Journal of Biosciences and Medicines, 2026, 14(3), 29-41
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Research Progress on the Role of Bone Marrow Mesenchymal Stem Cell Homing in the Repair of Diabetic Foot Ulcers

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How to cite this paper: Wang, J.H., Wu, R.Z., Xu, H.D., Ban, D.P., Xu, E.X., Wang, G.Z., Yang, S.C., Zhou, H.D. and Wei, J.H. (2026) Research Progress on the Role of Bone Marrow Mesenchymal Stem Cell Homing in the Repair of Diabetic Foot Ulcers. *Journal of Biosciences and Medicines*, **14**, 29-41.
https://doi.org/10.4236/jbm.2026.143004

Received: January 16, 2026
Accepted: February 28, 2026
Published: March 3, 2026

Abstract

Diabetic foot ulcer (DFU), as one of the most common and severe complications of diabetes, imposes a heavy medical burden on patients and society due to its refractory nature. Bone marrow mesenchymal stem cells (BMSCs), with their potent multidirectional differentiation potential, immunomodulatory capabilities, and tissue regeneration-promoting properties, have emerged as a highly promising strategy for DFU treatment. This review summarizes the mechanisms and application progress of BMSCs in DFU treatment. Firstly, the pathophysiological basis of DFU is elucidated, including hyperglycemia-induced oxidative stress, dysregulated inflammatory responses, and sensory neuropathy. Secondly, the biological characteristics of BMSCs are introduced, including their sources, multidirectional differentiation potential, and key immunomodulatory functions. The core section focuses on the molecular mechanisms of BMSCs homing to injury sites, involving chemokine signaling pathways such as SDF-1/CXCR4, cell adhesion molecules like integrins, and the coordinated regulation of the matrix metalloproteinase (MMPs) system. On this basis, the review summarizes the multiple pathways through which BMSCs promote DFU healing, including angiogenesis promotion, growth factor secretion, immune microenvironment regulation, and direct participation in tissue regeneration. However, the diabetic pathological microenvironment impairs the homing efficiency and functionality of BMSCs. Therefore, the review further discusses strategies to enhance their homing efficiency, such as genetic modification, hypoxia or cytokine preconditioning, and combination with biological scaffolds. Finally, the challenges and future research directions are

discussed, emphasizing the need to further optimize cell delivery and functional maintenance strategies to advance BMSC therapy toward safer and more efficient clinical translation.

Keywords

Diabetic Foot Ulcer, Mesenchymal Stem Cells, Stem Cell Homing, Wound Healing

1. Introduction

Diabetes mellitus affects more than 440 million people worldwide. In China, with a population of 1.4 billion, there are over 110 million diabetic patients, with a prevalence rate as high as 11%, ranking first globally [1]. Diabetic foot ulcer (DFU) is one of the most common complications of diabetes, severely affecting patients' quality of life and imposing a significant medical burden [2]. Traditional treatment methods often fail to effectively promote ulcer healing, making the exploration of new therapeutic strategies crucial. In recent years, bone marrow mesenchymal stem cells (BMSCs) have shown great potential in the treatment of DFU due to their multidirectional differentiation potential, immunomodulatory effects, and ability to promote tissue regeneration [3]. The therapeutic effects of BMSCs are mainly achieved through several mechanisms: promoting angiogenesis, secreting growth factors, immunomodulation, and facilitating tissue regeneration. Among these, the homing ability of BMSCs, which refers to their migration to the injury site to exert therapeutic effects, is key to their efficacy [4]. However, in diabetic patients, the homing ability of BMSCs may be affected by various factors, such as hyperglycemia, inflammatory environment, and vascular dysfunction [5]. Therefore, understanding the molecular mechanisms of BMSC homing in depth and exploring strategies to enhance their homing efficiency are critical for improving the therapeutic outcomes of DFU.

2. The Pathophysiological Mechanisms of DFU

2.1. Enhanced Oxidative Stress

Mitochondrial dysfunction under hyperglycemic conditions is the central source of reactive oxygen species (ROS) burst. In the diabetic milieu, excessive glucose influx into cells—particularly in insulin-independent tissues such as skin, nerves, and vascular endothelium—increases tricarboxylic acid (TCA) cycle flux, leading to an imbalance in the mitochondrial NADH/NAD^+ ratio. This causes overreduction of the electron transport chain and ultimately results in massive leakage of superoxide ($O_2^- \cdot$). This mitochondria-derived ROS storm is regarded as the "unifying upstream event" that activates all downstream pathological pathways [6]. In DFU, the accumulation of intracellular ROS under hyperglycemia promotes the formation of advanced glycation end products (AGEs), activates the

polyol pathway and protein kinase C (PKC) signaling, and simultaneously suppresses the activity of endogenous antioxidant enzymes and compounds [7]. Upon binding to their specific receptor RAGE (Receptor for AGEs), AGEs activate key pro-inflammatory signaling cascades such as nuclear factor-kappa B (NF-κB), leading to sustained release of inflammatory cytokines including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). This perpetuates a state of chronic inflammation at the wound site, preventing the orderly transition to the proliferative phase of healing [8].

2.2. Inflammatory Response Dysregulation

The normal wound healing process requires a moderate inflammatory response to clear necrotic tissue and pathogens; however, wounds in diabetic patients often exhibit a chronic inflammatory state, leading to healing stagnation. This dysregulation of the inflammatory response is characterized by the overexpression of pro-inflammatory factors (e.g., IL-1β, TNF-α, IL-6) and insufficient anti-inflammatory factors [9]. During normal wound healing, macrophages transition from the M1 (pro-inflammatory) phenotype to the M2 (anti-inflammatory/repair) phenotype, promoting tissue repair [10]. However, in DFU, this balance between M1 and M2 macrophages is disrupted, with persistent M1 macrophages leading to chronic inflammation and impaired healing [10].

2.3. Sensory Neuropathy

Prolonged hyperglycemia causes microvascular damage and neuropathy, resulting in foot sensory loss, reduced blood flow, and tissue ischemia. Sensory neuropathy is one of the core initiating factors of DFU, primarily due to long-term hyperglycemia-induced axonal degeneration and dysfunction, which reduces the ability to perceive foot pain and increases the risk of trauma [11]. During the development of DFU, the accumulation of AGEs occurs; AGEs activate the NF-κB pathway, leading to the release of pro-inflammatory factors that cause neuronal apoptosis [12]. Consequently, patients lose sensitivity to minor stimuli, and abnormal foot pressure distribution triggers skin breakdown [13]. Approximately 15% of diabetic patients develop DFU over their lifetime, with neuropathy being a critical precursor; as indicated by recent epidemiological data [12], reflecting the prevalence of diabetic neuropathy in ulcer development.

3. The Biological Characteristics of BMSCs

3.1. The Source of BMSCs

BMSCs are a class of adult stem cells characterized by self-renewal capacity, multipotent differentiation potential, and immunomodulatory functions. They have demonstrated tremendous potential in tissue regeneration and repair, particularly attracting significant attention in research on DFU treatment. BMSCs are primarily derived from the bone marrow stroma. Bone marrow constitutes a complex microenvironment containing hematopoietic stem cells, mesenchymal stem cells,

adipocytes, osteoblasts, as well as various cytokines and extracellular matrix components [14]. BMSCs can be isolated from bone marrow using several methodologies. Common isolation techniques include: Whole bone marrow adherent culture method: This is one of the most widely used techniques. Bone marrow aspirates are diluted and centrifuged, and the mononuclear cell-containing layer is then plated onto culture dishes, where BMSCs selectively adhere to the plastic surface. Density gradient centrifugation method: A representative example is Ficoll density gradient centrifugation. Research has demonstrated that conventional culture under standard atmospheric oxygen tension (approximately 21% O_2) leads to rapid downregulation of CXCR4 expression in BMSCs [15]. This hyperoxic condition starkly contrasts with the physiological hypoxic microenvironment of the bone marrow niche, which typically maintains oxygen levels between 1% and 5% O_2. This native hypoxic milieu is critical for preserving BMSC stemness and homing capacity. Consequently, optimizing culture conditions to mimic the physiological hypoxia of the bone marrow has been shown to significantly upregulate CXCR4 expression and enhance the chemotactic migratory response of BMSCs toward stromal cell-derived factor-1α (SDF-1α) gradients. This enhanced migratory ability is essential for improving the therapeutic efficacy of BMSC-based interventions, as efficient homing to injury sites—mediated by the SDF-1α/CXCR4 axis—is a key determinant of successful tissue repair and regeneration.

3.2. Multipotent Differentiation Potential of BMSCs

One of the most prominent biological characteristics of BMSCs is their multipotent differentiation potential—under specific microenvironmental cues or inductive conditions, BMSCs can differentiate into multiple cell lineages, including osteoblasts, chondrocytes, and adipocytes. This property endows them with broad application prospects in tissue engineering and regenerative medicine [16]. This multipotency forms the foundation for BMSC-mediated repair of damaged tissues and organs. For instance, in DFU healing, BMSCs can promote neovascularization and tissue regeneration by differentiating into vascular endothelial cells and fibroblasts, thereby accelerating wound closure [17]. Beyond these classical trilineage differentiation capabilities, studies have also shown that under specific conditions, BMSCs possess the ability to differentiate into other cell types. For example, in a neuro-inductive environment, BMSCs can differentiate toward neural cells, suggesting their potential application in neural injury repair [16]. A deep understanding and precise control of BMSC differentiation fate are crucial for developing more effective and targeted cell-based therapeutic strategies. Especially in the context of complex chronic wounds such as DFU, precisely directing BMSCs to differentiate into desired cell types holds promise for achieving optimal therapeutic outcomes.

3.3. Immunomodulatory Functions of BMSCs

In the context of DFU—a chronic, non-healing wound—persistent low-grade in-

flammation and immune imbalance are key factors impeding healing. BMSCs, through their dynamic and plastic immunomodulatory capacity, can effectively reshape the local immune microenvironment, creating favorable conditions for the transition from the inflammatory phase to the proliferative phase of wound healing. The immunomodulatory function of BMSCs is not static or intrinsic; rather, it is a highly context-dependent response shaped by surrounding inflammatory signals. Upon stimulation by pro-inflammatory cytokines such as interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α), BMSCs become activated and upregulate the expression of multiple immunosuppressive molecules, thereby initiating their immunoregulatory program. This mechanism ensures that BMSCs exert suppressive effects only when needed, avoiding interference with normal immune surveillance. Their core mechanisms involve both direct cell–cell contact and paracrine signaling. At the level of direct contact, BMSCs can bind to T cells via surface molecules such as ICAM-1 and induce apoptosis of activated T cells through the Fas/FasL pathway, thereby precisely eliminating hyperactive immune cells [18]. More importantly, BMSCs exhibit potent paracrine activity. They secrete a range of soluble factors with immunomodulatory properties, forming a complex regulatory network. Notably, BMSCs can promote macrophage polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory, pro-repair M2 phenotype—evidenced by downregulation of iNOS and IL-1β (pro-inflammatory markers) and upregulation of Arg1, CD206, and IL-10 (M2 markers). This phenotypic shift is critical for clearing necrotic tissue, initiating angiogenesis, and facilitating extracellular matrix deposition in the wound bed [19].

4. Molecular Mechanisms of BMSCs Homing

The homing of BMSCs refers to the process by which these cells migrate from their original site or transplantation site and directionally engraft into specific microenvironments such as sites of injury, inflammation, or tumors. This process is a prerequisite for BMSCs to exert their tissue repair and immunomodulatory functions.

4.1. Chemokine Signaling Pathway

Chemokines are a class of small secreted proteins that mediate chemotactic cell movement by binding to their specific G protein-coupled receptors. In the homing process of BMSCs, the SDF-1/CXCR4 axis is one of the most extensively studied and functionally well-defined signaling pathways. Stromal cell-derived factor-1 (SDF-1), also known as CXCL12, is abundantly secreted by endothelial cells, fibroblasts, and inflammatory cells within injured tissues, establishing a concentration gradient. BMSCs highly express CXCR4—the sole receptor for SDF-1—on their surface, enabling them to initiate directional migration under the guidance of this gradient [20]. Experimental studies have demonstrated that SDF-1 significantly enhances the in vitro migratory capacity of BMSCs and promotes their accumulation at diabetic wound sites in animal models, thereby accelerating wound closure and

tissue regeneration [21]. Further mechanistic investigations revealed that the binding of SDF-1 to CXCR4 activates downstream PI3K/Akt and MAPK/ERK signaling pathways, which regulate actin cytoskeleton reorganization, pseudopod formation, and the expression of cell adhesion molecules, ultimately driving cellular migration [22].

4.2. Cell Adhesion Molecules

Integrins are a family of heterodimeric transmembrane receptors that primarily mediate adhesion between cells and the extracellular matrix (ECM), playing a central role in BMSC homing. Among them, β1-family integrins—particularly α4β1 and α5β1—are especially critical. The α4β1 integrin (also known as VLA-4) recognizes vascular cell adhesion molecule-1 (VCAM-1) expressed on the surface of vascular endothelial cells, facilitating the rolling, firm adhesion, and subsequent transendothelial migration of BMSCs at inflammatory sites. Research has shown that in areas of tissue injury, inflammatory cytokines such as TNF-α and IL-1β upregulate VCAM-1 expression on endothelial cells, creating "adhesion hotspots" that favor stem cell capture [23]. Additionally, α5β1 integrin mediates the anchoring and spreading of BMSCs within the wound matrix by binding to the RGD motif in fibronectin, providing structural support necessary for their proliferation and differentiation.

4.3. Matrix Metalloproteinases

Matrix metalloproteinases (MMPs) are a class of zinc-dependent endopeptidases capable of degrading ECM components such as collagen, fibronectin, and laminin, thereby creating structural pathways for BMSCs to traverse the vascular basement membrane and surrounding tissue barriers. In particular, MMP-2, MMP-9, and MT1-MMP act synergistically to degrade collagen and gelatin, serving as core effectors enabling BMSCs to complete transendothelial and interstitial migration [24] [25]. Moreover, the inflammatory microenvironment of DFU—rich in cytokines such as TNF-α and IL-1β—upregulates MMP expression in BMSCs, thereby enhancing their directional migration toward ulcer sites [26]. Following successful homing, MMPs secreted by BMSCs continue to participate in ECM remodeling and collagen metabolism in the wound area, which are critical steps in tissue regeneration and wound healing. MMPs thus serve as a key molecular bridge linking BMSCs to the repair process in DFU. They not only "pave the way" for BMSC homing through enzymatic degradation but are also activated and upregulated within the DFU inflammatory microenvironment, thereby increasing the efficiency of MSC recruitment.

5. The Role of BMSCs in the Treatment of DFU

5.1. Promotion of Angiogenesis

BMSCs have been demonstrated to promote angiogenesis through multiple mechanisms, thereby improving local blood perfusion and accelerating wound healing

[27]. BMSCs secrete various pro-angiogenic factors, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF). These factors can stimulate the proliferation, migration, and tube formation of endothelial cells, facilitating the generation of new blood vessels. Moreover, BMSCs can also differentiate into endothelial cells and directly participate in vessel formation [27]. A systematic review and meta-analysis highlighted the role of extracellular vesicles derived from bone marrow-derived stem cells (BMSC-EVs) in promoting angiogenesis, suggesting their potential as a cell-free therapy for DFU treatment, although this approach remains in the preclinical stage [28]. SDF-1 is abundantly secreted by damaged tissues under hypoxic and inflammatory conditions, forming a concentration gradient that guides the directional migration of BMSCs expressing CXCR4. When the expression level of CXCR4 is downregulated due to in vitro high oxygen culture (21% O_2), the chemotactic response of BMSCs to SDF-1 is significantly weakened, leading to homing failure, which in turn reduces their ability to locally release factors such as VEGF, ultimately affecting the efficiency of angiogenesis.

5.2. Secretion of Growth Factors

BMSCs possess robust paracrine capabilities and can secrete a wide array of bioactive molecules, including growth factors, cytokines, and chemokines, which play pivotal roles in the repair process of DFU. In addition to VEGF and bFGF mentioned above, BMSCs also secrete transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), and epidermal growth factor (EGF). These growth factors can enhance fibroblast activity, promote ECM remodeling and collagen synthesis, thereby accelerating wound contraction and tissue regeneration [29]. For instance, in a diabetic rat model, transplantation of bone marrow mesenchymal stem cells was shown to promote delayed wound healing, which may be attributed to the growth factors they secrete [30]. The paracrine effects of growth factors also depend on effective cell homing as a prerequisite. If cells become sequestered in the lungs or other non-target organs, they cannot establish a sufficient local concentration gradient of bioactive molecules at the wound site, thereby impairing the processes of ECM remodeling and re-epithelialization.

5.3. Immunomodulation

Chronic inflammation is a key reason why DFU is difficult to heal [31]. BMSCs exhibit significant immunomodulatory properties, capable of suppressing the release of pro-inflammatory cytokines (such as tumor necrosis factor-α and interleukin-1β) and promoting the secretion of anti-inflammatory cytokines (such as interleukin-10), thereby creating a microenvironment conducive to tissue repair [32]. This immunomodulatory effect helps alleviate local inflammatory responses, prevents further tissue damage, and sets the stage for subsequent tissue regeneration. For example, exosomes derived from M2 macrophages have been confirmed to possess anti-inflammatory properties, capable of modulating macrophage phenotype

and promoting diabetic wound healing [31]. Janus Liposozyme promotes healing by regulating the transformation of M1 macrophages into M2 macrophages, thereby reducing inflammatory responses [33]. This regulatory effect can only be effectively exerted after BMSCs successfully engraft into the inflammatory microenvironment, and the intensity of the immunomodulatory effect directly depends on the number of BMSCs reaching the lesion site and their functional integrity.

5.4. Promotion of Tissue Regeneration

As multipotent stem cells, BMSCs have the capacity to differentiate into various cell types, including keratinocytes, fibroblasts, and endothelial cells—key cellular components in skin repair and tissue regeneration [34]. Through either direct differentiation or paracrine actions, BMSCs can facilitate the regeneration and functional recovery of damaged tissues. During the healing process of DFU, BMSCs contribute to the formation of high-quality granulation tissue, promote re-epithelialization, and enhance the tensile strength of the wound, ultimately achieving effective wound repair [35]. The relationship between tissue regeneration and BMSC homing is not a simple linear one; rather, it constitutes a dynamic closed loop of "homing - engraftment - activation - regulation - regeneration." The efficiency of homing determines the threshold for initiating regeneration, while the functional state of the engrafted cells dictates the quality and durability of the regenerative outcome.

6. Strategies to Enhance the Homing Efficiency of BMSCs

Although BMSCs have demonstrated significant potential in the treatment of DFU, their low homing efficiency remains a major limitation, resulting in poor survival and retention of transplanted cells at the lesion site. To overcome this challenge, researchers are developing various strategies to improve the homing efficiency of BMSCs, thereby enhancing their therapeutic efficacy.

6.1. Genetic Modification

Genetic modification is an effective approach to enhance the targeting ability and functionality of BMSCs. By overexpressing specific chemokine receptors or pro-angiogenic factors in BMSCs, their homing capacity and therapeutic potential in vivo can be significantly improved. For instance, BMSCs engineered to overexpress the chemokine receptor CXCR4 exhibit enhanced responsiveness to stromal cell-derived factor-1 (SDF-1), which is highly expressed at DFU lesion sites, thereby improving homing efficiency [36]. Additionally, genetic modification of BMSCs to overexpress vascular endothelial growth factor (VEGF) or heme oxygenase-1 (HO-1) can augment their pro-angiogenic and antioxidant capacities, playing a more critical role in promoting DFU healing [37].

6.2. Preconditioning

Preconditioning BMSCs in vitro to mimic the pathophysiological environment in

vivo can enhance cell survival, migratory capacity, and paracrine function. Common preconditioning strategies include:

Hypoxic preconditioning: DFU lesions are often hypoxic. Preconditioning BMSCs under hypoxic conditions in vitro upregulates the expression of hypoxia-inducible factor-1α (HIF-1α), thereby enhancing cellular tolerance to hypoxia and increasing the secretion of pro-angiogenic factors [38].

Cytokine preconditioning: Pre-treatment of BMSCs with inflammatory cytokines such as IL-1β or TNF-α can activate intracellular signaling pathways, upregulate chemokine receptor expression, and improve homing ability [39].

Pharmacological preconditioning: Preconditioning BMSCs with specific drugs (e.g., statins, melatonin) or small-molecule compounds can enhance antioxidant capacity, reduce apoptosis, and promote migration and proliferation [37].

6.3. Biomaterial Scaffolds

Combining BMSCs with biomaterial scaffolds is an effective strategy to improve cell retention and local therapeutic outcomes [40]. Biomaterial scaffolds provide a three-dimensional microenvironment for transplanted BMSCs, protecting them from the harsh local milieu and supporting their survival, proliferation, and functional activity [41]. While ensuring cell retention, the scaffold can be endowed with the active capability to recruit endogenous stem cells. For instance, sustained-release chemokines such as SDF-1α can be incorporated into PEG or collagen scaffolds. This factor can establish a stable concentration gradient that attracts host circulating $CXCR4^+$ BMSCs to migrate toward the implantation site, thereby achieving synergistic enhancement between "exogenous cell retention" and "endogenous cell homing."

Injectable hydrogels: Injectable polyethylene glycol (PEG)-based hydrogels are widely used for cell delivery due to their excellent biocompatibility and controllable release properties [42]. For example, studies have shown that injectable reactive oxygen species (ROS)-degradable PEG hydrogels enhance stem cell retention and provide antioxidant protection [41].

Collagen scaffolds: As a natural component of the extracellular matrix, collagen exhibits excellent biocompatibility and biodegradability. Local application of BMSCs seeded on collagen scaffolds has been shown to promote ulcer healing and angiogenesis in diabetic rabbit models [30].

7. Conclusion

BMSCs demonstrate significant therapeutic potential in the treatment of DFUs through promoting angiogenesis, secreting growth factors, modulating chronic inflammation, and facilitating tissue regeneration. The efficacy of BMSCs fundamentally relies on their homing capacity—the ability to migrate to the lesion site and exert their therapeutic functions. Current research has elucidated that homing involves a complex interplay of chemokines, adhesion molecules, and MMPs. Strategies such as genetic modification, preconditioning, and the use of biomaterial

scaffolds have been developed to enhance homing efficiency. Nevertheless, substantial challenges remain: the diabetic microenvironment—characterized by hyperglycemia and oxidative stress—significantly impairs both the homing capability and functional integrity of BMSCs. Furthermore, there is no consensus across studies regarding the optimal cell source, dosage, or delivery method. Critical questions concerning long-term safety, immunogenicity, and the precise mechanisms governing in vivo regulation require deeper investigation. Future efforts must focus on refining cell-based therapies by integrating advances in biomaterials science and genetic engineering to overcome the hostile microenvironmental barriers, thereby enabling more efficient and safer clinical translation.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Ma, R.C.W. (2018) Correction to: Epidemiology of Diabetes and Diabetic Complications in China. *Diabetologia*, **61**, 1491-1491. https://doi.org/10.1007/s00125-018-4616-0

[2] Hetta, H.F., Elsaghir, A., Sijercic, V.C., Akhtar, M.S., Gad, S.A., Moses, A., *et al.* (2024) Mesenchymal Stem Cell Therapy in Diabetic Foot Ulcer: An Updated Comprehensive Review. *Health Science Reports*, **7**, e2036. https://doi.org/10.1002/hsr2.2036

[3] Yu, X., Liu, P., Li, Z. and Zhang, Z. (2023) Function and Mechanism of Mesenchymal Stem Cells in the Healing of Diabetic Foot Wounds. *Frontiers in Endocrinology*, **14**, Article 1099310. https://doi.org/10.3389/fendo.2023.1099310

[4] Sajjad, U., Ahmed, M., Iqbal, M.Z., Riaz, M., Mustafa, M., Biedermann, T., *et al.* (2024) Exploring Mesenchymal Stem Cells Homing Mechanisms and Improvement Strategies. *Stem Cells Translational Medicine*, **13**, 1161-1177. https://doi.org/10.1093/stcltm/szae045

[5] Luo, M., Zhao, Z. and Yi, J. (2023) Osteogenesis of Bone Marrow Mesenchymal Stem Cell in Hyperglycemia. *Frontiers in Endocrinology*, **14**, Article 1150068. https://doi.org/10.3389/fendo.2023.1150068

[6] Roohi, T.F., Faizan, S., Parray, Z.A., Baig, M.A.I., Mehdi, S., Kinattingal, N., *et al.* (2023) Beyond Glucose: The Dual Assault of Oxidative and ER Stress in Diabetic Disorders. *High Blood Pressure & Cardiovascular Prevention*, **30**, 513-531. https://doi.org/10.1007/s40292-023-00611-3

[7] Zhang, W., Chen, L., Xiong, Y., Panayi, A.C., Abududilibaier, A., Hu, Y., *et al.* (2021) Antioxidant Therapy and Antioxidant-Related Bionanomaterials in Diabetic Wound Healing. *Frontiers in Bioengineering and Biotechnology*, **9**, Article 707479. https://doi.org/10.3389/fbioe.2021.707479

[8] Bhatti, J.S., Sehrawat, A., Mishra, J., Sidhu, I.S., Navik, U., Khullar, N., *et al.* (2022) Oxidative Stress in the Pathophysiology of Type 2 Diabetes and Related Complications: Current Therapeutics Strategies and Future Perspectives. *Free Radical Biology and Medicine*, **184**, 114-134. https://doi.org/10.1016/j.freeradbiomed.2022.03.019

[9] Lv, D., Cao, X., Zhong, L., Dong, Y., Xu, Z., Rong, Y., *et al.* (2023) Targeting Phenylpyruvate Restrains Excessive NLRP3 Inflammasome Activation and Pathological

Inflammation in Diabetic Wound Healing. *Cell Reports Medicine*, **4**, Article 101129. https://doi.org/10.1016/j.xcrm.2023.101129

[10] Dörr, S., Lucke-Paulig, L., Vollmer, C. and Lobmann, R. (2019) Malignant Transformation in Diabetic Foot Ulcers—Case Reports and Review of the Literature. *Geriatrics*, **4**, Article 62. https://doi.org/10.3390/geriatrics4040062

[11] Moon, D., Cao, N. and Martinez, B. (2022) Shoe and Bracing Considerations for the Insensate Foot: Shoe Considerations for Diabetic Foot. *Physical Medicine and Rehabilitation Clinics of North America*, **33**, 845-856.

[12] Raja, J.M., Maturana, M.A., Kayali, S., Khouzam, A. and Efeovbokhan, N. (2023) Diabetic Foot Ulcer: A Comprehensive Review of Pathophysiology and Management Modalities. *World Journal of Clinical Cases*, **11**, 1684-1693. https://doi.org/10.12998/wjcc.v11.i8.1684

[13] Aldana, P.C., Cartron, A.M. and Khachemoune, A. (2022) Reappraising Diabetic Foot Ulcers: A Focus on Mechanisms of Ulceration and Clinical Evaluation. *The International Journal of Lower Extremity Wounds*, **21**, 294-302. https://doi.org/10.1177/1534734620944514

[14] Abdelrazik, H., Giordano, E., Barbanti Brodano, G., Griffoni, C., De Falco, E. and Pelagalli, A. (2019) Substantial Overview on Mesenchymal Stem Cell Biological and Physical Properties as an Opportunity in Translational Medicine. *International Journal of Molecular Sciences*, **20**, Article 5386. https://doi.org/10.3390/ijms20215386

[15] Pervin, B., Aydın, G., Visser, T., Uçkan-Çetinkaya, D. and Aerts-Kaya, F.S.F. (2021) CXCR4 Expression by Mesenchymal Stromal Cells Is Lost after Use of Enzymatic Dissociation Agents, but Preserved by Use of Non-Enzymatic Methods. *International Journal of Hematology*, **113**, 5-9. https://doi.org/10.1007/s12185-020-03043-0

[16] Christoffers, S., Seiler, L., Wiebe, E. and Blume, C. (2024) Possibilities and Efficiency of MSC Co-Transfection for Gene Therapy. *Stem Cell Research & Therapy*, **15**, Article No. 150. https://doi.org/10.1186/s13287-024-03757-6

[17] Cao, Y., Gang, X., Sun, C. and Wang, G. (2017) Mesenchymal Stem Cells Improve Healing of Diabetic Foot Ulcer. *Journal of Diabetes Research*, **2017**, 1-10. https://doi.org/10.1155/2017/9328347

[18] Chen, C., Akiyama, K., Yamaza, T., You, Y., Xu, X., Li, B., *et al*. (2014) Telomerase Governs Immunomodulatory Properties of Mesenchymal Stem Cells by Regulating FAS Ligand Expression. *EMBO Molecular Medicine*, **6**, 322-334. https://doi.org/10.1002/emmm.201303000

[19] Zheng, Y.H., Deng, Y.Y., Lai, W., *et al*. (2018) Effect of Bone Marrow Mesenchymal Stem Cells on the Polarization of Macrophages. *Molecular Medicine Reports*, **17**, 4449-4459. https://doi.org/10.3892/mmr.2018.8457

[20] Biyani, S., Patil, A. and Swami, V. (2024) The Influence of SDF-1 (CXCL12) Gene in Health and Disease: A Review of Literature. *Biophysical Reviews*, **17**, 127-138. https://doi.org/10.1007/s12551-024-01230-5

[21] Wang, Z., Xia, L., Cheng, J., Liu, J., Zhu, Q., Cui, C., *et al*. (2024) Combination Therapy of Bone Marrow Mesenchymal Stem Cell Transplantation and Electroacupuncture for the Repair of Intrauterine Adhesions in Rats: Mechanisms and Functional Recovery. *Reproductive Sciences*, **31**, 2318-2330. https://doi.org/10.1007/s43032-024-01465-3

[22] Wang, Z., Lao, A., Huang, X., Zhou, Y., Shen, S.G. and Lin, D. (2024) Apt-19s-Functionalized 3d-Printed Mesoporous Bioactive Glass Scaffold Promotes BMSC Recruitment in Bone Regeneration via SDF-1α/CXCR4 Axis and MAPK Signaling. *Advanced*

Functional Materials, **34**, Article 2316675.
https://doi.org/10.1002/adfm.202316675

[23] Zhou, X., Zhang, K., Wang, C., Teng, Y., Yu, P., Cai, W., *et al*. (2024) Isthmin-1 Promotes Growth and Progression of Colorectal Cancer through the Interaction with EGFR and YBX-1. *Cancer Letters*, **590**, Article 216868.
https://doi.org/10.1016/j.canlet.2024.216868

[24] Mahmoudvand, G., Karimi Rouzbahani, A., Razavi, Z.S., Mahjoor, M. and Afkhami, H. (2023) Mesenchymal Stem Cell Therapy for Non-Healing Diabetic Foot Ulcer Infection: New Insight. *Frontiers in Bioengineering and Biotechnology*, **11**, Article 1158484. https://doi.org/10.3389/fbioe.2023.1158484

[25] Lee, H.J., Kim, Y.H., Choi, D.W., *et al*. (2021) Tonsil-Derived Mesenchymal Stem Cells Enhance Allogeneic Bone Marrow Engraftment via Collagen IV Degradation. *Stem Cell Research & Therapy*, **12**, Article No. 329.
https://doi.org/10.1186/s13287-021-02414-6

[26] Naji, A., Eitoku, M., Favier, B., Deschaseaux, F., Rouas-Freiss, N. and Suganuma, N. (2019) Biological Functions of Mesenchymal Stem Cells and Clinical Implications. *Cellular and Molecular Life Sciences*, **76**, 3323-3348.
https://doi.org/10.1007/s00018-019-03125-1

[27] Wang, S., Miao, Z., Yang, Q., Wang, Y. and Zhang, J. (2018) The Dynamic Roles of Mesenchymal Stem Cells in Colon Cancer. *Canadian Journal of Gastroenterology and Hepatology*, **2018**, 1-8. https://doi.org/10.1155/2018/7628763

[28] Dama, G., Du, J., Zhu, X., Liu, Y. and Lin, J. (2023) Bone Marrow-Derived Mesenchymal Stem Cells: A Promising Therapeutic Option for the Treatment of Diabetic Foot Ulcers. *Diabetes Research and Clinical Practice*, **195**, Article 110201.
https://doi.org/10.1016/j.diabres.2022.110201

[29] Du, Y., Yan, S., Sun, Y., Han, X., Shi, H., Fan, W., *et al*. (2024) Extracellular Vesicles Secreted by Bone Marrow Stem Cells Mediate Angiogenesis for the Treatment of Diabetic Ulcers: A Systematic Review and Meta-Analysis of Preclinical Studies. *Heliyon*, **10**, e25762. https://doi.org/10.1016/j.heliyon.2024.e25762

[30] O'Loughlin, A., Kulkarni, M., Creane, M., Vaughan, E.E., Mooney, E., Shaw, G., *et al*. (2013) Topical Administration of Allogeneic Mesenchymal Stromal Cells Seeded in a Collagen Scaffold Augments Wound Healing and Increases Angiogenesis in the Diabetic Rabbit Ulcer. *Diabetes*, **62**, 2588-2594. https://doi.org/10.2337/db12-1822

[31] Wan, J., Xia, L., Liang, W., Liu, Y. and Cai, Q. (2013) Transplantation of Bone Marrow-Derived Mesenchymal Stem Cells Promotes Delayed Wound Healing in Diabetic Rats. *Journal of Diabetes Research*, **2013**, 1-11. https://doi.org/10.1155/2013/647107

[32] Zeng, J., Sun, Z., Zeng, F., Gu, C. and Chen, X. (2023) M2 Macrophage-Derived Exosome-Encapsulated Microneedles with Mild Photothermal Therapy for Accelerated Diabetic Wound Healing. *Materials Today Bio*, **20**, Article 100649.
https://doi.org/10.1016/j.mtbio.2023.100649

[33] Zaid, A. and Ariel, A. (2024) Harnessing Anti-Inflammatory Pathways and Macrophage Nano Delivery to Treat Inflammatory and Fibrotic Disorders. *Advanced Drug Delivery Reviews*, **207**, Article 115204. https://doi.org/10.1016/j.addr.2024.115204

[34] Deng, Z. and Zhang, M. (2024) Liposozyme for Wound Healing and Inflammation Resolution. *Nature Nanotechnology*, **19**, 1083-1084.
https://doi.org/10.1038/s41565-024-01656-8

[35] Sener, L. and Albeniz, I. (2015) Challenge of Mesenchymal Stem Cells against Diabetic Foot Ulcer. *Current Stem Cell Research & Therapy*, **10**, 530-534.

https://doi.org/10.2174/1574888x10666150519092931

[36] Yan, D., Song, Y., Zhang, B., Cao, G., Zhou, H., Li, H., *et al*. (2024) Progress and Application of Adipose-Derived Stem Cells in the Treatment of Diabetes and Its Complications. *Stem Cell Research & Therapy*, **15**, Article No. 3. https://doi.org/10.1186/s13287-023-03620-0

[37] Fang, J., Xu, J., Zhang, Y., Chen, H., Ma, Z., Huang, Z., *et al*. (2021) Stromal Cell-Derived Factor-1 May Play Pivotal Role in Distraction-Stimulated Neovascularization of Diabetic Foot Ulcer. *Medical Hypotheses*, **149**, Article 110548. https://doi.org/10.1016/j.mehy.2021.110548

[38] Hou, C., Shen, L., Huang, Q., Mi, J., Wu, Y., Yang, M., *et al*. (2013) The Effect of Heme Oxygenase-1 Complexed with Collagen on MSC Performance in the Treatment of Diabetic Ischemic Ulcer. *Biomaterials*, **34**, 112-120. https://doi.org/10.1016/j.biomaterials.2012.09.022

[39] Chen, L., Zheng, B., Xu, Y., Sun, C., Wu, W., Xie, X., *et al*. (2023) Nano Hydrogel-Based Oxygen-Releasing Stem Cell Transplantation System for Treating Diabetic Foot. *Journal of Nanobiotechnology*, **21**, Article No. 202. https://doi.org/10.1186/s12951-023-01925-z

[40] Sieńko, D., Szabłowska-Gadomska, I., Nowak-Szwed, A., Rudziński, S., Gofron, M., Zygmunciak, P., *et al*. (2024) The Potential of Mesenchymal Stem/Stromal Cells in Diabetic Wounds and Future Directions for Research and Therapy—Is It Time for Use in Everyday Practice? *International Journal of Molecular Sciences*, **25**, Article 12171. https://doi.org/10.3390/ijms252212171

[41] Martin, J.R., Patil, P., Yu, F., Gupta, M.K. and Duvall, C.L. (2020) Enhanced Stem Cell Retention and Antioxidative Protection with Injectable, ROS-Degradable PEG Hydrogels. *Biomaterials*, **263**, Article 120377. https://doi.org/10.1016/j.biomaterials.2020.120377

[42] Chen, J., Liu, Y., Zhang, J., Yang, Y., Liang, H., Li, T., *et al*. (2023) External Application of Human Umbilical Cord-Derived Mesenchymal Stem Cells in Hyaluronic Acid Gel Repairs Foot Wounds of Types I and II Diabetic Rats through Paracrine Action Mode. *Stem Cells Translational Medicine*, **12**, 689-706. https://doi.org/10.1093/stcltm/szad050