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Healing of diabetic cutaneous wound mediated by small extracellular vesicles derived from mesenchymal stem cells

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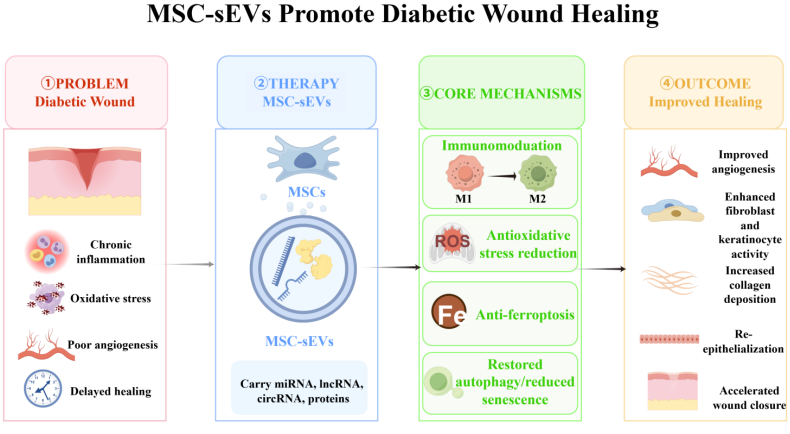
ABSTRACT: Diabetic cutaneous wounds, particularly diabetic foot ulcers, are among the most severe chronic complications of diabetes mellitus and remain a major clinical challenge because of persistent inflammation, oxidative stress, impaired angiogenesis, and delayed tissue regeneration. Although conventional therapies such as debridement, infection control, and growth factor application can partially improve wound conditions, their overall efficacy remains limited. Mesenchymal stem cell-derived small extracellular vesicles (MSC-sEVs) have recently emerged as a promising cell-free therapeutic strategy for diabetic wound repair. Increasing evidence indicates that MSC-sEVs can regulate multiple pathological processes involved in diabetic wounds, including macrophage polarization, neutrophil extracellular trap formation, oxidative stress, ferroptosis, cellular senescence, and autophagy dysfunction. Through these mechanisms, MSC-sEVs promote angiogenesis, collagen deposition, fibroblast proliferation, keratinocyte migration, and re-epithelialization, thereby accelerating wound closure and tissue regeneration. This review summarizes recent advances in MSC-sEV-based diabetic wound therapy by linking major pathological barriers with specific cellular targets and molecular mechanisms, thereby highlighting the mechanistic basis and potential advantages of MSC-sEVs over conventional cell-based strategies. Current limitations, including heterogeneity of MSC sources, insufficient standardization of sEV isolation and characterization, limited retention at wound sites, and incomplete clinical validation, are also discussed. Future research should focus on standardized production, functional engineering, carrier-based delivery systems, and well-designed preclinical and clinical studies to facilitate the cautious and evidence-based translation of MSC-sEVs for chronic diabetic wound management.



KEYWORDS: mesenchymal stem cells, small extracellular vesicles, diabetic cutaneous wound, macrophage, oxidative stress

1 Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from insufficient insulin secretion or impaired insulin action. It has become a growing global health burden, with an estimated 589 million adults aged 20-79 years living with diabetes worldwide in 2024, a number projected to increase to 853 million by 2050[1]. Diabetic skin wounds, especially diabetic foot ulcers (DFUs), represent one of the most severe complications, which are featured by delayed healing and high susceptibility to secondary infection and may even lead to amputation and even death, imposing heavy economic and social burdens on health care systems worldwide[2,3]. Current clinical interventions for DFUs mainly include debridement, hyperbaric oxygen therapy, and the application of growth factors. Although these strategies can delay disease progression to a certain extent, the overall therapeutic efficacy remains unsatisfactory, and functional wound healing is hardly achieved[4]. Therefore, the development of more stable and effective therapeutic strategies has become an urgent clinical challenge in the field of diabetic wound repair.

Mesenchymal stem cells (MSCs), recognized as core seed cells in regenerative medicine, are widely distributed in various tissues including bone marrow, umbilical cord, adipose tissue, periodontal ligament, and dental pulp. They possess remarkable self-renewal capacity, multilineage differentiation potential, and immunomodulatory properties. MSCs have been investigated in clinical studies for a broad range of diseases, including skeletal

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system repair, cardiovascular diseases, autoimmune disorders, and neurodegenerative diseases. Recent studies have confirmed that the therapeutic effects of MSCs are not primarily dependent on direct cell homing and differentiation, but rather on the release of bioactive substances through paracrine pathways, among which small extracellular vesicles (sEVs) serve as key functional mediators[5]. sEVs exhibit biological characteristics reminiscent of their parent cells, capable of promoting target cell self-repair, inducing tissue regeneration, and restoring local homeostasis through the delivery of functional molecules, thereby accelerating wound repair processes[6,7].

sEVs are cell-derived membranous structures ubiquitously present in biological fluids of eukaryotic organisms. Based on their biogenesis mechanisms, sEVs are broadly classified into two major categories: ectosomes (also referred to as microvesicles) and exosomes[8]. sEVs carry a diverse array of bioactive molecules, including mRNA, non-coding RNAs (such as miRNAs), proteins, lipids, cytokines, amino acids, and metabolites. Their specific molecular composition varies considerably depending on the cell type of origin and the microenvironmental context. Functioning as intercellular messengers, sEVs participate in cell-cell communication and metabolic regulation. Upon release into the extracellular space, sEVs can reach recipient cells and deliver their contents, thereby modulating target gene expression and biological functions, inducing phenotypic changes, and contributing to both physiological homeostasis maintenance and pathological process progression[9]. Accumulating evidence demonstrates that sEVs possess multifaceted biological functions, encompassing immunomodulation, angiogenesis promotion, regulation of cell proliferation and differentiation, and modulation of cell migration and apoptosis, positioning them as key players in tissue homeostasis and disease pathogenesis[10,11]. Compared with parent MSCs, MSC-derived sEVs (MSC-sEVs) offer several notable advantages as a cell-free therapeutic modality. They can efficiently deliver bioactive molecules to exert pro-reparative effects. Their lipid bilayer membrane protects the cargo and enhances stability. As nanosized particles, their dose, concentration, and route of administration are easier to standardize. In addition, because they lack autonomous proliferative capacity, MSC-sEVs may avoid the risks of ectopic growth and tumorigenesis associated with cell transplantation, thereby providing superior biosafety[10]. Notably, emerging evidence suggests that MSC-sEVs may exert superior therapeutic effects in wound healing and scar prevention compared to their parent stem cells.

2 Pathophysiological characteristics of diabetic wound healing

Wound healing generally proceeds through three overlapping yet distinct phases: inflammation, proliferation (characterized by cell proliferation and re-epithelialization), and remodeling. During the initial inflammatory phase, thrombus formation achieves hemostasis, followed by the deposition of a fibrin matrix that serves as a scaffold for subsequent cell migration. Monocyte-derived macrophages infiltrate the wound site during this stage. The second proliferative phase is primarily characterized by the proliferation and migration of various cell types, including fibroblasts, keratinocytes, and endothelial cells, coupled with angiogenesis, culminating in the formation of granulation tissue. In the final remodeling phase, all processes activated following injury gradually subside and terminate. The majority of endothelial cells, macrophages, and myofibroblasts undergo apoptosis or exit the wound site, leaving a relatively acellular mass composed predominantly of collagen and other extracellular matrix proteins[12].

Unlike the orderly and self-limiting progression observed in normal wound healing, diabetic wounds are characterized by persistent delayed healing and remain trapped in a chronic, non-progressive inflammatory state (Fig. 1). This pathological condition arises from a vicious cycle involving multiple interconnected factors, including sustained unresolved inflammation, excessive oxidative stress, impaired immune function, neuropathy, endothelial dysfunction, defective angiogenesis, peripheral vascular disease, and increased susceptibility to infection. Persistent hyperglycemia further exacerbates mitochondrial dysfunction and reactive oxygen species accumulation, leading to chronic inflammatory activation and dysfunction of fibroblasts, keratinocytes, macrophages, and endothelial cells. Consequently, extracellular matrix deposition, angiogenesis, re-epithelialization, and tissue remodeling are severely impaired, ultimately resulting in chronic non-healing diabetic wounds.

3 Core mechanisms of MSC-sEVs in promoting diabetic wound healing

Chronic non-resolving inflammation constitutes a primary driver of impaired wound healing[13]. This pathological feature is closely associated with phenotypic abnormalities and functional disturbances in various immune cell populations. MSC-sEVs are capable of modulating macrophages polarization, oxidative stress, ferroptosis, cellular senescence, and autophagy, thereby reshaping the immune microenvironment (Table 1).

3.1 Macrophage polarization

Macrophages are essential immune effector cells involved in almost all stages of wound healing, and their remarkable phenotypic plasticity enables them to respond dynamically to changes in the local wound microenvironment. In normal wound repair, macrophages undergo a tightly regulated phenotypic transition from a pro-inflammatory state to a pro-reparative state. During the early inflammatory phase after injury, macrophages predominantly exhibit the classically activated M1 phenotype. M1 macrophages participate in pathogen clearance, phagocytosis of necrotic tissue and cellular debris, and initiation of the inflammatory response. They produce pro-inflammatory mediators, including interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), IL-6, inducible nitric oxide synthase (iNOS), and reactive oxygen species (ROS), which are necessary for early host defense and wound decontamination. However, as wound repair progresses, macrophages gradually shift toward the alternatively activated M2 phenotype. M2 macrophages secrete anti-inflammatory and pro-reparative factors, such as IL-10, transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and arginase-1 (Arg-1), thereby promoting inflammation resolution, angiogenesis, fibroblast activation, collagen deposition, extracellular matrix remodeling, and tissue regeneration[14,15]. Therefore, the timely transition from M1 to M2 macrophages is critical for the progression of wound healing from the inflammatory phase to the proliferative and remodeling phases. In diabetic wounds, this orderly macrophage phenotypic transition is severely disrupted. The hyperglycemic microenvironment,

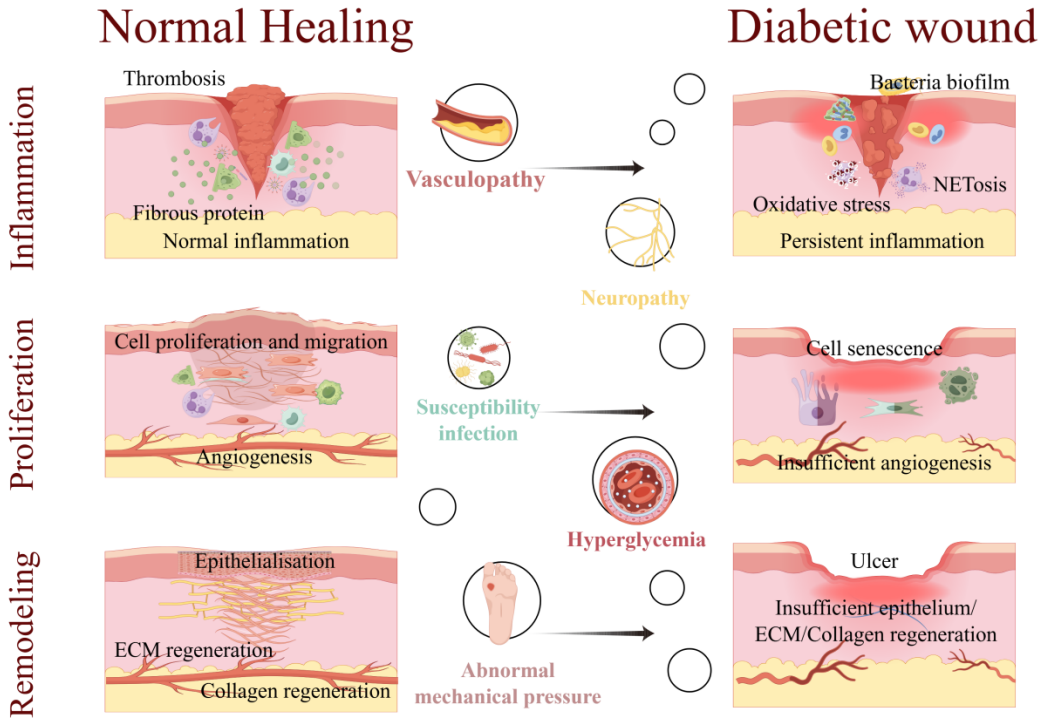

Figure 1 Normal wound healing progresses through coordinated inflammatory, proliferative, and remodeling phases, involving controlled inflammation, angiogenesis, cell proliferation and migration, re-epithelialization, and ECM/collagen remodeling. In contrast, diabetic wounds show persistent inflammation, oxidative stress, NETs, bacterial biofilm formation, insufficient angiogenesis, cellular senescence, and defective epithelialization and ECM regeneration. These abnormalities are mainly driven by hyperglycemia, neuropathy, vasculopathy, infection susceptibility, and abnormal mechanical pressure, ultimately leading to delayed closure and chronic non-healing. This figure was generated by figdraw.

together with excessive oxidative stress, advanced glycation end products, persistent bacterial stimulation, impaired vascular perfusion, and dysregulated immune signaling, maintains macrophages in a prolonged M1-dominant state[16]. As a result, M2 polarization is impaired, whereas M1 macrophages persistently accumulate in the wound bed. This imbalance leads to sustained overproduction of pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6, thereby amplifying local inflammation and preventing the normal resolution of the inflammatory phase. In addition, persistent M1 activation is often accompanied by increased matrix metalloproteinase (MMP) activity, which accelerates extracellular matrix degradation and disrupts the structural scaffold required for cell migration and tissue reconstruction[17]. Excessive inflammatory cytokines and proteases further impair the functions of keratinocytes, fibroblasts, endothelial cells, and other repair-related cells, ultimately suppressing re-epithelialization, angiogenesis, collagen deposition, and granulation tissue formation. Therefore, restoring the balance between M1 and M2 macrophages and promoting macrophage transition toward a pro-reparative phenotype have become important therapeutic targets for diabetic wound repair. In this context, MSC-sEVs have attracted increasing attention because of their ability to modulate macrophage function and reshape the inflammatory microenvironment[18-20].

MSC-sEVs are enriched with diverse bioactive molecules, including miRNAs, circRNAs, lncRNAs, proteins, lipids, enzymes, and metabolites. These cargos can be internalized by recipient macrophages and regulate multiple inflammation-related signaling pathways, thereby promoting macrophage phenotypic switching and attenuating chronic inflammation[21-23]. Among these pathways, the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway plays an important role in macrophage polarization, cell survival, metabolism, and inflammatory regulation. Aberrant PI3K/Akt signaling is closely associated with chronic inflammatory activation and delayed repair in diabetic wounds. Phosphatase and tensin homolog (PTEN) is an important negative regulator of this pathway and can exert anti-inflammatory effects by inhibiting Akt phosphorylation[24]. Studies have shown that exosomes derived from melatonin-pretreated bone marrow MSCs can upregulate PTEN expression, inhibit Akt phosphorylation, promote macrophage polarization toward the M2 phenotype, reduce local inflammatory responses, and accelerate the transition of diabetic wounds from the inflammatory phase to the proliferative phase[25]. In addition to the PI3K/Akt pathway, the p38 mitogen-activated protein kinase (p38 MAPK) pathway is another crucial signaling cascade involved in macrophage-mediated inflammatory amplification. Sustained activation of p38 MAPK is closely related to persistent inflammation and impaired tissue regeneration in diabetic wounds[26-31]. Bone marrow MSC-derived exosomes have been reported to inhibit the p38 MAPK pathway, promote M2 macrophage polarization, and downregulate the expression of pro-inflammatory mediators, including IL-1β, TNF-α, interferon-γ (IFN-γ), IL-6, and C-C motif chemokine ligand 3 (CCL3). By suppressing p38 MAPK-mediated inflammatory signaling, MSC-sEVs can reduce excessive inflammatory cell activation and create a more favorable microenvironment for subsequent angiogenesis, fibroblast proliferation, matrix deposition, and epithelial repair.

Non-coding RNAs carried by MSC-sEVs are also key molecular effectors in the regulation of macrophage polarization. For example,

exosomes derived from hypoxia-preconditioned bone marrow MSCs can deliver miR-4645-5p into macrophages. This miRNA suppresses mitogen-activated protein kinase-activated protein kinase 2 (MAPKAPK2) and TNF-α expression and attenuates sterol regulatory element-binding protein 2(SREBP2)activation, thereby inducing macrophage transition from the M1 phenotype to the M2 phenotype[32]. Hypoxic preconditioning may enhance the reparative capacity of MSC-sEVs by altering their molecular cargo composition, allowing them to exert stronger anti-inflammatory and pro-regenerative effects under ischemic and high-glucose conditions. In another mechanism, circ-Snhg11 can competitively bind miR-144-3p, thereby relieving its inhibitory effect on hypoxia-inducible factor-1α (HIF-1α). This process subsequently activates the HIF-1α/VEGF and HIF-1α/STAT3 signaling axes, which not only promotes angiogenesis but also facilitates M2 macrophage polarization. Through the combined regulation of immune remodeling and neovascularization, circ-Snhg11-containing MSC-sEVs can significantly improve diabetic wound repair under hyperglycemic conditions[33-35]. Furthermore, MSC-sEVs derived from lipopolysaccharide (LPS)-pretreated MSCs exhibit enhanced immunomodulatory activity. These exosomes can deliver let-7b to macrophages, suppress Toll-like receptor 4/nuclear factor-κB (TLR4/NF-κB)-mediated pro-inflammatory signaling, and activate STAT3/AKT-related anti-inflammatory pathways. As a result, macrophages are driven toward an M2-like phenotype, accompanied by increased expression of anti-inflammatory factors such as IL-10 and reduced production of pro-inflammatory cytokines[36-39]. This indicates that appropriate inflammatory preconditioning of MSCs may generate sEVs with stronger immune-regulatory potential, which may be particularly suitable for chronic diabetic wounds characterized by persistent inflammation.

Beyond regulating macrophage polarization, MSC-sEVs can also inhibit macrophage pyroptosis, another important inflammatory mechanism involved in diabetic wound non-healing. Pyroptosis is a pro-inflammatory form of programmed cell death mediated by inflammasome activation. In diabetic wounds, the NOD-like receptor protein 3 (NLRP3) inflammasome is often excessively activated, leading to caspase-1 activation, gasdermin D cleavage, and the release of inflammatory cytokines such as IL-1β and IL-18. This process further amplifies inflammatory injury and delays tissue repair. Apoptotic extracellular vesicles derived from umbilical cord MSCs have been shown to reduce NLRP3 inflammasome formation, suppress macrophage pyroptosis, and improve wound healing outcomes[40]. Taken together, MSC-sEVs regulate macrophage behavior through multiple complementary mechanisms. They promote M1-to-M2 phenotypic transition, inhibit excessive inflammatory signaling, suppress inflammasome activation and pyroptosis, and enhance the secretion of anti-inflammatory and pro-reparative factors. These effects collectively restore immune homeostasis in diabetic wounds and provide a favorable microenvironment for angiogenesis, extracellular matrix deposition, re-epithelialization, and tissue remodeling. Therefore, macrophage polarization represents one of the central mechanisms by which MSC-sEVs alleviate chronic inflammation and accelerate diabetic wound healing.

3.2 Oxidative stress

MSC-sEVs can also improve the functions of endothelial cells, fibroblasts, and keratinocytes by regulating cell-level mechanisms such as oxidative stress, ferroptosis, cellular senescence, and autophagy. Through these effects, they enhance angiogenesis, collagen deposition, and re-epithelialization in skin wounds, thereby accelerating the healing of diabetic cutaneous wounds[41,42].

Oxidative stress plays a central role in the occurrence and progression of diabetic wounds. ROS are a collective term for highly reactive oxygen-containing molecules or free radicals, including superoxide anions, hydrogen peroxide, hydroxyl radicals, and singlet oxygen. Under physiological conditions, moderate levels of ROS function as important signaling molecules and participate in normal wound repair. For example, low to moderate ROS levels can regulate cell proliferation, migration, angiogenesis, and host defense, thereby contributing to the orderly progression of wound healing[43,44]. However, in the hyperglycemic diabetic microenvironment, this redox balance is disrupted. Excessive glucose metabolism enhances mitochondrial oxidative phosphorylation and increases electron leakage from the mitochondrial respiratory chain, leading to excessive ROS generation. At the same time, hyperglycemia weakens endogenous antioxidant defense systems and induces persistent oxidative stress in macrophages, endothelial cells, fibroblasts, keratinocytes, and other local tissue cells. In essence, oxidative stress results from an imbalance between excessive ROS accumulation and insufficient antioxidant capacity[45]. Excessive ROS exert multiple detrimental effects in the pathophysiology of diabetic foot wounds. First, ROS can directly damage endothelial cells, impair endothelial barrier integrity, increase vascular permeability, and reduce nitric oxide bioavailability. These changes compromise vascular relaxation, microcirculatory perfusion, and oxygen delivery to the wound bed, ultimately aggravating local ischemia and hypoxia. Second, ROS can induce neuronal injury and further impair neurovascular regulation, which is particularly relevant to diabetic foot ulcers because peripheral neuropathy is one of the major pathological contributors to ulcer formation and delayed healing. Third, excessive ROS can activate multiple inflammatory signaling pathways, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), MAPK, and inflammasome-related pathways, thereby promoting the release of inflammatory mediators and sustaining chronic inflammation. This persistent inflammatory state further recruits immune cells and amplifies local tissue injury, forming a vicious cycle between oxidative stress and inflammation. In addition, excessive ROS can induce lipid peroxidation, protein oxidation, enzyme inactivation, and DNA damage, all of which impair cellular function and survival. Lipid peroxidation compromises membrane integrity and generates toxic lipid metabolites, whereas oxidative DNA damage can trigger cell-cycle arrest, cellular senescence, apoptosis, or necrosis. These pathological events suppress keratinocyte migration, fibroblast proliferation, collagen synthesis, and endothelial tube formation, thereby impeding granulation tissue formation and wound closure. Mitochondria are particularly important in this process. As key organelles responsible for energy production, metabolic regulation, and cellular homeostasis, mitochondria are both major sources and major targets of ROS. Under diabetic conditions, mitochondrial dynamics, including fission, fusion, mitophagy, and biogenesis, may become dysregulated. This dysfunction further promotes ROS accumulation and contributes to the progression of diabetic foot ulcers[46].

Recent studies have shown that MSC-sEVs can alleviate oxidative damage in diabetic wounds through multiple complementary mechanisms. First, MSC-sEVs can enhance the

antioxidant response centered on nuclear factor erythroid 2-related factor 2, also known as Nrf2. Nrf2 is a master transcriptional regulator of cellular antioxidant defense. Under oxidative stress, activated Nrf2 translocates into the nucleus and induces the expression of multiple antioxidant and cytoprotective genes, such as heme oxygenase-1, NAD(P)H quinone oxidoreductase 1, superoxide dismutase, catalase, and glutathione-related enzymes. These downstream molecules help eliminate excessive ROS, maintain redox homeostasis, and protect cells against oxidative injury. In diabetic wounds, insufficient Nrf2 activation may weaken antioxidant defense and aggravate tissue damage. Studies have demonstrated that bone marrow MSC-sEVs can increase Nrf2 levels in diabetic rat wounds and promote re-epithelialization, collagen deposition, and neovascularization. These findings indicate that activation of the Nrf2-mediated antioxidant program is an important mechanism by which MSC-sEVs improve the oxidative microenvironment of diabetic wounds[47]. Second, MSC-sEVs can reduce ROS accumulation by restoring mitochondrial homeostasis. Endothelial cells are highly sensitive to oxidative injury, and their dysfunction directly affects angiogenesis and wound perfusion. MSC-sEVs can significantly reduce ROS levels in human umbilical vein endothelial cells exposed to high glucose. Mechanistically, these exosomes improve mitochondrial membrane potential, restore mitochondrial function, and enhance antioxidant capacity through upregulation of the SIRT3/SOD2 axis[48-50]. sirtuin 3 (SIRT3) is a mitochondrial deacetylase that regulates mitochondrial metabolism and antioxidant defense, whereas superoxide dismutase 2 (SOD2) is a key mitochondrial antioxidant enzyme responsible for converting superoxide into hydrogen peroxide. Activation of the SIRT3/SOD2 pathway helps reduce mitochondrial oxidative damage and preserve endothelial cell function. As a result, MSC-sEV treatment can improve endothelial proliferation, migration, and tube formation, thereby supporting neovascularization in diabetic wounds.

Human umbilical cord MSC-sEVs have also been shown to alleviate high glucose-induced oxidative injury in endothelial cells. These exosomes reduce the expression of reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase isoforms nicotinamide adenine dinucleotide phosphate oxidase 1 (NOX1) and NOX4, both of which are important enzymatic sources of ROS under diabetic conditions. By suppressing NOX1/NOX4-related ROS generation, human umbilical cord MSC-derived exosomes improve HUVEC proliferation and tube formation in vitro. In vivo, they increase wound perfusion and enhance CD31-positive vascular density, suggesting improved angiogenesis and microvascular reconstruction[51 52]. Therefore, MSC-sEVs can regulate oxidative stress not only by enhancing endogenous antioxidant defenses but also by suppressing excessive ROS production at its enzymatic sources.In addition to protecting endothelial cells, MSC-sEVs can also preserve the function of keratinocytes, which are essential for re-epithelialization. Under high-glucose conditions, keratinocytes are vulnerable to oxidative damage, lipid peroxidation, and ferroptosis. Ferroptosis is an iron-dependent form of regulated cell death characterized by excessive lipid peroxidation and impaired antioxidant defense. Increasing evidence suggests that ferroptosis contributes to delayed epithelial repair in diabetic wounds. Coenzyme Q10-engineered MSC-derived exosomes have been reported to deliver miR-548ai and miR-660 to keratinocytes. These miRNAs downregulate acyl-CoA synthetase long-chain family member 4 (ACSL4), which is a key regulator of lipid peroxidation and ferroptosis. By suppressing ACSL4 expression, these engineered exosomes inhibit lipid peroxidation and ferroptosis under high-glucose conditions, restore keratinocyte viability, migration, and proliferation, and promote wound closure in diabetic mice[53]. This finding suggests that MSC-sEV-based engineering strategies may further enhance the antioxidant and cytoprotective functions of sEVs.

Overall, MSC-sEVs regulate oxidative stress in diabetic wounds through several major mechanisms: enhancement of Nrf2-mediated endogenous antioxidant defense, suppression of NOX-related ROS generation, restoration of SIRT3/SOD2-mediated mitochondrial redox homeostasis, and inhibition of ACSL4-associated lipid peroxidation and ferroptosis. Through these pathways, MSC-sEVs reduce oxidative injury in endothelial cells, keratinocytes, and other wound-resident cells. More importantly, the antioxidant effects of MSC-sEVs are closely integrated with their anti-inflammatory, pro-angiogenic, anti-senescent, and pro-re-epithelialization activities. By interrupting the vicious cycle between hyperglycemia, ROS accumulation, mitochondrial dysfunction, inflammation, and cell death, MSC-sEVs help reconstruct a more favorable wound microenvironment and ultimately promote diabetic wound healing[54 55].

3.3 Ferroptosis

Ferroptosis is an iron-dependent form of programmed cell death driven by lipid peroxidation, and it is distinct from classical forms of cell death such as apoptosis, necrosis, and autophagy. Morphologically, ferroptosis is mainly characterized by mitochondrial shrinkage, reduced mitochondrial cristae, and increased membrane density, while nuclear morphology remains relatively intact. Biochemically, its major features include intracellular ferrous iron (Fe^{2+}) overload, depletion of glutathione (GSH), inactivation of glutathione peroxidase 4 (GPX4), and excessive accumulation of ROS[56]. In recent years, the critical role of ferroptosis in the pathological progression of chronic non-healing diabetic wounds has received increasing attention. The hyperglycemic microenvironment can induce ferroptosis in wound tissues through multiple pathways. First, high glucose disrupts intracellular iron metabolism, causing upregulation of transferrin receptor expression and impairment of iron efflux, thereby leading to free iron overload. Second, high glucose-induced oxidative stress depletes reduced glutathione, resulting in insufficient substrate availability for GPX4. Third, inflammation-related signaling pathways activated by high glucose can suppress the transcription of GPX4 and solute carrier family 7 member 11 (SLC7A11), the core subunit of the cystine/glutamate antiporter (System Xc^-). Together, these factors impair the clearance of lipid peroxides and subsequently trigger ferroptosis in key reparative cells, including fibroblasts, vascular endothelial cells, and keratinocytes, resulting in massive cell loss, impaired matrix synthesis, and defective angiogenesis, ultimately causing persistent wound non-healing. Studies have shown that the expression levels of the anti-ferroptotic genes GPX4 and SLC7A11 are significantly downregulated in diabetic wound tissues, whereas the key pro-ferroptotic enzyme ACSL4 is markedly upregulated in diabetic skin tissue[57 58]. Recent studies have shown that MSC-sEVs can exert anti-ferroptotic effects through multiple molecular mechanisms. First, MSC-sEVs can restore cellular antioxidant defense through non-coding RNA-mediated regulation. It has been reported that circ-Snhg11 in exosomes derived from bone marrow mesenchymal stem cells acts

as a molecular sponge for miR-144-3p, thereby relieving the inhibitory effect of miR-144-3p on SLC7A11, activating the GPX4-dependent antioxidant defense axis, reducing lipid peroxide accumulation, and alleviating ferroptosis in wound cells[53,59]. Second, MSC-sEVs can enhance cellular antioxidant capacity and attenuate high glucose-induced cellular injury and ferroptosis through activation of the Nrf2/HO-1 signaling pathway[60]. Third, exosomes derived from coenzyme Q10-preconditioned human umbilical cord mesenchymal stem cells are enriched in miR-548ai and miR-606, and they suppress the key lipid metabolism molecule ACSL4, thereby reducing the synthesis of polyunsaturated fatty acid phospholipids and inhibiting lipid peroxidation and ferroptosis at their source. In addition, MSC-sEVs can indirectly attenuate ferroptosis-related injury by improving organelle function. Studies have shown that MSC-sEVs can deliver functional mitochondria to neutrophils, maintain mitochondrial homeostasis, and activate the PI3K/AKT signaling pathway, thereby suppressing the formation of neutrophil extracellular traps (NETs) and reducing the release of inflammatory mediators. Because NETs can further induce oxidative injury and ferroptosis in endothelial cells, inhibition of this pathological process by MSC-sEVs helps restore endothelial cell proliferation and angiogenic capacity, improve local blood supply, and thereby indirectly alleviate ferroptosis-mediated tissue damage[31]. In summary, ferroptosis is an important mechanism underlying oxidative stress-induced injury and impaired repair in diabetic wounds. MSC-sEVs can accelerate wound healing by restoring the SLC7A11/GPX4 antioxidant system, activating the Nrf2/HO-1 pathway, inhibiting ACSL4-mediated lipid peroxidation, and indirectly reducing endothelial ferroptosis through maintenance of mitochondrial homeostasis and suppression of NETs formation. Collectively, these effects improve the highly oxidative microenvironment of diabetic wounds, preserve the function of key reparative cells, and promote angiogenesis and tissue regeneration.

3.4 Cellular senescence

Cellular senescence refers to a state of stable cell-cycle arrest that occurs when cells respond to various stressors. Unlike quiescence or terminal differentiation, senescent cells cease proliferating but remain metabolically active and secrete a complex mixture of bioactive molecules, a phenomenon known as the senescence-associated secretory phenotype (SASP)[61]. SASP factors include pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), chemokines (IL-8, MCP-1), growth factors (HGF, TGF-β), and matrix-remodeling enzymes (MMPs), all of which can profoundly affect the local microenvironment. In chronic diabetic wounds, aberrant cellular senescence has become an important pathological factor that impedes healing. Through inducing oxidative stress, mitochondrial dysfunction, and DNA damage responses, the hyperglycemic environment drives key reparative cells, including fibroblasts, endothelial cells, and keratinocytes, into premature senescence[62]. Mitochondrial dysfunction plays a central role in both the initiation and maintenance of cellular senescence. A large body of evidence indicates that mitochondrial dysfunction is not only a hallmark of cellular senescence, but is also closely associated with the induction and persistence of the senescent state[63]. Dysfunctional mitochondria in senescent cells generate excessive ROS, leading to oxidative DNA damage and activation of DNA damage response signaling pathways, which in turn promote cell-cycle arrest[64].

Recent studies have shown that MSC-sEVs can alleviate cellular senescence in diabetic wounds through multiple molecular mechanisms. First, in fibroblasts, exposure to 35 mM high glucose can successfully induce a senescence model in human dermal fibroblasts (HDFs), characterized by reduced proliferative capacity, impaired migration, weakened anti-apoptotic ability, and insufficient ECM synthesis. Placenta-derived mesenchymal stem cell extracellular vesicles (P-MSC-sEVs) can significantly inhibit high glucose-induced fibroblast senescence and apoptosis, restore their proliferative and migratory capacities, and thereby promote diabetic wound healing[65]. Mechanistic studies have shown that miR-145-5p carried by P-MSC-sEVs can enter recipient fibroblasts, target the cyclin-dependent kinase inhibitor CDKN1A (p21), and activate the ERK/Akt signaling pathway, thereby alleviating high glucose-induced cell-cycle arrest and the senescent phenotyp.

Second, MSC-sEVs can suppress cellular senescence by regulating metabolic reprogramming and longevity-related signaling pathways. SIRT1 plays an important role in glucose metabolism, maintenance of insulin sensitivity, and regulation of cellular senescence[66]. Studies have shown that placenta-derived mesenchymal stem cell extracellular vesicles can upregulate lncRNA VIM-AS1, activate PPAR-γ to improve glycolysis, and attenuate senescence in fibroblasts and vascular endothelial cells through a SIRT1-related pathway, while also promoting angiogenesis and inhibiting oxidative stress-induced injury[43].

Third, MSC-sEVs can improve the function of senescent cells by regulating mitochondrial metabolism-related molecules. Pyruvate dehydrogenase kinase 4 (PDK4) is an important enzyme involved in mitochondrial metabolic regulation and is highly expressed in tissues with high energy demand[67]. Studies have shown that PDK4 expression is upregulated during normal wound healing but is markedly insufficient in diabetic wounds; overexpression of PDK4 can improve the proliferation and migration of senescent HDFs under high-glucose conditions. Further studies suggest that this protective effect is associated with metabolic reprogramming and regulation of the Yes-associated protein (YAP) and c-Jun N-terminal kinase (JNK) pathways. As a core effector of the Hippo pathway, YAP plays an important role in skin tissue and dermal fibroblast senescence, and its downstream effector connective tissue growth factor (CTGF) can promote fibroblast proliferation and collagen deposition.

In addition, MSC-sEVs can attenuate the senescence of endothelial progenitor cells and endothelial cells by enhancing antioxidant defense. Studies have shown that exosomes derived from adipose-derived mesenchymal stem cells with Nrf2 overexpression can effectively prevent high glucose-induced endothelial progenitor cell senescence by suppressing ROS accumulation and inflammatory cytokine expression.

On the other hand, senescent endothelial cells undergo marked changes in gene expression, replicative capacity, and cellular morphology, and they compromise vascular endothelial integrity because of reduced regenerative and angiogenic capacity[68]. Oxidative stress induced by high glucose is considered one of the major causes of endothelial cell senescence[69]. Studies have shown that MSC-sEVs can significantly reduce the expression of senescence markers such as SA-β-gal in senescent endothelial cells and decrease the secretion of SASP factors. At the same time, they can improve angiogenic capacity, migratory ability, mitochondrial dysfunction, and ROS accumulation in oxidative stress-induced senescent endothelial cells in vitro, and promote wound closure and neovascularization in vivo. Mechanistic studies suggest that miR-

146a and Src signaling in MSC-sEVs may play key roles in these effects, and miR-146a may partially mediate the pro-angiogenic and wound-healing-promoting effects and further influence the dephosphorylation status of Src[70].

3.5 Autophagy

Autophagy is an important lysosome-dependent metabolic process in living organisms and plays a critical role in maintaining normal cellular physiology (Fig. 2). As a key mechanism of cellular quality control, autophagy is an essential catabolic process responsible for the clearance of damaged proteins and organelles within cells. It is crucial for the degradation and recycling of misfolded proteins and injured organelles, directly affects cellular bioactivity, and is closely associated with disease progression[71]. Studies have shown that, as a regulator of intracellular homeostasis, autophagy participates in all stages of wound repair and plays a pivotal role in the orderly and rapid healing of wounds[72]. Under the hyperglycemic conditions of diabetes, skin cells often exhibit mitochondrial dysfunction, ROS accumulation, enhanced oxidative stress, and excessive activation of inflammatory responses, ultimately leading to delayed wound healing. Autophagy can protect cellular function and improve the wound microenvironment by clearing damaged mitochondria, reducing excessive ROS generation, and alleviating oxidative stress[73]. In addition, autophagy helps maintain the survival, migration, and proliferation of key reparative cells, including fibroblasts, endothelial cells, and keratinocytes. Therefore, impaired autophagy is considered an important pathological mechanisms underlying chronic non-healing diabetic wounds.

Recent studies have shown that MSC-sEVs can promote diabetic wound healing by regulating autophagy in multiple cell types. First, in keratinocytes, studies using a wound model in type 1 diabetic mice found that the level of autophagy in injured epidermal cells was significantly lower than that in healthy controls. Exosomes derived from adipose-derived mesenchymal stem cells (ADSC-sEVs) can activate epidermal cell autophagy, restore the suppressed autophagic flux under high-glucose injury conditions, and enhance cell proliferation and migration, thereby accelerating re-epithelialization and promoting wound repair. The underlying mechanism may be related to upregulation of nicotinamide phosphoribosyltransferase (NAMPT) expression and activation of the autophagy-NAD axis[74].

In addition, MSC-sEVs can promote keratinocyte autophagy by regulating mTOR-related signaling. As a core negative regulator of autophagy, mTORC1 can regulate autophagic flux by affecting autophagosome-lysosome reorganization and lysosomal homeostasis[75]. Whereas MAPKAPK2, an important downstream effector of the p38 MAPK pathway, has been shown to participate in the amplification of inflammatory responses. Studies have shown that miR-4645-5p contained in exosomes derived from hypoxia-preconditioned bone marrow mesenchymal stem cells (hyBMSC-sEVs) can inhibit MAPKAPK2-mediated abnormal activation of AKT-mTORC1 signaling in keratinocytes, thereby restoring autophagy, enhancing keratinocyte proliferation and migration, and ultimately improving diabetic wound healing[76].

In addition to keratinocytes, the regulation of macrophage autophagy by MSC-sEVs is also an important mechanism for improving the inflammatory microenvironment of diabetic wounds. Under combined stimulation by high glucose and lipopolysaccharide (LPS), macrophages often exhibit mitochondrial dysfunction, decreased lysosomal activity, and impaired autophagy,

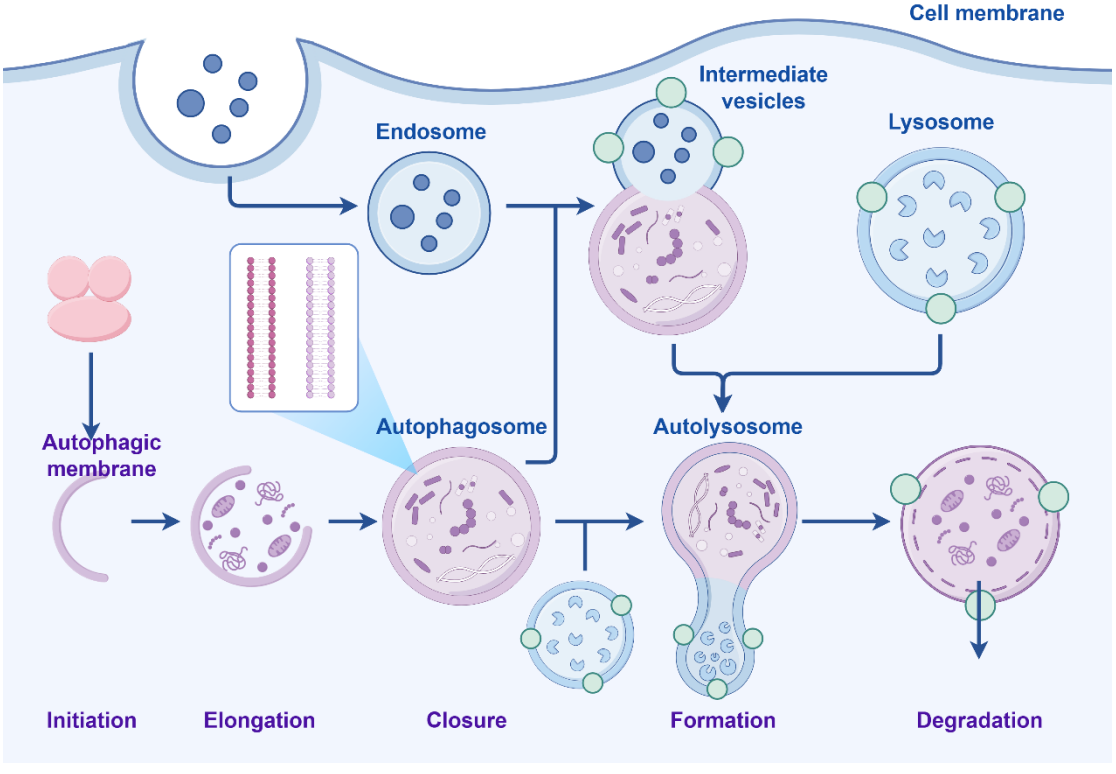

Figure 2 After autophagy initiation, the isolation membrane elongates and engulfs damaged organelles and protein aggregates to form an autophagosome. The autophagosome then fuses with lysosomes to generate an autolysosome, where the cargo is degraded and recycled. This process helps maintain cellular homeostasis and contributes to diabetic wound repair. This figure was generated by figdraw.

Table 1 Effects of MSC-sEVs on diabetic wound.

MSCs sources	In vitro effects	In vivo effects	Exosomes reactive molecules	Underlying mechanisms	Animal models	Application patterns	References
huMSCs	enhanced the proliferation and migration of HaCaT cells under HG conditions.	accelerated skin wound healing.	miR-548ai and miR-606	Q10-Exo downregulated the ferroptosis indicator ACSL4 in the keratinocytes by delivering miR-548ai and miR-606.	DB/DB diabetic mice	Q10-engineered huMSC-derived exosomes	[53]
ADSCs	increased senescent HUVEC migration and recovered tube formation.	promoted wound closure and blood vessel formation.	miR-146a	Regulated miR-146a and downregulated Src signal pathway.	Type 2 diabetes mice	hydrogel-based local sustained release	[69]
ADSCs	improved autophagic flux in a HG environment.	activated autophagy to accelerate wound repair.	——	Activated the autophagy-NAD axis by increased NAMPT expression.	Type 2 diabetic mice	hydrogel-based local sustained release	[73]
huMSCs	1.promoted the proliferation and migration of fibroblasts. 2.downregulation the ROS level.	1.more extensive collagen deposition. 2.downregulation of CHOP protein level. 3.better improvement of wound healing.	miR-17-5p	miR-17-5p overexpression in sEVs downregulates TLR4/ROS/MAPK pathway and inhibits NET formation	DB/DB diabetic mice	Therapeutic agent: Hypoxia-pretreated hucMSC-sEVs	[31]
P-MSCs	improving the functions of HG-induced senescent HDFs in terms of inhibiting senescence and apoptosis and inducing proliferation and migration in vitro.	promote diabetic wound healing and collagen deposition and improve fibroblast senescence	miR-145-5p	MiR-145-5p improved the function of HG-induced HDFs by targeting CDKN1A to activate the Erk/Akt pathway	DB/DB diabetic mice,	Therapeutic agent: placental mesenchymal stem cell-derived extracellular vesicles	[65]
UC-MSCs	1. enhanced glucose metabolism in fibroblasts. 2.increased the viability of fibroblasts. 3.enhance fibroblast migration 4.mitigate ROS levels. 5.increased the cellular activity of HUVECs. 6.increased formation of tube-like structures. 7.reducing cellular senescence in fibroblasts and vascular endothelial cells.	promote diabetic wound healing and collagen deposition and improve fibroblast senescence.	lncRNA VIM-AS1	——	STZ-induced diabetic SD rats	Therapeutic agent: HuMSCs-EVs loaded with lncRNA VIM-AS1	[43]
BMSCs	potentiated keratinocyte functions, including autophagy, proliferation and migration.	increased neo-epithelial tissue formation and keratinocyte proliferation.	miR-4645-5p	BMSC-Exo-mediated transfer of miR-4645-5p inactivated MAPKAPK2-induced AKT-mTORC1 signaling in keratinocytes.	DB/DB diabetic mice,	Therapeutic agent: hypoxia-pretreated BMSC-derived exosomes	[51]
BMSCs	MSC-sEVs effectively facilitate M1-to-M2 macrophage polarization, thereby attenuating inflammatory responses	promoted diabetic wound healing,achieved complete re-epithelialization and a well-organized dermis,indicating enhanced skin regeneration.	——	suppress inflammation through promoting M1 to M2 macrophage polarization by inhibiting the p38 MAPK signaling pathway.	STZ-induced diabetic SD rats	sEVs@MS microspheres were directly applied to the wound surface	[25]
ADSCs	promotes M2-like macrophage polarization under HG conditions.	had more significant therapeutic effect including significantly promoting angiogenesis in the ulcer site tissue and significantly decreasing IL-6, IL-1β, and TNF-α expression levels.	circ-Snhg11	circ-Snhg11 probably through activation of the miR-144–3p/HIF-1α/VEGF and miR-144–3p/HIF-1α/STAT3 signaling pathway.	STZ-induced diabetic mice	Subcutaneous perilesional injection of hypoxic ADSC-exosomes	[33]

thereby maintaining a pro-inflammatory M1 polarization state and releasing large amounts of inflammatory mediators. Studies have shown that ADSC-sEVs can restore macrophage autophagy by activating the SIRT1 signaling pathway, promote mitochondrial functional recovery, and drive macrophage polarization toward the anti-inflammatory M2 phenotype, thereby reducing the release of pro-inflammatory factors and reshaping an anti-inflammatory microenvironment favorable for wound healing[77].

Moreover, autophagy activation mediated by MSC-sEVs may also be closely associated with improved angiogenesis. By promoting the clearance of damaged components in vascular endothelial cells and alleviating oxidative stress, autophagy can enhance endothelial cell proliferation, migration, and tube formation, thereby improving insufficient local blood supply in diabetic wounds. At the same time, activation of the autophagy pathway may also enhance the anti-inflammatory effects of MSC-sEVs, reduce NETs formation, lower the risk of infection, and optimize the wound-healing environment[78]. In summary, impaired autophagy is an important mechanism underlying persistent chronic inflammation, delayed re-epithelialization, and insufficient angiogenesis in diabetic wounds. MSC-sEVs can restore autophagy in multiple repair-related cell types, including keratinocytes and macrophages, by regulating key signaling pathways such as NAMPT, the autophagy-NAD axis, MAPKAPK2/AKT-mTORC1, and SIRT1. In doing so, they alleviate oxidative stress, promote anti-inflammatory polarization, enhance re-epithelialization and angiogenesis, and ultimately accelerate diabetic wound healing.

4 Conclusion

In summary, the chronic non-healing of diabetic wounds is not caused by a single factor, but is jointly driven by multiple pathological processes, including persistent inflammation, enhanced oxidative stress, insufficient angiogenesis, cellular senescence, ferroptosis, and impaired autophagy. MSC-sEVs as a novel cell-free therapeutic strategy, can inherit the paracrine reparative advantages of their parent cells and comprehensively regulate the diabetic wound microenvironment by delivering active cargos such as miRNAs, lncRNAs, circRNAs, proteins, and metabolism-related molecules. Their core effects are mainly reflected in promoting macrophage polarization from the M1 phenotype to the M2 phenotype, inhibiting inflammatory pathways such as p38 MAPK and TLR4/NF-κB, and reducing NLRP3 inflammasome activation and pyroptosis. Meanwhile, MSC-sEVs can activate antioxidant pathways such as Nrf2 and SIRT3/SOD2, decrease ROS accumulation, improve mitochondrial function, and inhibit ACSL4-related lipid peroxidation and ferroptosis. In addition, MSC-sEVs can alleviate the senescence of fibroblasts, endothelial cells, and keratinocytes, restore autophagic flux, and enhance cell proliferation, migration, collagen deposition, re-epithelialization, and angiogenesis, thereby promoting the transition of wounds from a chronic inflammatory state to the tissue regeneration phase.

Although existing studies have demonstrated the considerable potential of MSC-sEVs in diabetic wound repair, their clinical translation still faces several challenges, including differences in vesicle sources, a lack of standardized isolation and purification methods, unclear effective dosage and administration routes, and insufficient evidence regarding long-term safety. Future studies should further improve the quality control system for MSC-sEVs, optimize engineered modifications and delivery platforms such as hydrogels, and verify their efficacy and safety through higher-quality animal experiments and clinical studies. Overall, MSC-sEVs are expected to become an important new direction for the treatment of chronic diabetic wounds and provide a new theoretical basis and practical pathway for achieving more stable, safer, and more efficient tissue repair.

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Data available statement

N/A

Author contribution

T.L. designed the study, searched literature, analyzed data and wrote the article. W.Z., Y.S., X.Z. and Y.S. searched literature and analyzed data. G.D. designed the study, wrote the article and supervised the study. All authors read and approved the final manuscript.

Ethics approval and consent

N/A

Consent for publication

All authors agree to publish.

Conflicts of interest

Author Gang Ding is an editorial board member of this journal, but he is not involved in the peer-review or decision of this article.

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