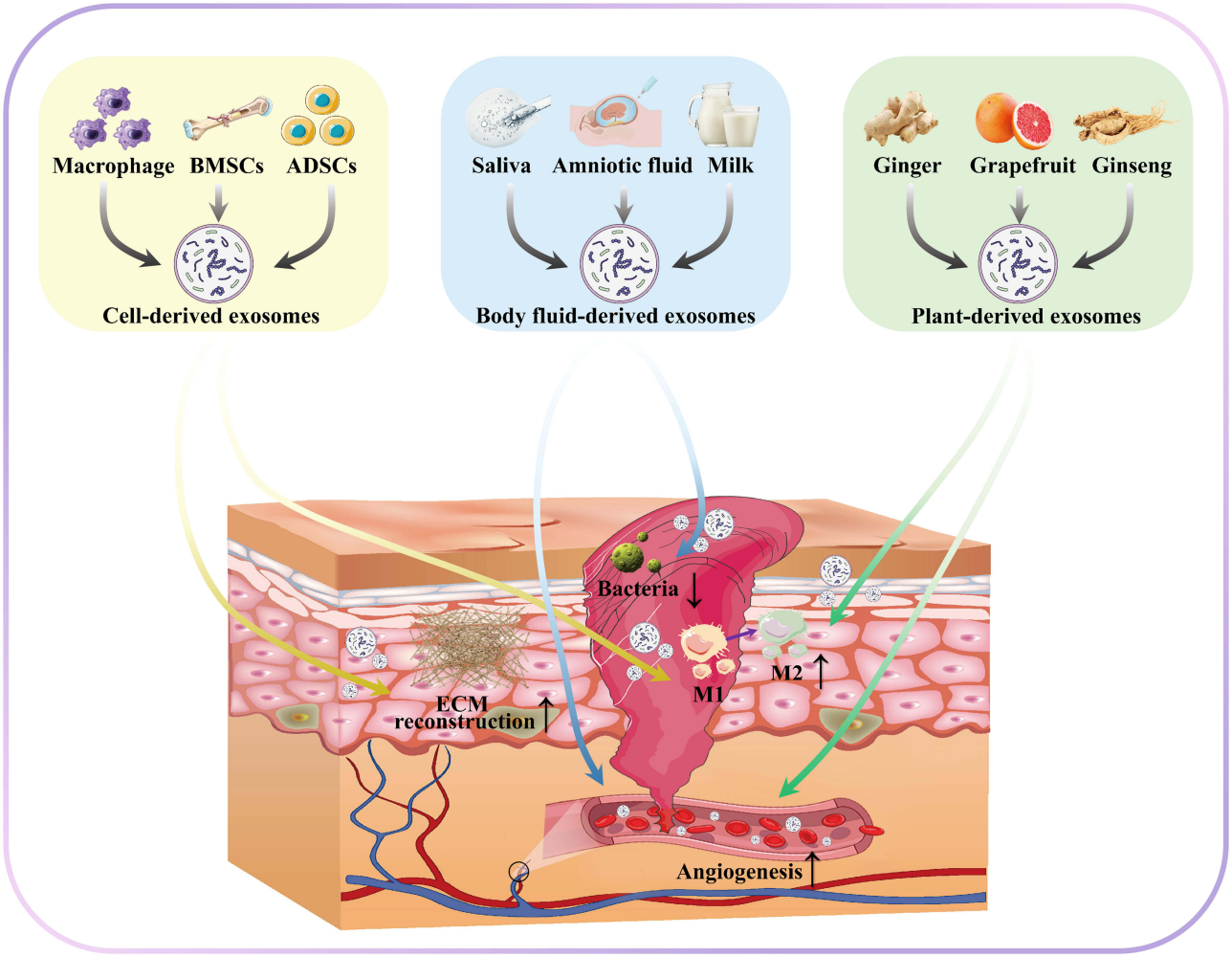
Graphical Abstract



in severely infected wounds and cannot effectively control deep tissue infection; in addition, frequent dressing changes can exacerbate patient pain.[15–17] Second, hyperbaric oxygen therapy requires specialized hyperbaric chambers and professional operation teams, with treatment cycles lasting 20–30 sessions, not only increasing the patient's financial burden but also potentially causing complications such as middle ear barotrauma and oxygen toxicity.[18] Therefore, developing new therapeutic systems with high biocompatibility, low immunogenicity, and targeted delivery capabilities is needed to improve diabetic wound treatment, providing a clear research direction for exosome-based regenerative medicine strategies.

To address the abovementioned issues, exosome-based regenerative medicine can be useful. Exosomes demonstrate unique therapeutic potential, providing multilevel repair mechanisms for diabetic wounds.[19] They are extracellular vesicles approximately 30–150 nm in diameter that play a key role in intercellular communication by carrying bioactive molecules such as miRNAs, long non-coding RNAs, and functional proteins.[20] Compared to traditional therapies, structural characteristics of exosomes address key barriers in drug delivery. Although their nanoscale size and lipid bilayer structure provide excellent tissue penetration capability, their vesicular nature makes them ideal carriers for biological molecules, capable of simultaneously delivering multiple therapeutic factors that work synergistically, such as vascular endothelial growth factor (VEGF) and transforming growth factor β (TGF-β).[21] Furthermore, in terms of

inflammation regulation, exosomes can promote the transformation of macrophages from proinflammatory M1 type to anti-inflammatory M2 type, substantially reducing local inflammation.[22] Additionally, a single exosome can continuously release active components over an extended period, circumventing the issue of repeated interventions required by methods such as hyperbaric oxygen therapy.[23] Finally, due to the absence of nuclear structures, exosomes circumvent the potential tumorigenesis risks associated with stem cell therapy.[24] In the complex pathological environment of diabetic wounds, exosomes simultaneously regulate local inflammation, angiogenesis, and extracellular matrix remodeling to address multiple barriers in diabetic wound repair, providing an alternative for shortening existing treatment cycles and reducing recurrence rates.[25]

Considering the abovementioned properties, researchers aim to optimize the therapeutic efficacy of exosomes in wound healing through precise regulation strategies. The cross-integration of biomaterials science and nano-delivery systems has resulted in the development of exosome-hydrogel composite systems. These intelligent carriers not only extend the retention time of exosomes in the wound microenvironment but also achieve spatiotemporally controlled release of bioactive factors through microenvironment-responsive mechanisms.[26–28] Surface chemical modification of exosomes by reshaping their membrane structural characteristics can significantly enhance tissue targeting and molecular loading, providing a structural foundation for precision treatment.[29–31] Moreover, the composition and function of exosomes vary depending on their source. Based on their origin, exosomes can be classified into two major categories: mammalian-derived exosomes (MDEs) and plant-derived exosome-like nanoparticles (PELNs)[32] (Figure 1). The former has a lipid bilayer constructed with cholesterol and glycosphingolipids as core scaffold, providing it with unique structural rigidity and biological stability,[33,34] whereas the latter presents a differentiated lipid distribution pattern, characterized by enhanced membrane fluidity and biological solubility.[35] MDEs can be isolated from various cell types, from mesenchymal stem cells to immune cells as well as from biological fluids such as blood and amniotic fluid, each having distinctive immunomodulatory capabilities and tissue repair functions.[36] However, PELNs, extracted from various plant matrices, have garnered attention due to their rich natural components and relatively low immunogenicity and are abundant in natural active ingredients such as polyphenols and flavonoids, demonstrating unique advantages in oxidative stress regulation and inflammatory balance.[37]

Unlike previous studies focusing on a single exosome source, this review comprehensively compares the mechanisms of action between mammalian and plant-derived exosomes in diabetic wound healing. Through a detailed discussion of the functional characteristics of exosomes from different sources, this review reveals the critical impact of exosome origin on their therapeutic effects. This innovative research on multisource exosomes provides a theoretical basis for developing individualized treatment plans, while exploring challenges and opportunities in exosome scale-up production, quality control, and clinical translation, establishing a foundation for innovative therapeutic strategies for diabetic wound healing.

Mammalian-Derived Exosomes

MDEs have become the focus of research in the field of diabetic wound healing due to their excellent biocompatibility, precise tissue targeting, and ability to carry various bioactives. MDEs can be classified as cell-derived (eg, MSCs, neural stem cells) and body fluid-derived (eg, plasma, amniotic fluid), based on their source. MDEs play a vital role in modulating inflammatory responses, fostering angiogenesis, augmenting cell proliferation and migration, and orchestrating ECM remodeling. Thus, a novel therapeutic strategy using exosomes can offer hope for treating diabetic wounds.

Cell-Derived Exosomes

MSC-Exos

MSCs are a subset of adult nonhematopoietic stem cells of mesodermal origin, which can be isolated from various tissues, such as bone marrow, umbilical cord blood and tissues, placental tissues, and adipose tissue. MSCs have the ability to self-renew and differentiate into various specialized cell types.[38] MSC-Exos exhibit effects similar to MSCs in inducing cell proliferation and differentiation as well as angiogenesis in vitro, but their therapeutic effect on the injury site is much better than that of MSCs.[39] MSCs-Exos coordinate various stages of wound healing by regulating

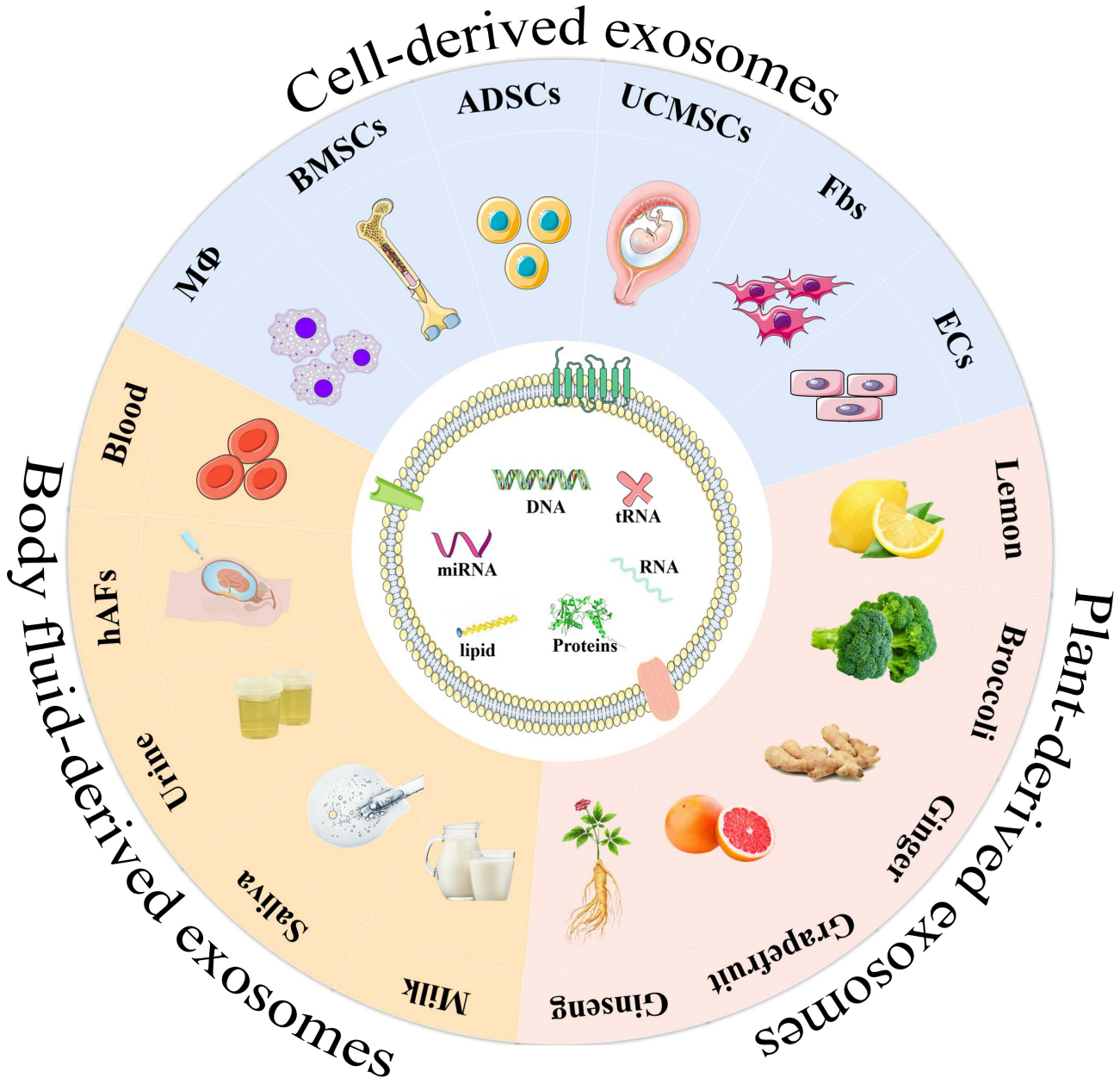


Figure 1 Derived from cells, body fluids, and plant exosomes.

inflammatory responses, promoting cell proliferation, enhancing cell migration ability, and stimulating angiogenesis.[40] This section describes the mechanisms of action of the three main MSC-derived exosomes in diabetic wound healing.

BMSC-Exos

Bone marrow MSCs (BMSCs) are the earliest isolated MSCs and have been extensively researched and applied in stem cell therapy.[41] BMSC-Exos have the advantages of a low infection rate by pathogenic microorganisms, stable biological performance, low immune rejection rate after transplantation, and high number of generations.[42] BMSC-Exos play an anti-inflammatory, angiogenesis-promoting, and cell proliferation-promoting role in wound healing. Moreover, in the context of wound healing, BMSC-Exos exhibit anti-inflammatory properties, facilitate angiogenesis, and promote cellular proliferation.

First, during the inflammatory phase of wound healing, BMSC-Exos accelerate the polarization of M2 macrophages, thereby shortening the duration of inflammation.[43] Luo et al observed that intramuscular injection of BMSC-Exos after muscle contusion reduced inflammation. This was attributed to the promotion of M2 macrophage polarization and anti-inflammatory factor expression as well as a reduction in inflammatory cytokine production in the inflammatory microenvironment.[44] Additionally, BMSC-Exos significantly decreased M1 macrophage polarization and increased M2 macrophage polarization in a diabetic mouse air pocket model and a diabetic rat model of whole skin trauma. In contrast, melatonin-stimulated BMSC-Exos (MT-Exos) had a stronger effect.[45] In a study, multifunctional BMSC-Exos-loaded carboxyethyl chitosan (CEC)-dialdehyde carboxymethylcellulose (DCMC) hydrogel (MSC-Exos@CEC-DCMC HG) promoted chronic diabetic wounds by modulating wound inflammation through the promotion of macrophage conversion from proinflammatory M1-type to reparative M2-type and significantly inhibiting bacterial growth to enhance antimicrobial effect repair.[46]

Moreover, stimulation of angiogenesis, particularly through the modulation of vascular endothelial growth factor A (VEGFA), is one of the key strategies for promoting neovascularization and accelerating wound repair in diabetic wound therapy.[47] Han et al found that BMSC-Exos carry Kruppel-like factor 3 antisense RNA1, which promotes the proliferation of chondrocytes and cardiomyocytes and facilitates VEGFA signaling and cutaneous wound healing in patients with diabetes by downregulating miR-383.[48] Similarly, Zhang et al found that endothelial-specific miRNA-126 (miR-126) derived from BMSC-Exos activated the PI3K/AKT signaling pathway by targeting phosphatidylinositol 3-kinase regulatory subunit 2 through in vitro experiments, upregulated the expression of angiogenesis-associated VEGF and Ang-1 genes, and promoted angiogenesis in HUVECs. In vivo experiments confirmed that the application of Exo-miR-126 considerably enhanced angiogenesis at the wound site and promoted wound healing.[49] Tang et al found that circ-Snhg11 of BMSC-Exos promoted SLC7A11/GPX4-mediated anti-iron apoptotic signaling through sponge miR-144-3p and promoted angiogenesis.[50] In another study, atorvastatin (ATV)-pretreated BMSC-Exos (ATV-Exos) upregulated the AKT/eNOS signaling pathway and enhanced the angiogenesis-promoting function of BMSC-Exos, which accelerated diabetic wound repair and regeneration.[51] Further studies revealed that IFN-γ pretreated BMSC-Exos miR-126-3p promoted angiogenesis through the SPRED1/Ras/ERK axis, showing higher therapeutic efficacy than NExos in diabetic wound healing.[52]

The pathogenesis of diabetic wounds involves abnormalities in various cellular biological processes, such as epidermal-specific macrophage/autophagy damage, cell proliferation, and apoptosis.[53] Notably, culturing BMSCs in a hypoxic environment enhanced the regenerative and cytoprotective effects of BMSCs.[54] Shi et al conducted an innovative study revealing that exosomes from hypoxic bone marrow mesenchymal stem cells (hyBMSC-Exos) significantly enhance diabetic wound healing through a specific epidermal autophagy mechanism. Their research demonstrated that hyBMSC-Exos can deliver miR-4645-5p, which targets and inhibits MAPKAPK2 expression, to keratinocytes. This inhibition prevents MAPKAPK2-mediated activation of the AKT-mTORC1 signaling pathway, a known suppressor of cellular autophagy. The resulting restoration of keratinocyte autophagy promotes cell proliferation and migration, accelerating the re-epithelialization process essential for wound closure (Figure 2).[55] By contrast, Shen et al found that miR-93-3p from BMSC-Exos restored cell function and inhibited apoptosis in epithelial HaCaT cells by inactivating apoptotic peptidase-activating factor 1—a finding that may help establish a new therapeutic strategy for skin wound healing.[56] Furthermore, BMSC-Exos reduced the expression of transforming growth factor beta 1 (TGF-β1) and upregulated the expression of TGF-β3 and Smad7 in the TGF-β/Smad signaling pathway, effectively promoting the proliferation of human keratinocytes (HaCaT) and human dermal fibroblasts and facilitating skin wound healing.[57]

These findings provide a theoretical basis for the practical application of BMSC-Exos in the clinic. However, the speed of cultivating and amplifying germinated stem cells is slow, making it impossible to obtain a large number of BMSCs in a short time period. Second, red blood cell contamination is a risk during separation. Additionally, eliminating the invasion of MSCs from the bone marrow is a challenge.[58] These issues may limit the clinical application of BMSCs-Exos. Therefore, further research and innovation is required to overcome these challenges.

ADSC-Exos

Adipose MSC-derived exosomes (ADSC-Exos) are highly stable and easy to store. Compared to MSCs derived from the

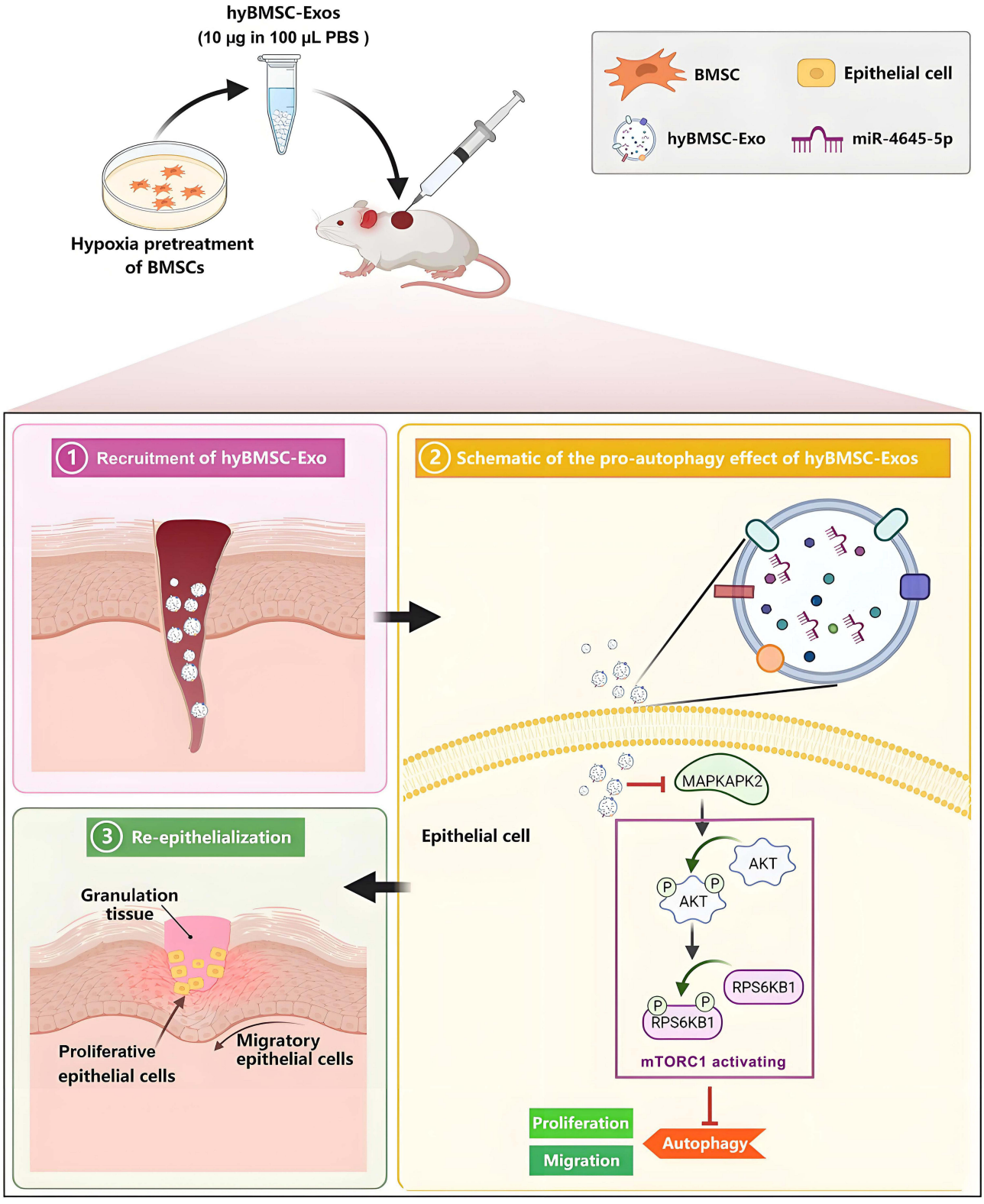


Figure 2 Schematic of the therapeutic effect of hyBMSC-Exos on diabetic wounds. The complete treatment process is as follows. (1) Recruitment of hyBMSC-Exos at the wound site following injection. (2) Molecular mechanism showing hyBMSC-Exos delivering miR-4645-5p to epithelial cells, where it inhibits MAPKAPK2, preventing phosphorylation of AKT and subsequent activation of mTORC1, ultimately promoting autophagy. (3) The resulting increased keratinocyte proliferation and migration leads to enhanced re-epithelialization and wound closure. Reproduced with permission from Shi Y, Wang S, Liu D et al. Exosomal miR-4645-5p from hypoxic bone marrow mesenchymal stem cells facilitates diabetic wound healing by restoring keratinocyte autophagy. Burns Trauma. 2024;12. Copyright (2024) Oxford University Press.[55]

bone marrow, ADSCs have many advantages.[59] First, the amount of derived from the adipose tissue is approximately 500 times more than that of those derived from the bone marrow, making the sources for ADSCs abundant. ADSCs can also be obtained with high purification efficiency.[60] Next, the extraction of ADSCs is relatively painless and less traumatic, and these can be obtained through liposuction surgery.[42] Studies have shown that ADSC-Exos has a better effect than BMSC-Exos, ADSC-Exos are a more ideal source of cells. In wound repair, ADSCS-Exos regulates immune response and inflammation, promotes blood vessel production, accelerates the proliferation of skin cells and re-epithelization, and regulates collagen to reshape, thereby suppressing scar hyperplasia.

Studies have found that ADSC-Exos regulate macrophages to inhibit inflammation.[61] Specifically, ADSC-Exos can directly interact with macrophages, resulting in the suppression of the macrophages' nuclear factor κB (NF-κB) activity and specific inflammatory genes, which eventually leads to the reduction of inflammation in the mediators of macrophages. Studies have found that ADSC-Exos reduced the inflammatory response in mice RAW264.7 cells, reduced the level of impression of macrophages and inflammatory cytokines, and increased the secretion of anti-inflammatory cytokines.[62] In macrophages, MiR-155 generated by ADSC-Exos combined its target SOCS1 and adjusted the JAK/STAT signal to promote M1 macrophage polarization and reduce chronic inflammation.[63] Li et al found that ADSC-Exos overexpressing Nrf2 effectively reduced the levels of reactive oxygen species and inflammatory factors, promoted foot wound healing, and reduced the ulcer area in diabetic rats.[64] By contrast, refractory diabetic wounds create a persistent inflammatory and hypoxic environment. Xiao et al found that under hypoxic conditions, HypADSCs-Exos exhibited higher survival and proliferation than that under normal oxygen conditions. The expression profiles of miRNAs in these exosomes change, and they may promote wound healing by regulating cell metabolism, differentiation, and TGF-β functions. Additionally, under hypoxic conditions, the exosomes derived from fattened cells promoted high-quality healing of diabetic wounds by activating the PI3K/AKT pathway.[65]

ADSC-Exos have proven that miRNA-125A can be transferred to endothelial cells and promote vascular production by inhibiting the expression of Delta-like protein 4 (DLL4).[66] Zhang et al developed a HaCaT cell model and a mouse wound healing model to study the effect of ADSC-Exos on wound healing. Results showed that ADSC-Exos promoted the proliferation and migration of HaCaT cells by regulating the activation of the AKT/HIF-1α signaling pathway, thereby promoting wound healing.[67] Wang et al showed that ADSC-Exos regulated the ratio of type III collagen: type I collagen, TGF-β3:TGF-β1, and MMP3:TIMP1 as well as regulated the differentiation of fibroblasts to reduce the formation of scars and promote ECM reconstruction in skin wound repair.[68] Another study found that miRNA-146a-modified ADSC-Exos, by upregulating serine protease inhibitor family H member 1 and phosphorylating ERK, promoted fibroblast migration and proliferation as well as neovascularization to promote wound healing.[69]

ADSC-Exos help reduce scar formation. In specific cases, miR-192-5p present in ADSC-Exos regulates the Smad pathway in proliferative scar fibrosis by targeting IL-17RA and inhibits fibroblast proliferation, excessive collagen synthesis, and ECM deposition, thereby impeding scar formation.[70] ADSC-Exos impeded the differentiation of fibroblasts to myofibroblasts by activating the ERK/MAPK pathway. This process led to an elevated COL-3/COL-1 ratio, TGF-β3/TGF-β1 ratio, and MMP3/TIMP1 ratio, promoting the reconstruction of the ECM during skin wound healing and reducing scar formation.[71] Although ADSC-Exos accelerate wound healing, they may affect melanoma migration and invasion through the fatty acid oxidation pathway.[42] Therefore, future studies must focus on the in-depth understanding of their mechanism of action as well as the safety assessment for clinical applications.

Umbilical Cord MSCs-Exos

Umbilical cord MSCs (UCMSCs) are present in neonatal umbilical cord tissue and are a versatile and ideal source of stem cells. They synthesize and secrete various trophic factors and cytokines, promoting the proliferation and function of other cell types.[72] Compared to different types of stem cells, UCMSC-Exos have low immunogenicity and high stability. Moreover, as a drug carrier, it is easy to control their route of administration and dosage. UCMSC-Exos are safe and reliable for long-term application without liver or kidney toxicity. In addition, they have a high differentiation rate when applied in vivo and are not potentially tumorigenic. UCMSC-Exos are now widely used in regenerative medicine and for treating various diseases.[73]

UCMSC-Exos promote angiogenesis during wound healing through multiple mechanisms. Similar to BMSC-derived exosomes, UCMSC-Exos upregulated VEGF expression and induced the upregulation of VEGF and HIF-1a expression, thereby promoting angiogenesis in a rat model. The efficacy of HIF-1a in enhancing UCMSC-Exos-induced VEGF expression and promoting angiogenesis has been demonstrated by specific RNA inhibitors or siRNA.[74] Zhang et al identified miR-21 in UCMSC-Exos as a potential intercellular messenger, activating the NOTCH1/DLL4 pathway and promoting the proliferation, migration, and angiogenesis of endothelial progenitor cells (EPCs).

UCMSC-Exos stimulates cell proliferation and collagen synthesis through multiple mechanisms. Kim et al demonstrated the ability of UCMSC-Exos to promote human dermal fibroblast proliferation and collagen synthesis.[75] Application of UCMSC-Exos to the treatment of human skin trauma led to increased expression of COL-I and elastin. Furthermore, Teng et al showed that HucMSCs-exo grafts increased diabetic wound healing. In vitro, HucMSCs-exo promoted the proliferation of human umbilical vein endothelial cells (HUVECs) and NIH-3T3 cells. In vivo, HucMSCs-exo reduced wound area and inflammatory infiltration and increased collagen fibers. Furthermore, wound tissues in the HucMSCs-exo group had higher CD206, CD31, and VEGF expression than the control group at 14 days and lower TNF-α levels. The results suggest that HucMSCs-exo promotes diabetic wound repair by inducing anti-inflammatory macrophages and promoting angiogenesis and collagen deposition.[43] Cytokine profiling showed that HucMSCs-Exos contained high doses of IL-6, IL-8, and other cytokines. HucMSCs-exos could stimulate cell proliferation and resist hydrogen peroxide-induced apoptosis, promote cell proliferation, and protect against oxidative stress-induced apoptosis by activating ERK1/2 and p38, thereby promoting wound healing.[76]

The role of UCMSC-Exos in inhibiting scar formation was also confirmed. Myofibroblast aggregation is a key factor in scar formation. Based on this, Fang et al used high-throughput RNA sequencing and functional to verify that the presence of certain miRNAs (eg, miR-21, −23a, −125b, and −145) in UCMSC-Exos that blocked the TGF-β2/SMAD2 pathway. In vitro and in vivo, these effectively impeded myofibroblast aggregation and reduced scar formation. During the organizational restructuring phase, the HucMSC-Exos-derived Wnt4 factor promotes nuclear translocation and activity of p-catenin. This enhances skin cell proliferation and migration.[77] Additional studies have found that HucMSC-Exos increased the in vivo expression of CK19, PCNA, and collagen I. During the in vitro heat stress response, HucMSC-Exos promoted skin cell proliferation and inhibited apoptosis, thereby accelerating wound healing.[78] In the treatment of type 2 diabetes, HucMSC-Exos showed remarkable potential. They attenuated the damage of insulin β-cells in rats, reversed insulin resistance in peripheral tissues, and improved glucose uptake and utilization by liver and muscle. This reduced blood glucose levels, providing a new strategy for treating diabetes.[79] Studies have reported that HUCMSC-derived exosomes bind to gelatin methyl acrylate. Inhibition of vein graft restenosis was done by enhancing endothelial function.[80] This provides new ideas for vascular repair and diabetic wound therapy.

Macrophage-Derived Exosomes

Macrophages are natural immune cells. They create an optimal microenvironment for reducing inflammation through paracrine mechanisms.[81] Macrophage-derived Exos act as important messengers. They pay an important role in communication with neighboring cells by regulating the levels of cytokines and miRNA, thereby alleviating the inflammatory response of the recipient cells.[82] In recent years, macrophage-derived exosomes (M-Exos) have exhibited a beneficial role in immunomodulation, cancer therapy, infection defense, and tissue repair.[83] Dysfunction of macrophages constitutes a major obstacle in diabetic wound healing. Macrophages tend to favor M1 polarization, leading to difficulties in wound closure, poor neovascularization, and reduced collagen deposition. In addition, it exacerbates the inflammatory response and inhibits wound healing.[84]

Studies have shown that M-Exos play important immunomodulatory roles in diabetic wound repair. Exosomes can effectively stimulate the polarization of macrophages, especially promoting the transition from the M1 phenotype to M2 phenotype, which is crucial for wound healing.[85] First, M-Exos reduce inflammation by decreasing the secretion of proinflammatory factors, such as TNF-α and IL-6. M-Exos promote wound re-epithelialization and neovascularization, thus accelerating diabetic wound healing.[86] M-Exos can promote the shift of macrophages from proinflammatory M1 type to anti-inflammatory M2 type in vivo, which effectively ameliorates the inflammatory response of receptor cells and stimulates angiogenesis.[87] A related report suggested that macrophage-derived exosomes attenuated thermal hyperalgesia in a mouse model of inflammatory pain, suggesting that they play a role in inflammatory dysregulation.[88] In addition,

M-Exos adjusted the level of cytokines and miRNAs. Another study showed that M2-Exo inhibited the expression of phosphatase and tensin homolog in HUVECs by transferring miR-21 and activating the AKT/mTOR pathway. By injecting M2-Exo into mouse skin wounds, it was demonstrated that M2-Exo acted as a promoter of angiogenesis and regeneration in vivo and accelerated skin healing.[89]

Additional reports indicate that macrophage-derived exosomes loaded with curcumin (Exos-cur) have good stabilizing, anti-inflammatory, antioxidant, and other biological activities. In in vitro experiments, Exos-cur promoted the proliferation, migration, and angiogenesis of HUVECs. It reduced the reactive oxygen species produced by high glucose-induced HUVECs and inhibited oxidative stress and inflammation. In vivo, Exos-cur activated the Nrf2/ARE pathway, promoting angiogenesis and accelerating wound healing, inhibiting the inflammatory response in diabetic rats.[90] Zeng et al investigated an MEs@PMN hydrogel with good biocompatibility and considerable photothermal effect. MEs released from MEs@PMN hydrogels significantly promoted the shift in macrophage phenotype from a proinflammatory M1 phenotype to an anti-inflammatory M2 phenotype, inhibited inflammation, and promoted angiogenesis to accelerate diabetic wound healing.[91] These studies suggest, M-Exos not only participate in disease progression but also serve as a new target for therapy, providing new research directions for disease diagnosis and treatment.

Endothelial Cells-Derived Exosomes

Current research has demonstrated that endothelial cells secrete exosomes and capture exosomes from various cell types.[92] In a high glucose environment, endothelial cells release increased amounts of exosomes. These exosomes promote the repair of endothelial cells and enhance their migration, thus accelerating wound healing.[93] Additionally, EPCs promote endothelial cell regeneration through a paracrine mechanism rather than through differentiation toward mature endothelial cells.[94] The high-glycemic environment and inflammatory response in diabetic wounds can lead to a decrease in the number of EPCs. Proliferation, adhesion, migration, and other abilities to assist in vascular synthesis are diminished, inhibiting the function of blood vessels. The vessel wall's advanced glycosylation end products (AGEs) reduce EPC activity. This hinders wound angiogenesis and reduces the rate of wound healing.[95] Exosomes are key components of paracrine secretion and represents an important intercellular communication through the delivery of functional RNAs and proteins.[96]

EPC-Exos significantly promoted neoangiogenesis and accelerated skin wound healing in diabetic rats. One study found that Erk1/2 signaling plays a key role in the proangiogenic effects of EPC-Exos on endothelial cells, and inhibition of this signaling significantly blocked the proangiogenic effects of exosomes. Subsequently, Li et al[97] found that EPC-derived exosomes increased the expression of angiogenesis-related molecules, including FGF-1, VEGFA, VEGFR-2, ANG-1, and several other factors, by stimulating endothelial cells. These factors eventually promoted wound healing by regulating the proliferation, migration, and tube formation function of vascular endothelial cells. Xu et al[98] found that miRNA-221-3p in EPCs-Exos increased the protein expression levels of angiogenesis-associated factors VEGF and CD31 and the cell proliferation marker Ki67. miRNA-221-3p in EPCs-Exos may be involved in diabetic complications, cell cycle, and p53-mediated AGE-RAGE signaling pathway to promote skin wound healing in diabetic mice.

HUVEC is a type of endothelial cell. It is widely used to study mechanisms of tumor angiogenesis and cardiovascular diseases.[99] HUVEC-Exos have shown promising results in promoting wound healing by modulating the immune response, reducing inflammation, promoting angiogenesis, accelerating skin proliferation and epithelialization, and modulating collagen remodeling to inhibit scar proliferation.[100] miRNA-containing exosomes secreted by human coronary artery endothelial cells and a human microvascular endothelial cell line (HMEC-1) can be internalized by the recipient EC, thereby regulating gene expression and stimulating EC proliferation and migration.[101] When inflammatory cells are restricted, there is an inadequate supply of oxygen and nutrients within the wound. Inadequate angiogenesis and impaired wound healing can occur.[64] A study found that the GelMA/PEGDA microneedle patch of HUVECs-Exos loaded with tazarotene accelerated blood circulation, providing the necessary nutrients and oxygen for the repair of damaged tissues.[100] This treatment has promising clinical applications. It provides a new direction for the clinical treatment of diabetic wounds.

Fibroblasts-Derived Exosomes

Fibroblasts are often defined as structural cells that are exclusively responsible for the deposition and remodeling of the ECM; they are essential for maintaining tissue integrity. Moreover, fibroblasts are closer to the skin than MSCs, and they can be obtained from the skin using less invasive techniques.[102] Fibroblasts contribute to tissue homeostasis, wound healing, defense against pathogens and injury, and metabolism; however, they may become dysregulated during disease, leading to fibrosis, chronic inflammation, poor wound healing, and cancer. Research has found that fibroblasts play key roles in various chronic inflammatory diseases, such as rheumatoid arthritis, Lyme arthritis, scleroderma, and atopic dermatitis.[103,104]

Although research on fibroblast-derived exosomes in diabetic wound healing is relatively limited, it has been shown that in contrast to cell-based therapies, exosomes exhibit easier endocytosis and higher loading efficiency due to their unique structure.[105] These exosomes are enriched with various growth factors and cytokines, such as TGF-β and matrix metalloproteinase. They can promote cell proliferation and migration and regulate the expression of type I and type III collagen and fibronectin. This promotes angiogenesis and accelerates wound healing.[106] Fibroblast exosomes promote wound healing and improve the quality of wound healing by regulating the remodeling of the ECM.[107] Investigators performed histopathologic of skin wound biopsies from a rat model of total skin ulceration and found that fibroblast-Exos can be used as a viable cell-free treatment to effectively treat skin wounds with a significant boost in repair.[108] Dermal fibroblasts (DFs) produce abundant collagen and cytokines that are essential for skin regeneration and damage repair.[109] Han et al discovered that DF-Exo significantly improved the functional properties of type 2 diabetes rat skin cells, leading to accelerated healing of diabetic skin wounds through the activation of the Akt/β-catenin pathway. By studying the role of miR-125b in exogenous body delivery in aging fibroblast FMT and migration, the treatment potential of miR-125b in age-related defect wound healing was tested. The findings revealed that young fibroblasts stimulated exogenous old-aged fibroblasts to increase miR-125b in the aging fiber cells, thereby promoting migration and FMT, which eventually accelerated wound healing in elderly mice.[110] Although high-quality evidence on the specific mechanism of fibroblast-Exo in wound healing is lacking, these results provide new perspectives and therapeutic strategies for the use of fibroblast-Exo in cutaneous wound repair.

Other Cell-Derived Exosomes

Numerous studies have shown during wound healing, stem cell-derived exosomes can modulate inflammation and promote trabecular angiogenesis, migration and proliferation, collagen formation, and ECM remodeling. They can be encapsulated in biocompatible scaffolds to exert biological effects.[111,112] On this basis, periodontal MSC-derived exosomes show potential applications in periodontal disease treatment, bone regeneration, and wound healing.[113,114] These exosomes inhibited the inflammatory response of M1-type macrophages and reduced lipid accumulation in a hyperlipidemic microenvironment. This provides a new therapeutic strategy for the treatment of periodontitis associated with hyperlipidemia.[115] Kuang et al demonstrated that keratinocyte-derived exosomal MALAT1 plays a crucial role in diabetic wound healing through a specific molecular pathway (Figure 3). This mechanism is based on MALAT1's ability to act as a competitive RNA for miR-1914-3p, thereby preventing MFGE8 inhibition in macrophages. The increased MFGE8 expression drives three key beneficial effects in macrophages-enhanced phagocytosis, polarization toward the M2 phenotype, and reduced apoptosis. By modulating the TGFB1/SMAD3 signaling axis, this pathway effectively promotes tissue regeneration and wound closure in diabetic conditions.[116] Subsequently, Zhou et al reported that keratinocyte-derived exosomes carry miRNAs that directly determine the number and function of macrophages within the granulation tissue. This is critical for functional wound healing. These exosomes regulate intercellular signaling and promote proliferation and migration of keratinized cells, thereby accelerating wound healing.[117] In summary, exosomes derived from different sources have shown significant therapeutic potential in wound healing and tissue regeneration (Table 1) and hold promise in regenerative medicine and precision therapy.

Body Fluid-Derived Exosomes

Low yield of exosomes in cell culture supernatants is a challenge, limiting the potential application of exosomes in the field of drug delivery.[133] To address this challenge, researchers are actively exploring more efficient ways to produce

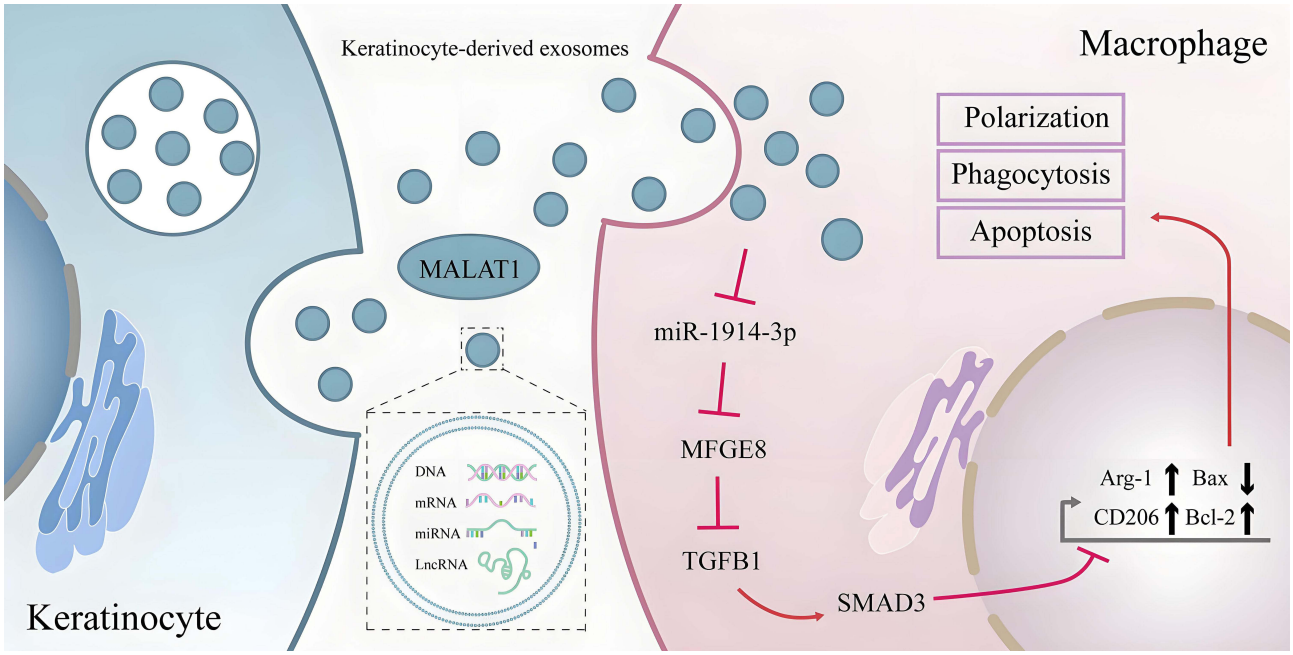


Figure 3 Schematic showing how human keratinocyte-derived exosomal MALAT1 promotes diabetic wound healing by suppressing miR-1914-3p to activate MFGE8, resulting in enhanced macrophage function and inhibition of the TGFB1/SMAD3 pathway. Reproduced with permission from Kuang L, Zhang C, Li B et al. Human keratinocyte-derived exosomal MALAT1 promotes diabetic wound healing by upregulating MFGE8 via microRNA-1914-3p. International Journal of Nanomedicine. 2023;18:949–970. Copyright (2023) Taylor & Francis Group.[116]

exosomes in large quantities. Exosomes from bodily fluids, such as the serum, saliva, breast milk, and amniotic fluid, are not only abundant but they also carry mRNAs that can be analyzed. Moreover, genetic material can be isolated and analyzed by minimally invasive techniques, providing new ways to gain insight into the host transcriptome.[115] This property gives exosomes derived from of bodily fluids the potential to be used as a diagnostic tool.

Table 1 Targets and Functions of Different Exosome Sources in Diabetic Wound Healing

Exosomes Sources	Target	Function	Ref.
DPSC-Exos	Cdc42/p38 MAPK pathway	Promotes angiogenesis and accelerates wound healing	[118]
DFAT-Exos	Wnt/β-catenin signaling	Enhances angiogenesis and attenuates high glucose-induced cell proliferation and migration	[119]
hAEC-Exos	PI3K-AKT-mTOR signaling	Activates fibroblasts, promotes angiogenesis, and inhibits scar formation	[120]
DETC-Exos	EPSCs	Promotes EPSCs' proliferation and accelerates re-epithelialization of skin wounds	[121]
PMN-Exos	VEGF	Acts as a VEGF carrier, promotes angiogenesis, and combats bacterial infections	[122]
OSCC Ti-Exos	PI3K/Akt signaling	Promotes proliferation and migration of endothelial cells, keratinocytes, and fibroblasts	[123,124]
FDMSC-Exos	Notch signaling	Promotes cell migration and secretion as well as extracellular matrix deposition	[125]
EPSC-Exos	miR-425-5p, miR-142-3p	Inhibits TGF-β1 activity, reduces FMT differentiation, and inhibits scar formation	[126]
HTSF-Exos	Smad and TAK1 signaling	Promotes fibroblast proliferation and differentiation, and increases fibronectin and collagen expression	[127]
AnSC-Exos	TGF-β signaling	Inhibits FMT and effectively promotes wound healing in regenerated skin	[128]

(*Continued*)

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Table 1 (Continued).

Exosomes Sources	Target	Function	Ref.
MenSC-Exos	VEGF, NF-κB p65	Modulates inflammation, promotes angiogenesis, and accelerates re-epithelialization to reduce scarring	[129]
CB-Treg-Exos	Mononuclear cells	Promotes M2-type macrophage polarization and enhances endothelial fibroblast migration	[130]
CDENs	Inflammatory factors, vascular endothelial cells, fibroblasts	As an antioxidant, inhibits inflammation, promotes cell migration and angiogenesis, and accelerates collagen deposition	[131]
G-Exos	Endothelial cell glycolysis	Promotes angiogenesis and restores endothelial cell function	[132]

Abbreviations: DPSC, dental pulp stem cells; DFATs, dedifferentiated fat cells; hAECs, human amniotic epithelial cells; DETCs, dendritic epidermal T cells; EPSCs, epidermal stem cells; PMN, polymorphonuclear neutrophil; VEGF, vascular endothelial growth factor; OSCC Ti, oral squamous cell carcinoma tissue; FDMSCs, fetal dermal mesenchymal stem cells; TGF-β1,transforming growth factor-β1; HTSFs, hypertrophic scar fibroblasts; SMAD, small mother against decapentaplegic; AnSCs, adjacent antler stem cells; FMT, fibroblast-to-myofibroblast transition; MenSCs, menstrual blood-derived mesenchymal stem cells; CB)-Tregs, cord blood-Regulatory T cells; CDENs, coriander-derived exosome-like nanovesicles; G-Exos, exosomes derived from ginseng.

Blood-Derived Exosomes

Studies have shown that blood-derived exosomes are not only potential biomarkers but also provide new wound healing treatment avenues. Xiong et al also emphasized that miR-15a-3p-enriched in Dia-Exos could downregulate the NOX5/reactive oxygen species (ROS) signaling pathway, thus impairing angiogenesis and diabetic wound healing.[134] Human umbilical cord blood (UCB) is an excellent source of transplantable stem cells for wound repair. It has several distinct advantages, such as no risk to the donor, easy accessibility, and low incidence of graft-versus-host disease.[135] However, the direct use of stem cells for therapeutic purposes is limited by many risk factors, such as tumor formation, thrombosis, and unwanted immune reactions.[136] Some studies have reported that local injection of exosomes secreted by human UCB-derived stem cells can promote the proliferation and migration of skin fibroblasts and angiogenesis in animal models of diabetes or burns and promote wound healing.[137] Another study found that miR-21-3p enriched with UCB-Exos, a miRNA that is a key mediator of UCB-Exos-induced regulation of functional properties of fibroblasts and endothelial cells. Furthermore, inhibition of phosphatase and tensin homolog as well as germination homolog 1 promotes angiogenesis and fibroblast function, thus enhancing skin wound healing.[138] Blood-derived exosomes act by carrying and releasing growth factors, such as platelet-derived growth factor and TGF-β, to promote cell migration and proliferation and accelerate wound healing.[139] For example, serum-derived exosomes promote migration of NIH-3T3 cells and tube formation of HUVECs to enhance angiogenesis and ECM generation to accelerate diabetic wound healing.[140]

Additionally, platelet-rich plasma (PRP) has been widely used for tissue repair and regeneration. PRP promotes wound healing by releasing antimicrobial peptides, growth factors, and micro-RNAs.[141,142] PRP has anti-inflammatory and proproliferative effects for the treatment of DFUs by regulating miR-21 and PDCD4, inhibiting NF-κB activity, and providing new targets for the treatment of refractory wounds.[143] Sphingosine-1-phosphate (S1P) is a key regulator of vascular homeostasis and angiogenesis. Chen et al isolated exosomes from PRP by ultracentrifugation and used diabetic mouse models to evaluate the effects of PRP-Exos on wound healing. They confirmed that PRP-Exos significantly promote angiogenesis and accelerate healing of diabetic wounds by activating the S1PR1/protein kinase B/FN1 signaling.[144] Additionally, Rui et al explored how the diabetic environment affects PRP-Exos and their potential impact on neutrophil extracellular traps. They found that the miRNA-26b-5p contained in PRP-Exos promotes wound healing by reducing neutrophil infiltration by targeting MMP-8.[145] Notably, different PRP activation methods affect the quantity, quality, and growth factor content of exosomes, with thrombin and calcium gluconate mixed activation producing exosomes with optimal biological function in promoting HUVEC cell proliferation, migration, and angiogenesis.[146]

Human Urine-Derived Exosomes

As isolation of MSCs from adult tissues is invasive and often limited by the source, finding a new source of autologous stem cells that can be easily obtained through noninvasive methods is imperative. Urine can replace plasma as a potential

source of disease biomarkers. Stem cell-like cells were extracted from adult urine, showing self-renew ability. They have multifaceted differentiation ability and superior proliferation capacity.[147,148] After serial propagation, hUSCs retained a normal karyotype with advanced colony-forming ability.[149] Urinary exosomes contain various biologically active molecules that reflect the physiological and pathological state of the body. They promoted cell proliferation and migration and enhanced wound healing.[150]

In recent years, several studies have applied USCs to repair bone, cartilage defects, and wounds with favorable therapeutic results.[151] USCs differentiated into osteoblasts, adipocytes, and chondrocytes. Urine-derived stem cell exosomes (USC-Exos) exhibit a cup- or sphere-shaped morphology, with a mean diameter of 51.57 ± 2.93 nm and are positive for CD63 and TSG101. USC-Exos enhance the angiogenic activity of endothelial cells. Specifically, a proangiogenic protein known as malignant brain tumor delete 1 is highly expressed in USC-Exos. Chen et al showed that USCs-Exos promoted angiogenesis in diabetic mice by upregulating the expression of the malignant brain tumor delete 1 gene.[152] Additional studies have found that compared to conventional USC-Exos, exosomes from $CD133^+$ human urine-derived stem cells ($CD133^+$ USC-Exos) promoted the chondrogenic differentiation of BMSCs more effectively. This in turn promoted bone–tendon interface healing in rotator cuff injury repair.[153] In addition, urine output and urinary microalbumin excretion were reduced in rats by intravenous administration of USCs-Exo. It was found that USCs-Exo may prevent diabetic kidney injury by inhibiting apoptosis of podocytes, growth factors in USCs-Exo, angiopoietins, and bone morphogenetic protein-7, among other potential factors, promoting vascular regeneration and cell survival to prevent diabetic kidney injury.[154] These findings could be a promising treatment option for diabetic wound healing.

Although the origin of USCs remains controversial, USCs have more homology with the urinary system. Combining the advantages of USCs and exosomes, USC-Exos have less immune rejection, better differentiation, and a more stable and adequate supply.[155] Therefore, exosomes in urine as potential biomarkers would be a promising therapeutic approach in regenerative medicine.

Saliva-Derived Exos

Saliva contains large amounts of proteins and growth factors and is an important source of tissue regeneration factors,[156] especially during the healing of oral trauma. Salivary exosomes (SEs) are rich in growth factors and antimicrobial peptides; they can accelerate local tissue repair and have anti-inflammatory effects, thus promoting wound healing.[157] Mi et al showed that saliva-derived Exos induced the proliferation, migration, and angiogenesis of HUVECs in an in vitro experiment. In in vivo experiments, saliva-derived Exos showed a strong ability to promote skin wound healing.[158] Ubiquitin-binding enzyme E2O is one of the major mRNAs in SEs. Researchers have suggested that ubiquitin-binding enzyme E2O mainly acts by decreasing the level of SMAD homolog 6, which activates bone morphogenetic protein 2. The activation of bone morphogenetic protein 2 further induces angiogenesis. Although saliva-derived Exos represents a novel strategy to promote wound repair by promoting angiogenesis, saliva as an effective medium that promotes local health has not been widely recognized in the field of medicine and biomaterials. In-depth studies are needed to achieve clinical application.[159]

Notably, although exosomes from the saliva have been less studied, saliva-derived exosomes are thought to have greater versatility in the diagnosis and treatment of disease compared to exosomes from other body fluids. By contrast, SEs are being studied as an alternative to whole saliva. This is because whole saliva contains contaminating elements and higher levels of amylase. In addition to organ-specific pathologies, SEs have applications in systemic diseases, including autoimmune diseases, neurodegenerative diseases, and malignant tumors.[157] Saliva has been reported to carry DNA, RNA, and metabolites present in both blood and saliva. SEs collection is easy and noninvasive, which improves patient compliance. Thus SEs can be easily obtained from patients. Furthermore, saliva does not clot and SEs are stable in biological fluids, such as blood and gastric juices. Thus, drug delivery using SEs shows great therapeutic potential in numerous innovative applications.

Milk-Derived Exosomes

Breast milk exosomes are rich in miRNAs, proteins, lipids, and other biomolecules. These components can influence numerous biological processes. They are key regulators of gene expression networks in normal physiological and disease contexts. Moreover, these components show potential promise as disease biomarkers. Breast milk exosomes are not only

involved in the growth and development of newborns but also enhance their immune function.[160] By regulating the intestinal microbiota and promoting the repair of intestinal epithelial cells, they helps newborns resist infection and promote wound healing.[161] However, access to breast milk can be limited, and the quantity of breast milk can vary. Moreover, there may be ethical and privacy issues involved in the extraction and study of exosomes derived from breast milk. These issues affect the availability of exosomes. Therefore, researchers sought alternative sources, turning their attention to milk exosomes as a potential alternative.

In 1973, Plantz et al discovered milk exosomes, which are now considered promising candidates for the development of new drug delivery systems.[162] First, the relatively high yield of exosomes isolated from milk is the greatest advantage that cannot be matched by other exosome sources.[163] Additionally, milk-derived exosomes are highly resistant to the harsh gastrointestinal environment and can be used as an oral drug delivery system.[164] Yan et al developed milk-derived exosomes for miR-31-5p delivery to treat diabetic wounds. A pharmacokinetic of mEXO-31 revealed remarkable stability metrics, with approximately 60% of intact encapsulated miR-31-5p after a 5-day incubation at 37°C while free miRNA underwent near-complete degradation. Dosage optimization demonstrated that administration fo 1.0 μg/μL mEXO-31 at three timepoints (days 0, 5, and 10) produced optimal therapeutic efficacy. Quantitative biological responses established dose-dependent effects, with mEXO-31 inducing approximately 2-fold enhancement in endothelial cell proliferation and angiogenic tube formation, and an 1.5-fold increase in migration capacity (Figure 4).[165] In streptozotocin-induced diabetic mice and in methylglyoxal-treated HUVECs, the Keap1/Nrf2 signaling pathway is activated.

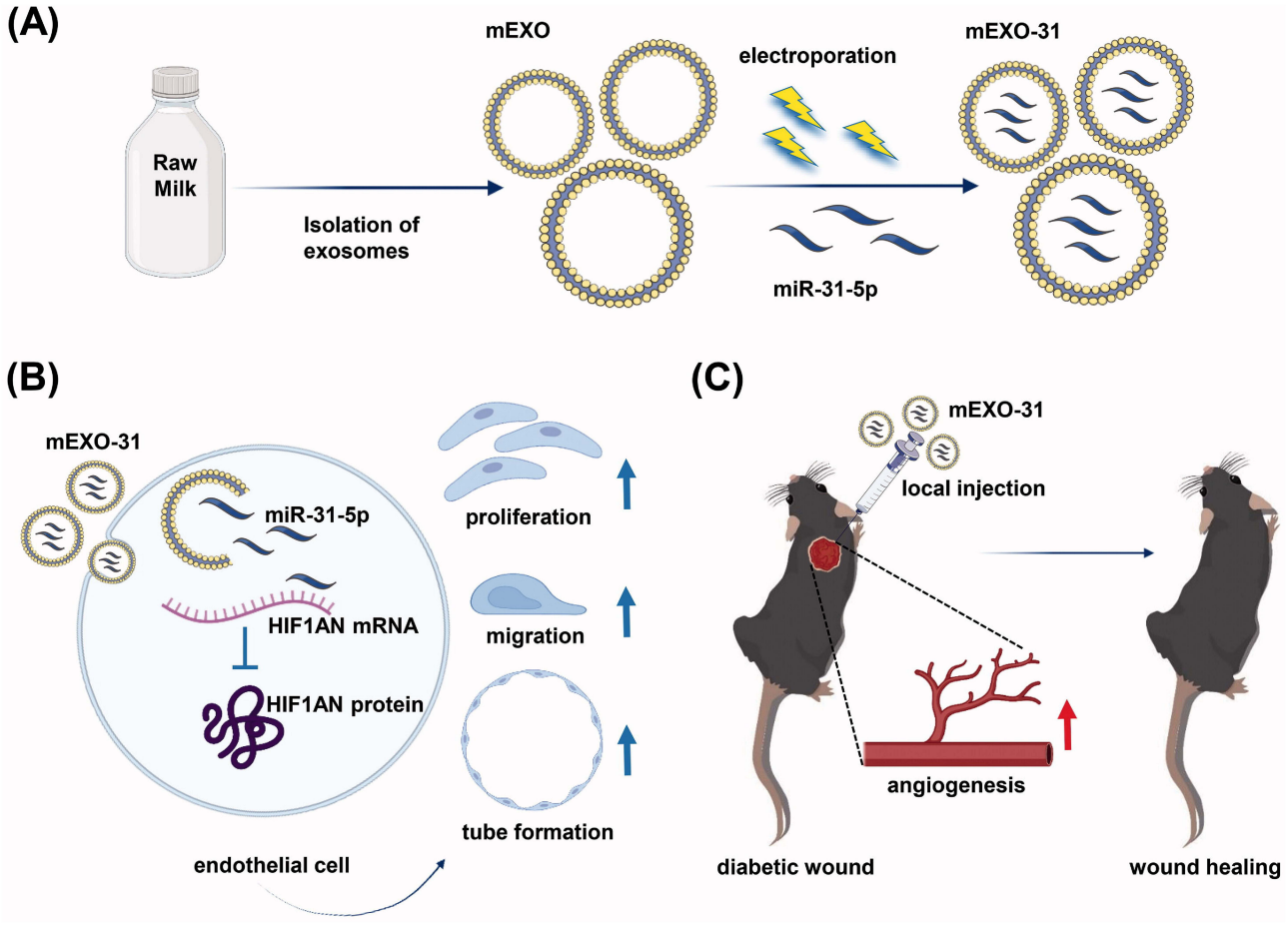

Figure 4 Schematic illustrating milk exosome-mediated miR-31-5p delivery for diabetic wound healing. (**A**) Isolation process of milk-derived exosomes (mEXO) and preparation of miR-31-5p-loaded exosomes (mEXO-31) via electroporation. (**B**) Molecular mechanism of mEXO-31 in endothelial cells, where internalized miR-31-5p targets HIF1AN mRNA, reducing HIF1AN protein expression and consequently enhancing endothelial cell proliferation, migration, and tube formation. (**C**) Therapeutic application of mEXO-31 in diabetic wound model, showing local injection promotes angiogenesis and accelerates wound closure. Reproduced with permission from Yan C, Chen J, Wang C et al. Milk exosomes-mediated miR-31-5p delivery accelerates diabetic wound healing through promoting angiogenesis. Drug Delivery. 2022;29(1):214–228. Copyright (2022) Taylor & Francis Group.[165]

Lactogenic exosomes acted as novel, efficient, and nontoxic siRNA carriers. The injection of M-Exos-siKeap1 significantly accelerated wound healing in a diabetic mouse wound model, enhancing collagen deposition and neovascularization.[166] These results demonstrate the feasibility of milk exosomes as an siRNA delivery system and milk-derived exosomes can promote diabetic wound healing by ameliorating oxidative stress.

Amniotic Fluid-Derived Exosomes

In the field of reproductive biology, exosomes are associated with embryogenesis, placentation, maintenance of pregnancy, and delivery based on exosome characteristics (number, cargo content, and function) in various biological samples during pregnancy.[167] These samples consist mainly of maternal plasma, cervicovaginal fluid, UCB, and amniotic fluid. Due to the enrichment of fetal exosomes in amniotic fluid, amniotic fluid exosomes play an important role in fetal development. They can support fetal growth and development by regulating intercellular signaling and provide protection when the fetus is exposed to stress.[168] Fetal exosomes in maternal circulation account for approximately 35% of the total circulating exosomes.[169] Although the collection of amniotic fluid involves ultrasound-guided invasive methods, amniotic exosomes provide valuable information about the status of the pregnancy and can reflect the functional status of the fetus in utero.[167]

The successful application of adult stem cells is limited because they retain epigenetic alterations even after reprogramming.[170,171] Fetal stem cells can overcome this limitation, especially those derived from amniotic fluid collected during cesarean section, late gestational amniotic reduction, or routine amniocentesis.[172] Studies have shown that human amniotic fluid stem cells accelerated skin wound healing with less fibrotic scarring, similar to fetal wound healing.[173] It was later demonstrated that human amniotic fluid stem cells (hAFSC-exo) improved the regeneration of hair follicles, nerves, and blood vessels and increased skin cell proliferation and the natural distribution of collagen during wound healing; thus, demonstrated significant antifibrotic scarring properties during wound healing.[174] Overall, human amniotic fluid stem cells independently produce paracrine effectors and are secreted in exosomes, thereby modulating local immune cell activity. They possessed anti-inflammatory and immunomodulatory properties, modulated the physicochemical microenvironment of the wound, and promoted complete wound regeneration, especially in scarless wound healing.[175] Although studies addressing the specific mechanisms of amniotic fluid exocytosis in diabetic wound healing are limited, the results of the studies that have been conducted suggest their potential application in this field.

Plant-Derived Exosome-Like Nanoparticles

In recent years, researchers have gradually discovered and isolated exosomes from plants with particle sizes in the range of 30–500 nm and characterized them.[176] It was found that plant-derived exosomes can be isolated from a wide range of fruits and vegetables, and some even from traditional herbs and fungi[177] (Table 2). PENs from a wide range of sources have a specialized subcellular structure. As drug carriers, they can enhance drug stability and cellular uptake.[178] Reports indicate that PENs have great potential in regulating immune function, inflammation, the microbiome, and tissue regeneration.[179] PENs promote cell proliferation, migration, and angiogenesis, among other mechanisms, and can significantly accelerate wound healing. Wheat-derived PENs were found to have dose-dependent proliferative and migratory effects on endothelial cells, epithelial cells, and DFs in vitro. They promoted formation of tubular structures in endothelial cells and increased the transcription levels of type I collagen. Additionally, it promotes endothelial cell angiogenesis through the ERK and AKT/mTOR pathways, repairing full-thickness diabetic skin ulcers.[180–182]

A ginseng-derived exosome (G-Exo) was successfully prepared and proved to promote diabetic wound healing.[197] Applying G-Exos to mouse skin wounds showed that they can promote skin cell proliferation, accelerate injured skin recovery, and reduce inflammation.[198] Additionally, in animal models, G-Exos assisted in nerve regeneration by upregulating PI3K signaling to promote nerve repair, and by intervening in the RAS/ERK pathway to promote the expression of neurotrophic factors and accelerate nerve regeneration.[199] Xiong et al developed a whole-course-repair hydrogel system (HA-ADH/OSA@Mg@sEVs) based on engineered ginseng-derived small extracellular vesicles (G-sEVs). This system promoted diabetic wound healing through neurogenesis-angiogenesis crosstalk and macrophage reprogramming. Furthermore, G-sEVs carrying didymin (DM) facilitated M1 to M2 macrophage transition while the released Mg^{2+} synergistically enhanced angiogenesis with differentiated neural cells. In STZ-induced diabetic mice, the

Table 2 Fruit, Vegetable, and Herb-Derived PELNs for Wound Healing

PLANT TYPE	Plant Source	Pathway	Function	Advantages	Disadvantages	Ref.
Fruit	Lemon	Promotes TRAIL-mediated apoptosis, inhibits secretion of VEGF-A, IL-6 and IL-8 as well as ERK1/2-NF-κB signaling and activates AhR/Nrf2 signaling	Promotion of angiogenesis Anti-inflammatory Inhibition of oxidative stress	Outstanding antioxidant capacity High safety Drug delivery potential	Single function Unstable output	[183–185]
	Sweet orange	Inhibits the release of inflammatory factors such as IL-1β	Anti-inflammatory			[186,187]
	Apple	Inhibits the NF-κB pathway and decreases TNF-α levels	Anti-inflammatory			[188]
	Coffee	Scavenges ROS and free radicals, inhibiting the release of inflammatory factors IL-6, TNF-α	Antioxidant Anti-inflammatory			[180,181]
Vegetables	Broccoli	Enhances antioxidant enzyme activity, reduces IFN-γ and TNF-α release, and inhibits the activation of the NLRP3 inflammasome	Antioxidant Anti-inflammatory	Antiviral and metabolic modulation	Highly heterogeneous Dependent on pre-processing	[189]
	Garlic	Inhibits multidrug-resistant bacteria (MRSA); down-regulates M1 and up-regulates mRNA levels of M2-type inflammatory factors	Biofilm formation Anti-inflammatory	Intestinal targeting Wide range of sources		[190,191]
	Potato	Inhibits the expression of MMP and inflammatory cytokines, prevents collagen degradation, and promotes cell proliferation	Anti-inflammatory UV-induced photodamage to the skin			[192]
Herb	Wolfberry	Activates Nrf2/HO-1, inhibits NF-κB, and regulates SIRT1	Anti-inflammatory Antioxidant	Polypharmacy Natural synergies	Complex preparation, Potential toxicity Unclear composition	[193]
	Dendrobium	Inhibits IL-1β expression	Anti-inflammatory	Clinical translation potential		[194]
	Pueraria lobata	Promotes M2 macrophage polarization;	Anti-inflammatory			[195]
	Dandelion	Neutralizes *Staphylococcus aureus* exotoxins and sustains release of vesicles together with hydrogels	Promotes healing of infected wounds			[196]

Abbreviations: ROS, reactive oxygen species; TNF-α, tumor necrosis factor-alpha; NF-κB, nuclear factor kappa B; MRSA, methicillin-resistant Staphylococcus aureus; MMP, matrix metalloproteinase; HO-1, heme oxygenase-1; SIRT1, sirtuin 1; Nrf2, nuclear factor erythroid 2-related factor 2; AhR, aryl hydrocarbon receptor.

system significantly accelerated wound healing without systemic toxicity, demonstrating its therapeutic potential as it addresses multiple phases of the wound healing process (Figure 5).[200] Additionally, exosomes derived from aloe vera cortex (rAEVs) enhance the migration ability of HaCaT and HDF cells by scavenging free radicals and ROS. Moreover, rAEVs can promote tube formation by endothelial cells, increase blood supply, and reduce the secretion of inflammatory factors. They improve skin texture and scar appearance through heat shock proteins, promoting skin regeneration.[201–203]

Plant-derived exosomes can also regulate multiple cell signaling pathways, such as the Wnt/β-catenin signaling pathway and the TGF-β signaling pathway, thereby promoting the function of fibroblasts and endothelial cells.[204,205] PENs enhanced the formation of tubular structures in HUVECs, marking an important milestone in therapeutic approaches to wound healing. Grapefruit-derived exos upregulated the expression of proliferation- and migration-

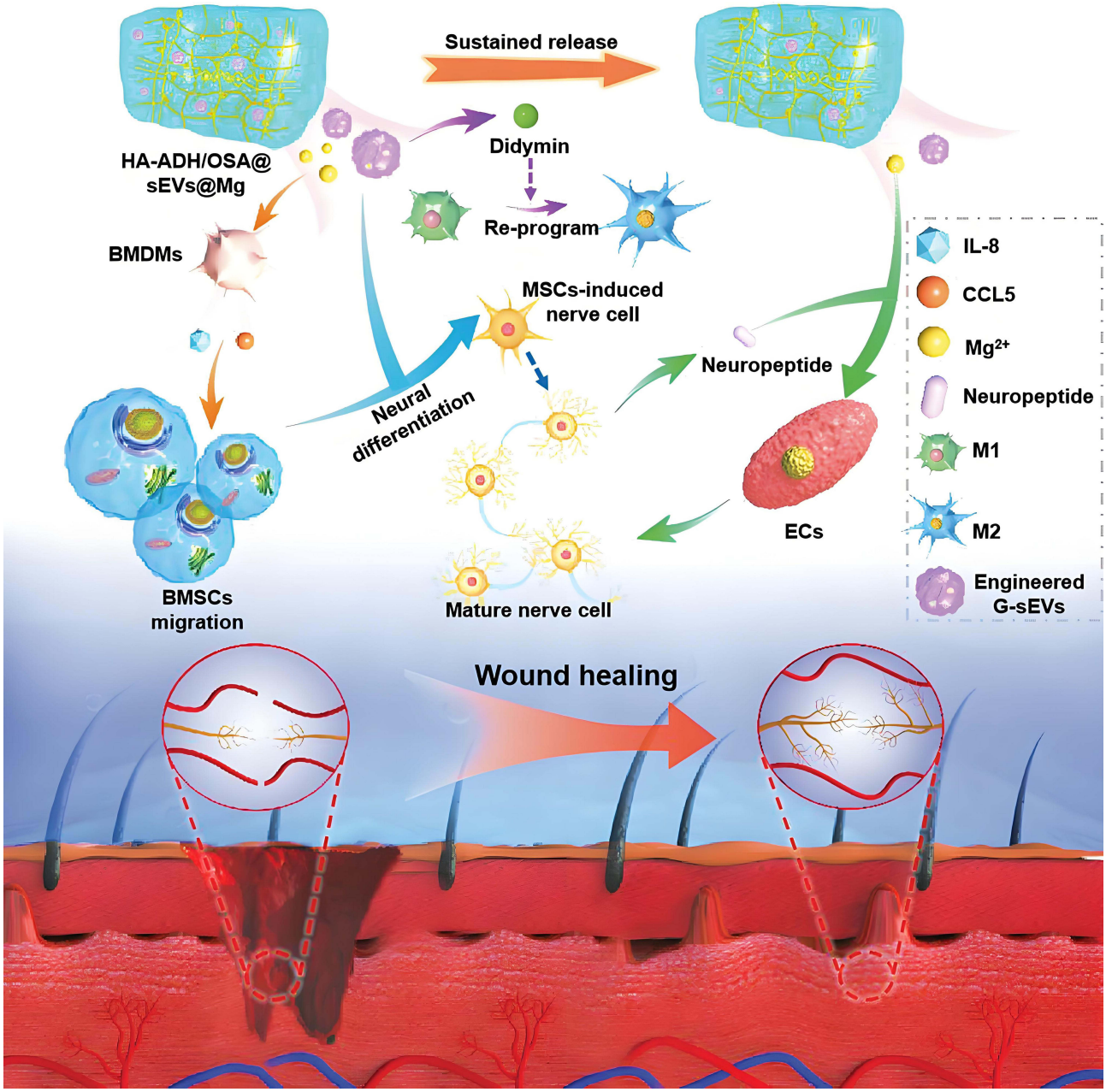

Figure 5 Schematic of the beneficial role of HA-ADH /OSA @ Mg@sEVs hydrogel. The one-step preparation of HA-ADH/OSA@Mg hydrogel encapsulates G-sEVsDM without compromising their activity. With its Mg^{2+} release, the hydrogel recruits mesenchymal stem cells and induces neurogenic differentiation and macrophage reprogramming, promoting a prohealing environment. This leads to enhanced angiogenesis and a neurogenesis-angiogenesis cycle at the wound site. Reproduced with permission from Xiong Y, Lin Z, Bu P et al. A Whole-Course-Repair System Based on Neurogenesis-Angiogenesis Crosstalk and Macrophage Reprogramming Promotes Diabetic Wound Healing. Advanced Materials. 2023, 35, 2212300. Copyright (2023) Wiley Online Library.[200]

related genes in a dose-dependent manner, increased the tube-forming capacity of HUVECs, in the HaCaT cell model,[206] and played a dominant role in the anti-inflammatory regulation of Wnt.[207] Another study found that ginger-derived exosomes can promote Nrf2 nuclear translocation and preferentially induce the expression levels of antioxidant HO-1 and anti-inflammatory cytokine IL-10, stimulating the production of anti-inflammatory cytokines, thereby effectively exerting their anti-inflammatory efficacy.[178] Interestingly, human BMSCs internalized strawberry-derived exos, and incubation for 120 h did not produce negative effects. BMSCs pretreated with strawberry-derived exos were resistant to hydrogen peroxide-induced oxidative stress and possessed potentially beneficial activities.[208] These findings may yield

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valuable insights for exploring the regenerative capacity of PENs in various tissues, requiring extensive empirical evidence to validate their therapeutic potential.[209]

In addition to acting as therapeutic agents for disease intervention, PELNs can function as carriers to deliver various therapeutic molecules (such as proteins, siRNA, and therapeutic drugs) to relevant disease sites. Moreover, their endogenous bioactive components can exert synergistic therapeutic effects, significantly enhancing clinical efficacy.[210] Compared to mammalian exosomes, PELNs have unique advantages such as being less easily detected by the immune system as well as higher bioavailability and low toxicity[211] (Table 3).

These structural and compositional differences directly influence the selection of delivery strategies, MDEs are typically combined with albumin or hyaluronic acid-based hydrogel systems to form controlled-release complexes for local administration, and can enhance their in vivo circulation time and targeting through covalent modification methods such as PEGylation;[219,220] whereas PELNs, due to their unique phospholipid composition and stable membrane structure, are more suitable for combination with polysaccharide or polymer matrices, such as chitosan and polylactic acid, through non-covalent modification methods like electrostatic interactions, significantly enhancing their stability in the gastrointestinal environment and oral bioavailability.[221] With respect to the drug release mechanism, MDEs commonly use pH-responsive strategies to accommodate endosomal/lysosomal escape needs, whereas PELNs, due to their special membrane composition, are more compatible with photosensitive and redox-sensitive materials for constructing intelligent responsive release systems.[215,222,223] Understanding the structure-function relationship of these two types of extracellular vesicles can guide the development of complementary delivery platforms with combined advantages, providing new approaches for precision treatment of challenging conditions such as diabetic wounds.

Challenges in Exosomes Application

Exosomes have promising potential for treating diabetic wounds; however, several challenges must be overcome before their broad clinical use. The first issue is the stability and targeting of the exosomes. Research indicates that half-life of

Table 3 Comparison of MDEs and PELNs Used for Diabetic Wound Healing

	MDEs	**PELNs**
Source	Many animal cell tissues and body fluids	Vegetables, fruits, herbal
Separation method	Ultracentrifugation, density gradient centrifugation, ultrafiltration	Ultracentrifugation, sedimentation, membrane filtration
Component composition	Lipid composition contains cholesterol, large amounts of protein, abundant messenger RNA, microRNA, and lncRNA	Lipid composition does not contain cholesterol; low variety of proteins and low content, mainly proteins regulating glycolipid metabolism or associated with membranes and vesicles, etc.; nucleic acids are mainly miRNAs, low variety
Characteristic	High stability, low mobility and solubility	Low stability, high mobility and solubility
Animal model	Rat, mouse	Rat, mouse
Route of administration	Local injection, nanocarrier delivery	Topical application, oral administration
Distribution	Liver, kidney, spleen, lungs, brain, stomach, intestine	Liver, lungs, spleen, kidney, stomach, intestine, brain
Function	Anti-inflammatory, anti-tumor, antioxidant, immunomodulatory, and drug carrier properties	Anti-inflammatory, anti-tumor, antioxidant, gut microbiota modulation, tissue regeneration, drug carrier, etc.
Advantages	High biocompatibility, noninvasive biomarkers, and potential therapeutic benefits	Promising large-scale production, rich in bioactivity, low toxicity, higher biosafety, and environmentally friendly
Disadvantages	Complex preparation steps, low productivity, high production costs, high heterogeneity, and potential pathogen contamination	Highly heterogeneous, seasonal harvesting, and lack of standardized isolation methods
Clinical research	Clinical trials and mechanistic studies are more mature and animal experimental data support its efficacy	Few clinical studies have been conducted mainly focusing on mechanism exploration and optimization of the extraction process
Ref.	[212–214]	[37,215–218]

exosomes in the body typically ranges from just a few minutes to several hours, primarily due to their rapid clearance by the immune system. This short retention period substantially restricts the effectiveness of exosomes within the body.[224] To address this, altering the surface properties of exosomes through modifications, such as PEGylation and incorporation of nanoparticles, can enhance their circulatory stability and extend their in vivo retention time, thereby augmenting their therapeutic impact. The second issue is that exosome contents and functions are influenced by the type and state of the secreting cells, with involve intricate signaling pathways. The transfer of unknown bioactive molecular mixtures in exosomes may produce unpredictable biological effects and pose a safety hazard. Thus, further investigation is essential to gain a comprehensive understanding of the exosome composition as well any potential toxicity associated with the exosomes.[225] The third issue is that the large-scale production of exosomes faces multiple challenges. First, exosome production primarily relies on cell culture, requiring serum and growth factors that are expensive and cumbersome to obtain. Second, existing bioreactors have limited capacity, and large-scale cultivation increases contamination risks. Meanwhile, difficulties in quality control, batch-to-batch consistency issues, and the high associated costs limit the clinical application of exosomes in diabetic wound healing. To address these issues, cultivation conditions can be optimized by developing serum free or synthetic media to reduce costs and introducing automated equipment to decrease manual operations and improve efficiency. Additionally, standardized isolation and characterization techniques, including developing automated isolation and purification equipment, as well as a combination multiple technologies such as ultrafiltration and affinity chromatography to reduce purification steps while preserving exosome activity need to be established[226] (Figure 6). These improvements not only increase yield and quality but also lay the foundation for exosome characteristics and safety assessment, promoting their clinical translation. Lastly, exosomes are temperature-sensitive, with harsh storage and transportation conditions, and freezing and thawing may affect their biological activity. The development of new exosome stabilization technology to ensure the consistency of its quality in the process of transformation and application is also a key direction worthy of attention.

Beyond the numerous challenges inherent to exosomes, their application in the treatment of diabetic wounds introduces particular complexities. Patients with diabetes commonly experience peripheral neuropathy and vascular disorders, which can cause minor injuries to evolve into refractory ulcers. This progression not only increases susceptibility to infections but also hinders wound healing. Thus, the delivery of exosomes needs more exacting standards, and a single injection method may be inadequate. Developing innovative exosome delivery systems is imperative to enhance targeting precision and therapeutic effectiveness in the treatment of diabetic wounds. Furthermore, the preponderance of exosome research in wound healing has been conducted in rodent models, leaving open the question of whether these findings can be extrapolated to patients with diabetes.[227] To the best of our knowledge, there have been no documented cases of exosome usage in individuals with either diabetic or nondiabetic wounds to date, because most clinical study products have yet to receive approval for human application.[228] This constraint hampers our capacity to fully grasp the true efficacy of exosome therapy in the context of diabetic wound treatment. As pathophysiological mechanisms of diabetic wounds differ from those of typical wounds, it is essential to develop a diabetic animal model that more accurately represents human physiology and assess the therapeutic promise of exosomes within such a model.

Summary and Outlook

In the field of diabetic wound repair, exosomes are rapidly advancing from basic research to clinical application. Clinical trials have demonstrated that exosome-hydrogel composites together with negative pressure wound therapy can reduce healing time by up to 40% without increasing infection risk.[229,230] Moreover, the combination of photodynamic therapy with exosomes has significant synergistic effects in eliminating multi-drug resistant bacterial biofilms. To better understand their mechanisms of action, researchers have developed diabetic foot ulcer organoid models, which not only facilitate treatment evaluation but also promote the development of personalized medicine strategies. By analyzing patients' genetic backgrounds and differences in wound microenvironments, researchers can screen for exosome subgroups with specific miRNA or protein profiles, thereby achieving precision treatment. More importantly, using gene editing technology to modify HLA molecules in ADSC-Exos effectively addresses the key clinical challenge of immune rejection.[231] Accordingly, interdisciplinary innovation further expands their application prospects. The integration of biomaterials science and nanoengineering enables silk fibroin patches to extend exosome retention time to over

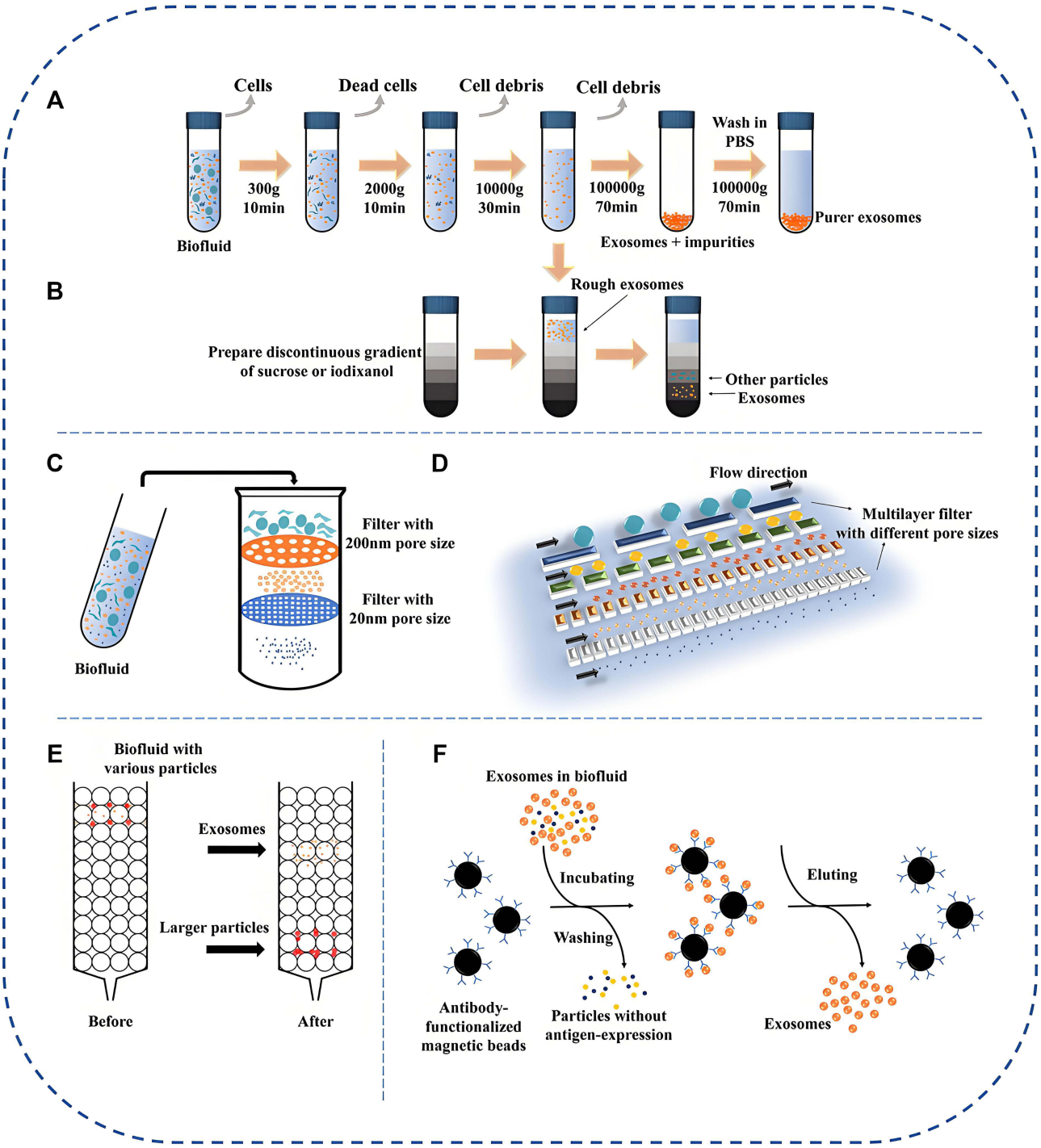

Figure 6 Schematic of common exosomal separation techniques. (**A**) Ultracentrifugation, (**B**) density gradient centrifugation, (**C**) dead-end filtration (DEF), (**D**) tangential flow filtration (TFF), (**E**) size-exclusion chromatography, and (**F**) immunoaffinity. Reproduced with permission from Chen J et al. Review on Strategies and Technologies for Exosome Isolation and Purification. Frontiers in Bioengineering and Biotechnology. 2022;9:811971. Copyright (2022) Frontiers Media.[226]

72 h, achieving precise release of growth factors through pH-responsive mechanisms. Meanwhile, the combination of biomimetic scaffolds and optogenetic technology can regulate NO release, directly improving wound angiogenesis.[232] These technological advances can have synergistic effects with artificial intelligence systems, providing data support for clinical decision-making.[233]

This review describes the current status of application of exosomes from various sources in diabetic wound healing. Although exosome research is still in the developmental stage, there has been substantial progress in clinical translation. With growing research into tissue repair mechanisms, this therapy aims to offer more effective treatment options for patients with diabetic wounds, fulfilling the translational medicine objective of moving from laboratory to bedside.

Abbreviations

DFUs, diabetic foot ulcers; ECM, extracellular matrix; MSC-Exos, mesenchymal stem cell-derived exosomes; BMSC-Exos, bone marrow mesenchymal stem cell-derived exosomes; ADSC-Exos, adipose-derived mesenchymal stem cell-derived exosomes; UCMSCs, umbilical cord mesenchymal stem cells; HUVECs, human umbilical vein endothelial cells; M-Exos, macrophage-derived exosomes; EPC-Exos, endothelial progenitor cell-derived exosomes; DF-Exos, dermal fibroblast-derived exosomes; USC-Exos, urine-derived stem cell-derived exosomes; SEs, salivary exosomes; MT-Exos, melatonin-stimulated bone marrow stem cell-derived exosomes; ATV-Exos, atorvastatin-pretreated bone marrow stem cell-derived exosomes; hyBMSC-Exos, hypoxic bone marrow mesenchymal stem cell-derived exosomes; UCB, umbilical cord blood; AGEs, advanced glycation end products; HBOT, hyperbaric oxygen therapy; PI3K, phosphoinositide 3-kinase; mTOR, mammalian target of rapamycin; S1P, sphingosine-1-phosphate; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; DM, didymin; rAEVs, exosomes derived from aloe vera cortex.

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Disclosure

The authors report no conflicts of interest in this work.

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