Postprint: Research Advances on Exosomal microRNA in Diabetic Foot Ulcer Repair

Authors: Cen Nimiao, Wei Yunshi, Lina Huang, WU Biaoliang, Wu Biaoliang

Date: 2024-10-15T00:00:00+00:00

Abstract

Diabetic foot ulcer (DFU), often accompanied by varying degrees of peripheral neuropathy and vascular disease, is a type of refractory wound. Its delayed healing process is primarily characterized by impaired neovascularization, persistent wound inflammatory response, impaired wound re-epithelialization, and abnormal fibroblast proliferation. Exosomal microRNA (miRNA), as an important mediator of intercellular communication, participates in various biological processes and can regulate the transcription and translation of multiple target genes that affect DFU healing. This article aims to briefly review the regulatory roles of exosomal miRNA in neovascularization, inflammatory response, wound re-epithelialization, and fibroblast proliferation during DFU repair, in order to provide new insights for DFU treatment.

Full Text

Research Progress of Exosomal miRNA Involvement in the Repair of Diabetic Foot Ulcers

CEN Nimiao[1],[2], WEI Yunshi[2], HUANG Lina[1],[2], WU Biaoliang[1]*

[1]Department of Endocrinology, Affiliated Hospital of Youjiang Medical University for Nationalities, Baise 533000, China
[2]Graduate School of Youjiang Medical University for Nationalities, Baise 533000, China

Corresponding author: WU Biaoliang, Chief Physician/Doctoral Supervisor; E-mail: yymucun@ymun.edu.cn

Abstract

Diabetic foot ulcer (DFU) is typically accompanied by varying degrees of peripheral neuropathy and vasculopathy, representing a difficult-to-heal wound.

The delayed healing process is primarily attributed to impaired neovascularization, persistent wound inflammation, defective wound re-epithelialization, and abnormal fibroblast proliferation. Exosomal microRNA (miRNA), as a crucial mediator of intercellular communication, participates in numerous biological processes and can regulate the transcription and translation of various target genes that affect DFU healing. This review aims to summarize the regulatory roles of exosomal miRNAs in neovascularization, inflammatory response, wound re-epithelialization, and fibroblast proliferation during DFU repair, thereby providing new insights for DFU treatment.

Keywords: Diabetic foot ulcer; Exosomes; MicroRNA; Review

Diabetic foot ulcer (DFU) is one of the most severe complications in diabetic patients, characterized by deep tissue damage resulting from foot infection, vascular abnormalities, and neuropathy [1]. According to global estimates, the prevalence of diabetes in 2021 was 536 million people, projected to rise to 783 million by 2045 [2]. The incidence of DFU ranges from 19% to 34% [3-4], with lower extremity non-traumatic amputation rates reaching 20% [5]. In China, the 5-year mortality rate after amputation is as high as 40% [1]. The high prevalence, disability, and mortality rates of DFU severely impact patients' quality of life and impose a heavy burden on society [6-7]. Therefore, actively investigating the factors that contribute to delayed DFU healing is crucial for developing more effective therapeutic strategies.

The main factors contributing to delayed DFU healing include: (1) hyperglycemia-induced vascular endothelial dysfunction and imbalance of angiogenesis-related factors that directly impair normal angiogenesis [8]; (2) persistent wound inflammation induced by chronic hyperglycemia [9]; and (3) impaired wound re-epithelialization and abnormal fibroblast proliferation [10].

In recent years, the role of exosomal microRNAs (miRNAs) from various sources in regulating DFU tissue repair has become a research focus. This review primarily discusses the regulatory effects of miRNAs derived from DFU tissue exosomes and exogenous (mesenchymal stem cell) exosomal miRNAs on DFU repair, including their roles in regulating neovascularization, inflammatory response, wound re-epithelialization, and fibroblast proliferation, aiming to provide new insights and therapeutic approaches for DFU treatment.

1. Exosomal miRNA and DFU

Exosomes are nanoscale vesicles (50–150 nm in diameter) with a phospholipid bilayer membrane, secreted by various cells as a type of extracellular vesicle containing proteins, RNA, DNA, and lipids. As mediators of cell-cell communication, exosomes play crucial roles in both physiological and pathological processes [11-13]. Previous studies have demonstrated that exosomes are involved in the development of diabetes and its complications, with increasing researchers con-

sidering exosomes as potential biomarkers for diabetes and its complications [14]. miRNAs are endogenous small non-coding RNAs in eukaryotes, approximately 22 nucleotides in length, that function in destabilizing target mRNA, inhibiting target mRNA translation, and mediating post-transcriptional gene silencing [15-16]. Exosomes mediate intercellular information transmission by carrying and transferring miRNAs between cells, participating in various biological processes including transcriptional regulation in target cells [17-18].

2.1 Regulation of Neovascularization

Angiogenesis provides oxygen and nutrients to DFU tissues. When neovascularization is impaired, ulcer wounds become ischemic and hypoxic, leading to delayed healing. Chronic glucose metabolism disorders in DFU patients result in the accumulation of advanced glycation end products (AGEs) in the skin, which impairs vascular endothelial cell proliferation and reduces vascular endothelial growth factor expression, thereby obstructing new blood vessel formation and causing ischemia and hypoxia in DFU wounds that ultimately fail to heal [19-20].

Endothelial cells, primarily located in the vascular intima, are polygonal and tightly interconnected to form a complete vascular intimal structure. During angiogenesis, endothelial cells rapidly proliferate and migrate to the stimulation site upon extracellular matrix stimulation, eventually inducing new blood vessel and network formation through cell accumulation. Exosomal miRNAs serve as important molecules in DFU repair mechanisms, capable of inhibiting or promoting angiogenesis by regulating endothelial cell function (Table 1).

XIONG et al. [21] observed significant upregulation of miR-20b-5p in plasma exosomes from diabetic patients and demonstrated that knocking down miR-20b-5p in diabetic mice markedly promoted wound healing, confirming that circulating exosomal miR-20b-5p inhibits human umbilical vein endothelial cell (HUVEC) function and angiogenesis by regulating Wnt9b signaling. XU et al. [22] found that miRNA-24-3p in human serum exosomes was upregulated in DFU, and inhibiting miRNA-24-3p accelerated wound repair in diabetic mice. They validated that circulating exosomal miRNA-24-3p suppresses HUVEC function by reducing phosphoinositide-3-kinase regulatory subunit gamma (PIK3R3) expression. NADPH oxidase 5 (NOX5) was identified as a potential target of miR-15a-3p; inhibiting NOX5 reduces reactive oxygen species release, thereby impairing HUVEC function. XIONG et al. [23] found that exosomal miR-15a-3p expression was upregulated in peripheral blood of DFU patients, and high expression of miR-15a-3p inhibited wound healing in diabetic mice by downregulating NOX5 expression and subsequently suppressing HUVEC function. YAN et al. [24] reported that miR-31-5p expression was significantly reduced in full-thickness wounds of diabetic mice, and milk exosome-mediated miR-31-5p delivery markedly improved endothelial cell function and promoted wound healing in diabetic mice by downregulating hypoxia-inducible factor-1 (HIF1AN) expression. These findings demonstrate that endothelial cells play a critical role in angiogenesis, and maintaining their structural integrity facilitates nor-

mal blood circulation, thereby increasing blood supply to DFU and accelerating healing.

Vascular endothelial growth factor (VEGF) is a glycoprotein that serves as the most direct angiogenic factor, promoting vascular remodeling and inducing angiogenesis in vivo. As a primary regulator of pro-angiogenic processes, VEGF has been shown to significantly promote diabetic wound healing [25-28]. LIU et al. [29] confirmed in both in vivo and in vitro experiments that miR-195-5p and miR-205-5p in extracellular vesicles isolated from DFU wound exudate inhibit angiogenesis by negatively regulating vascular endothelial growth factor A (VEGF-A) expression. ZHU et al. [30] found that miR-205-5p was highly expressed in human mesenchymal stem cell-derived exosomes and impaired wound healing in diabetic mice, primarily by interacting with the 3' -UTR of VEGF mRNA to inhibit VEGF protein translation and obstruct neovascularization. Additionally, protein kinase B (AKT) is a serine/threonine kinase that serves as an important information hub for various cellular functions, playing a key role in mediating angiogenesis and cell proliferation signaling. Mitogen-activated protein kinase (MAPK) is a critical transducer of signals from the cell surface to the nucleus. Under hypoxic conditions, VEGF binds to VEGF receptors on endothelial cell membranes, activating MAPK and manifesting VEGF' s mitogenic properties to induce endothelial cell proliferation and promote new blood vessel network formation. Studies have shown that human bone marrow mesenchymal stem cell exosomal miR-21-5p promotes angiogenesis and optimizes ischemic repair in diabetic rat foot ulcers by upregulating vascular endothelial growth factor receptor (VEGFR) expression and activating AKT and MAPK signaling pathways [31]. Research has also demonstrated that endothelial progenitor cell exosomal miRNA-221-3p promotes neovascularization and accelerates wound healing in diabetic mice by increasing protein expression levels of VEGF, platelet-endothelial cell adhesion molecule (CD31), and cell proliferation nuclear antigen (Ki67) [32]. These findings collectively demonstrate that exosomal miRNAs participate in DFU repair by targeting VEGF expression levels.

In summary, neovascularization plays a critical role in wound healing, and both intact endothelial cell function and high VEGF expression can induce new blood vessel formation. Based on the mechanism by which exosomal miRNAs regulate neovascularization by modulating endothelial cell function and angiogenic factor expression, exosomal miRNAs hold promise as novel therapeutic targets for DFU.

2.2 Regulation of Inflammatory Response

Chronic hyperglycemia can induce persistent inflammatory responses in DFU, which represents one of the key mechanisms delaying wound healing. This occurs by altering the epidermal microenvironment of the foot and inhibiting wound healing, specifically through increased pro-inflammatory factors, decreased anti-inflammatory factors, and impaired conversion of macrophages from the M1

phenotype to the M2 phenotype [33]. The transition from pro-inflammatory M1 macrophages to anti-inflammatory M2 macrophages is considered an important factor in accelerating wound healing [34]. Toll-like receptor 4 (TLR4), a member of the TLR family, is a key mediator of pro-inflammatory responses. Nuclear factor B (NF- B), as an important intracellular transcription factor, participates in inflammatory responses, immune responses, stress reactions, and apoptosis. Therefore, activation of the TLR4/NF- B signaling pathway promotes the production of pro-inflammatory cytokines.

Studies have shown that mouse mesenchymal stem cell-derived exosomal miRNA-23a and miRNA-125b synergistically inhibit the TLR4/NF- B signaling pathway to promote conversion of inflammatory M1 macrophages to the M2 phenotype, significantly reducing pro-inflammatory cytokine levels and alleviating neurovascular dysfunction in diabetic peripheral neuropathy mice [35]. GUO et al. [36] found that adipose stem cell exosomal miR-125b reduced inflammation-related protein expression of TLR-4 and interleukin-6 (IL-6), decreased inflammatory infiltration, and promoted granulation tissue formation and wound healing in DFU rats. Mouse bone marrow mesenchymal stem cell exosomal miR-146a attenuated inflammatory responses and promoted wound healing in diabetic mice by downregulating expression of pro-inflammatory genes including interleukin-1 receptor-associated kinase 1 (IRAK-1), tumor necrosis factor receptor-associated factor 6 (TRAF-6), and NF- B [37]. GE et al. [38] discovered that mouse adipose stem cell exosomal miR-132 induced M2 macrophage polarization possibly by downregulating phosphorylated p65 and NF- B inhibitor protein (I B) expression, thereby inhibiting the NF- B signaling pathway, further reducing inflammation and promoting angiogenesis in diabetic mouse wound tissues.

In summary, persistent inflammatory responses are characteristic of chronic wounds in diabetic patients, and abnormal wound inflammation represents an important factor impeding wound repair. Sustained inflammatory responses lead to prolonged accumulation of pro-inflammatory cytokines, exacerbating wound inflammation and impairing neovascularization, ultimately resulting in delayed wound healing. The aforementioned studies confirm that exosomal miRNAs can regulate inflammatory responses and neovascularization mechanisms by modulating inflammatory cells and cytokine expression, providing novel therapeutic strategies for DFU.

2.3 Regulation of Wound Re-Epithelialization and Fibroblast Proliferation

The DFU healing process is complex, involving various biological processes including wound re-epithelialization and granulation tissue formation. Keratinocyte proliferation and migration are crucial for wound re-epithelialization, while fibroblast proliferation and migration are essential for granulation tissue formation.

GONDALIYA et al. [39] demonstrated that inhibiting bone marrow mesenchymal stem cell exosomal miR-155 promoted fibroblast growth factor 7 (FGF-7) protein expression, enhanced keratinocyte proliferation and migration, and actively promoted wound re-epithelialization in diabetic mice, ultimately accelerating wound healing. The MAPK signaling pathway serves as a core information transmission network in eukaryotes, playing a vital regulatory role in cell proliferation, differentiation, and apoptosis. Mitogen-activated protein kinase-activated protein kinase 2 (MAPKAPK2) and extracellular regulated protein kinases 1/2 (ERK1/2) are key proteins in the MAPK signaling pathway that play important roles in DFU repair. Previous studies have found that bone marrow mesenchymal stem cell-derived exosomal miR-4645-5p induces AKT-mTORC1 signaling pathway inactivation by targeting MAPKAPK2, thereby activating keratinocyte autophagy, proliferation, and migration to promote wound healing in diabetic mice [40]. Human umbilical vein endothelial cell (HUVEC)-derived exosomal miR-106b-5p delayed wound healing in diabetic rats by downregulating ERK1/2 expression, activating fibroblast autophagy, and inhibiting collagen synthesis [41]. Transforming growth factor-$ 1(*TGF*− 1)*isakeyfactorinthefibroticprocess*,*promotingfibroblastactivationandproliferationaswellasextr*
128−1−5*ppromotedwoundhealingandinhibitedskinfibrosisindiabeticratsbydownregulatingtheTGF*− $1/Sm
signaling pathway [42].

In summary, keratinocyte and fibroblast proliferation and migration at the injury site are integral processes in tissue repair. The aforementioned studies reveal that exosomal miRNAs from different sources play important roles in regulating keratinocyte and fibroblast proliferation during wound healing, though the underlying mechanisms require further investigation. It is believed that through in-depth exploration of these mechanisms, exosomal miRNAs may be developed as novel therapeutic approaches for DFU.

3. Summary and Outlook

The pathogenesis of DFU is complex, and patients with concomitant lower extremity neuropathy and vasculopathy experience rapid progression and poor clinical prognosis [43], with DFU being the leading cause of amputation and disability in diabetic patients. Rapid and effective promotion of neovascularization, suppression of wound inflammation, and facilitation of wound re-epithelialization and fibroblast proliferation are crucial for promoting wound tissue repair. This review summarizes the important roles of exosomal miRNAs from different cellular sources in the development and progression of DFU, and how they regulate neovascularization, inflammatory response, wound re-epithelialization, and fibroblast proliferation to participate in DFU repair.

Although existing research has demonstrated broad application prospects for exosomes, most studies are animal experiments, with few clinical trials on exosomal miRNA in diabetic foot ulcer patients and limited effective clinical observations. Several issues currently hinder clinical application: First, exosome contents and functions are influenced by the type and state of secreting cells,

involving complex signaling pathways that remain unclear; second, exosome isolation, classification, and purification procedures are complicated and lack unified standards, preventing standardized and scalable production; third, while exosomes can be derived from different cells, determining their origin remains an urgent problem to solve; fourth, the feasibility and reliability of exosomal miRNA as biomarkers for DFU diagnosis and therapeutic targets require extensive research for further validation; fifth, domestic and international regulations on cells and their derivatives for human trials or clinical applications are strict.

Currently, exosome development and research are in early stages, with many challenges requiring urgent solutions. Exosomal miRNA provides new ideas for DFU treatment strategies, and with continuous technological advancement and improvement of regulatory systems, more animal experiments and clinical studies will emerge. Through collaborative efforts, exosomal miRNA therapy for DFU is expected to be widely applied in clinical practice.

Table 1. Effects and Mechanisms of Exosomal miRNA on Diabetic Ulcer Wounds

Exosome Source	miRNA	Change in DFU (Up↑/Down↓)	Target Gene	Mechanism
Diabetic patient plasma	miR-20b-5p	↑	Wnt9b	Inhibits HUVEC function and angiogenesis by regulating Wnt9b signaling
DFU patient peripheral blood	miR-24-3p	↑	PIK3R3	Suppresses endothelial cell function by reducing PIK3R3 expression
DFU wound exudate	miR-15a-3p	↑	NOX5	Inhibits endothelial cell function by downregulating NOX5 expression

Exosome Source	miRNA	Change in DFU (Up↑/Down↓)	Target Gene	Mechanism
Milk exosomes	miR-31-5p	↓	HIF1AN	Improves endothelial cell function by down-regulating HIF1AN expression
DFU wound exudate	miR-195-5p, miR-205-5p	↑	VEGF-A	Reduces angiogenesis by inhibiting VEGF-A expression
Human mesenchymal stem cells	miR-205-5p	↑	VEGF	Inhibits VEGF protein translation, obstructing neovascularization
Human bone marrow mesenchymal stem cells	miR-21-5p	↓	VEGFR	Promotes angiogenesis by upregulating VEGFR and activating AKT/MAPK pathways

Exosome Source	miRNA	Change in DFU (Up↑/Down↓)	Target Gene	Mechanism
Endothelial progenitor cells	miR-221-3p	↓	VEGF, CD31, Ki67	Promotes neovascularization by increasing VEGF, CD31, and Ki67 expression
Mouse mesenchymal stem cells	miR-23a, miR-125b	↓	TLR4, NF- B	Promotes M1→M2 macrophage conversion by inhibiting TLR4/NF- B, reducing pro-inflammatory cytokines
Adipose stem cells	miR-125b	↓	TLR-4, IL-6	Reduces inflammation by decreasing TLR-4 and IL-6 expression
Mouse bone marrow mesenchymal stem cells	miR-146a	↓	IRAK-1, TRAF-6, NF- B	Attenuates inflammation by downregulating IRAK-1, TRAF-6, and NF- B

Exosome Source	miRNA	Change in DFU (Up↑/Down↓)	Target Gene	Mechanism
Mouse adipose stem cells	miR-132	↓	Phosphorylated p65, I B	Inhibits NF- B pathway, induces M2 macrophage polarization, reducing inflammation
Bone marrow mesenchymal stem cells	miR-155	↑	FGF-7	Inhibition promotes FGF-7 expression, enhancing keratinocyte migration and re-epithelialization
Bone marrow mesenchymal stem cells	miR-4645-5p	↑	MAPKAPK2	Inactivates AKT-mTORC1, activates keratinocyte autophagy, proliferation, and migration
Umbilical vein endothelial cells	miR-106b-5p	↑	ERK1/2	Downregulates ERK1/2, activates fibroblast autophagy, inhibits collagen synthesis

Exosome Source	miRNA	Change in DFU (Up↑/Down↓)	Target Gene	Mechanism
Adipose mesenchymal stem cells	miR-128-1-5p	↓	TGF-$ $1, α-SMA	Promotes wound healing and inhibits fibrosis via down-regulating TGF-$ $1/Smad pathway

Note: Full names of target genes are provided below.

Note: PIK3R3 = Phosphoinositide-3-Kinase Regulatory Subunit Gamma; NOX5 = NADPH Oxidase 5; HIF1AN = Hypoxia Inducible Factor 1 Alpha Inhibitor; VEGF-A = Vascular Endothelial Growth Factor A; VEGF = Vascular Endothelial Growth Factor; VEGFR = Vascular Endothelial Growth Factor Receptor; CD31 = Platelet-Endothelial Cell Adhesion Molecule; Ki67 = Cell Proliferation Nuclear Antigen; NF- B = Nuclear Factor Kappa B; TLR4 = Toll-Like Receptor 4; IL-6 = Interleukin-6; IRAK-1 = Interleukin-1 Receptor-Associated Kinase 1; TRAF-6 = Tumor Necrosis Factor Receptor-Associated Factor 6; I B = NF- B Inhibitor Protein; FGF-7 = Fibroblast Growth Factor 7; MAPKAPK2 = Mitogen-Activated Protein Kinase-Activated Protein Kinase 2; ERK1/2 = Extracellular Regulated Protein Kinases 1/2; TGF-$ $1 = Transforming Growth Factor Beta 1; α-SMA = Alpha-Smooth Muscle Actin.

References

[1] Chinese Diabetes Society. Chinese guidelines for the prevention and treatment of type 2 diabetes mellitus (2020 edition) (Part II) [J]. Chinese Journal of Practical Internal Medicine, 2021, 41(9): 757-784. DOI: 10.19538/j.nk2021090106.

[2] SUN H, SAEEDI P, KARURANGA S, et al. Erratum to "IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045" [Diabetes Res Clin Pract 183 (2022) 109119] [J]. Diabetes Res Clin Pract, 2023, 204: 110945. DOI: 10.1016/j.diabres.2023.110945.

[3] ARMSTRONG D G, BOULTON A J M, BUS S A. Diabetic foot ulcers and their recurrence [J]. N Engl J Med, 2017, 376(24): 2367-2375. DOI: 10.1056/NEJMra1615439.

[4] WANG K J, WANG Y C, SHI W L, et al. Diagnosis and treatment of diabetic foot ulcer complicated with lower extremity vasculopathy: consensus

recommendation from the Chinese Medical Association (CMA), Chinese Medical Doctor Association (CMDA) [J]. Diabetes Metab Res Rev, 2024, 40(3): e3776. DOI: 10.1002/dmrr.3776.

[5] ZHANG Y Q, LAZZARINI P A, MCPHAIL S M, et al. Global disability burdens of diabetes-related lower-extremity complications in 1990 and 2016 [J]. Diabetes Care, 2020, 43(5): 964-974. DOI: 10.2337/dc19-1614.

[6] ZHANG P Z, LU J, JING Y L, et al. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis [J]. Ann Med, 2017, 49(2): 106-116. DOI: 10.1080/07853890.2016.1231932.

[7] MCDERMOTT K, FANG M, BOULTON A J M, et al. Etiology, epidemiology, and disparities in the burden of diabetic foot ulcers [J]. Diabetes Care, 2023, 46(1): 209-221. DOI: 10.2337/dci22-0043.

[8] OKONKWO U A, CHEN L, MA D, et al. Compromised angiogenesis and vascular integrity in impaired diabetic wound healing [J]. PLoS One, 2020, 15(4): e0231962. DOI: 10.1371/journal.pone.0231962.

[9] LIU X B. The role of blood glucose in diabetic wound healing and prognostic factors for diabetic foot [D]. Baise: Youjiang Medical University for Nationalities, 2020.

[10] REKHA P D, RAO S S, SAHANA T G, et al. Diabetic wound management [J]. Br J Community Nurs, 2018, 23(Sup9): S16-S22. DOI: 10.12968/bjcn.2018.23.Sup9.S16.

[11] COLOMBO M, RAPOSO G, THÉRY C. Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles for cell-to-cell communication [J]. Nat Cell Biol, 2019, 21(1): 9-17. DOI: 10.1038/s41556-018-0250-9.

[12] ZHANG Y, LIU Y F, LIU H Y, et al. Exosomes: biogenesis, biologic function and clinical potential [J]. Cell Biosci, 2019, 9: 19. DOI: 10.1186/s13578-019-0282-2.

[13] MATHIEU M, MARTIN-JAULAR L, LAVIEU G, et al. Specificities of secretion and uptake of exosomes and other extracellular vesicles for cell-to-cell communication [J]. Nat Cell Biol, 2019, 21(1): 9-17. DOI: 10.1038/s41556-018-0250-9.

[14] CASTAÑO C, NOVIALS A, PÁRRIZAS M. Exosomes and diabetes [J]. Diabetes Metab Res Rev, 2019, 35(3): e3107. DOI: 10.1002/dmrr.3107.

[15] FAN R G, XIAO C C, WAN X Q, et al. Small molecules with big roles in microRNA chemical biology and microRNA-targeted therapeutics [J]. RNA Biol, 2019, 16(6): 707-718. DOI: 10.1080/15476286.2019.1593094.

[16] GON Y, SHIMIZU T, MIZUMURA K, et al. Molecular techniques for respiratory diseases: microRNA and extracellular vesicles [J]. Respirology, 2020, 25(2): 149-160. DOI: 10.1111/resp.13756.

[17] GARCIA-MARTIN R, WANG G X, BRANDÃO B B, et al. MicroRNA sequence codes for small extracellular vesicle release and cellular retention [J]. Nature, 2022, 601(7893): 446-451. DOI: 10.1038/s41586-021-04234-3.

[18] AGBU P, CARTHEW R W. MicroRNA-mediated regulation of glucose and lipid metabolism [J]. Nat Rev Mol Cell Biol, 2021, 22(6): 425-438. DOI: 10.1038/s41580-021-00354-w.

[19] CHANG P C, TSAI S C, JHENG Y H, et al. Soft-tissue wound healing by anti-advanced glycation end-products agents [J]. J Dent Res, 2014, 93(4): 388-393. DOI: 10.1177/0022034514523785.

[20] HAN Y F, SUN T J, TAO R, et al. Clinical application prospect of umbilical cord-derived mesenchymal stem cells on clearance of advanced glycation end products through autophagy on diabetic wound [J]. Eur J Med Res, 2017, 22(1): 11. DOI: 10.1186/s40001-017-0253-1.

[21] XIONG Y, CHEN L, YAN C C, et al. Circulating exosomal miR-20b-5p inhibition restores Wnt9b signaling and reverses diabetes-associated impaired wound healing [J]. Small, 2020, 16(3): e1904044. DOI: 10.1002/smll.201904044.

[22] XU Y, OUYANG L, HE L, et al. Inhibition of exosomal miR-24-3p in diabetes restores angiogenesis and facilitates wound repair via targeting PIK3R3 [J]. J Cell Mol Med, 2020, 24(23): 13789-13803. DOI: 10.1111/jcmm.15958.

[23] XIONG Y, CHEN L, YU T, et al. Inhibition of circulating exosomal microRNA-15a-3p accelerates diabetic wound repair [J]. Aging, 2020, 12(10): 8968-8986. DOI: 10.18632/aging.103143.

[24] YAN C Q, CHEN J, WANG C, et al. Milk exosomes-mediated miR-31-5p delivery accelerates diabetic wound healing through promoting angiogenesis [J]. Drug Deliv, 2022, 29(1): 214-228. DOI: 10.1080/10717544.2021.2023699.

[25] ZHANG Y X, LI Q, YOUN J Y, et al. Protein phosphotyrosine phosphatase 1b (ptp1b) in calpain-dependent feedback regulation of vascular endothelial growth factor receptor (vegfr2) in endothelial cells: implications in vegf-dependent angiogenesis and diabetic wound healing [J]. J Biol Chem, 2017, 292(2): 407-416. DOI: 10.1074/jbc.M116.766832.

[26] QI S L, LIU Q, HE R L, et al. Effects of MEBO combined with microskin grafting on VEGF and EGF expression levels in diabetic foot wound tissue [J]. Chinese Journal of Burns Wounds & Surface Ulcers, 2022, 34(4): 240-243, 253. DOI: 10.3969/j.issn.1001-0726.2022.04.003.

[27] HE M J, GAN Z G, ZHENG A T, et al. Effects of hyperbaric oxygen on VEGF and EGF expression levels in diabetic foot wound tissue [J]. Chinese Journal of Burns Wounds & Surface Ulcers, 2021, 33(4): 237-242. DOI: 10.3969/j.issn.1001-0726.2021.04.003.

[28] ZHU Y, WANG Y M, JIA Y C, et al. Roxadustat promotes angiogenesis through HIF-1α/VEGF/VEGFR2 signaling and accelerates cutaneous wound

healing in diabetic rats [J]. Wound Repair Regen, 2019, 27(4): 324-334. DOI: 10.1111/wrr.12708.

[29] LIU J, WANG J H, FU W, et al. MiR-195-5p and miR-205-5p in extracellular vesicles isolated from diabetic foot ulcer wound fluid decrease angiogenesis by inhibiting VEGFA expression [J]. Aging, 2021, 13(15): 19805-19821. DOI: 10.18632/aging.203393.

[30] ZHU L Y, WANG G X, FISCHBACH S, et al. Suppression of microRNA-205-5p in human mesenchymal stem cells improves their therapeutic potential in treating diabetic foot disease [J]. Oncotarget, 2017, 8(32): 52294-52303. DOI: 10.18632/oncotarget.17012.

[31] HUANG C, LUO W F, WANG Q, et al. Human mesenchymal stem cells promote ischemic repairment and angiogenesis of diabetic foot through exosome miRNA-21-5p [J]. Stem Cell Res, 2021, 52: 102235. DOI: 10.1016/j.scr.2021.102235.

[32] XU J, BAI S W, CAO Y D, et al. miRNA-221-3p in endothelial progenitor cell-derived exosomes accelerates skin wound healing in diabetic mice [J]. Diabetes Metab Syndr Obes, 2020, 13: 1259-1270. DOI: 10.2147/DMSO.S243549.

[33] SALAZAR J J, ENNIS W J, KOH T J. Diabetes medications: impact on inflammation and wound healing [J]. J Diabetes Complications, 2016, 30(4): 746-752. DOI: 10.1016/j.jdiacomp.2015.12.017.

[34] KIM H, WANG S Y, KWAK G, et al. Exosome-guided phenotypic switch of M1 to M2 macrophages for cutaneous wound healing [J]. Adv Sci, 2019, 6(20): 1900513. DOI: 10.1002/advs.201900513.

[35] FAN B Y, LI C, SZALAD A, et al. Mesenchymal stromal cell-derived exosomes ameliorate peripheral neuropathy in a mouse model of diabetes [J]. Diabetologia, 2020, 63(2): 431-443. DOI: 10.1007/s00125-019-05043-0.

[36] GUO E Q, WANG L, WU J L, et al. Exosomes from microRNA-125b-modified adipose-derived stem cells promote wound healing of diabetic foot ulcers [J]. Curr Stem Cell Res Ther, 2024. DOI: 10.2174/011574888X287173240415050555.

[37] XU J W, WU W J, ZHANG L P, et al. The role of microRNA-146a in the pathogenesis of the diabetic wound-healing impairment: correction with mesenchymal stem cell treatment [J]. Diabetes, 2012, 61(11): 2906-2912. DOI: 10.2337/db12-0145.

[38] GE L F, WANG K Y, LIN H, et al. Engineered exosomes derived from miR-132-overexpresssing adipose stem cells promoted diabetic wound healing and skin reconstruction [J]. Front Bioeng Biotechnol, 2023, 11: 1129538. DOI: 10.3389/fbioe.2023.1129538.

[39] GONDALIYA P, SAYYED A A, BHAT P, et al. Mesenchymal stem cell-derived exosomes loaded with miR-155 inhibitor ameliorate diabetic wound healing [J]. Mol Pharm, 2022, 19(5): 1294-1308. DOI:

10.1021/acs.molpharmaceut.1c00669.

[40] SHI Y, WANG S, LIU D W, et al. Exosomal miR-4645-5p from hypoxic bone marrow mesenchymal stem cells facilitates diabetic wound healing by restoring keratinocyte autophagy [J]. Burns Trauma, 2024, 12: tkad058. DOI: 10.1093/burnst/tkad058.

[41] ZENG T T, WANG X Y, WANG W, et al. Endothelial cell-derived small extracellular vesicles suppress cutaneous wound healing through regulating fibroblasts autophagy [J]. Clin Sci, 2019, 133(9): CS20190008. DOI: 10.1042/CS20190008.

[42] LIANG Q, ZHOU D L, GE X Y, et al. Exosomes from adipose-derived mesenchymal stem cell improve diabetic wound healing and inhibit fibrosis via miR-128-1-5p/TGF-$ $1/Smad axis [J]. Mol Cell Endocrinol, 2024, 588: 112213. DOI: 10.1016/j.mce.2024.112213.

[43] NDOSI M, WRIGHT-HUGHES A, BROWN S, et al. Prognosis of the infected diabetic foot ulcer: a 12-month prospective observational study [J]. Diabet Med, 2018, 35(1): 78-88. DOI: 10.1111/dme.13537.

Author Contributions: CEN Nimiao conducted literature review, conceptualized and designed the article; WEI Yunshi and HUANG Lina revised the manuscript; WU Biaoliang revised and proofread the manuscript, finalized the version, and takes responsibility for the article.

Conflict of Interest: The authors declare no conflict of interest.

Note: Figure translations are in progress. See original paper for figures.