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EDITORIAL

Macrophages: Key players in diabetic wound healing

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Abstract

In this editorial, we discuss the article by Wen *et al* published. Diabetic foot ulcers are prevalent and serious complications of diabetes, significantly impacting patients' quality of life and often leading to disability or death, thereby placing a heavy burden on society. Effective diabetic wound healing is hindered by an imbalance in macrophage polarization; many macrophages fail to transition from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, which is crucial for tissue remodelling and repair. The wound healing process is both dynamic and complex. Healthy M1 macrophages, which have strong phagocytic abilities, are vital during the inflammatory phase of diabetic wound healing. However, the failure to transition to M2 macrophages during the proliferative phase hinders wound healing. We anticipate the development of new therapies that can repair damaged M1 macrophages during the inflammatory phase and promote M2 macrophage polarization during the proliferative phase, thereby enhancing the overall healing process.

Key Words: Diabetic wound healing; Macrophages; Inflammation; Exosomes; Natural medicines

Core Tip: In this editorial, we discuss the recently published article by Wen *et al*. Despite significant scientific efforts worldwide, diabetic foot ulcers remain a challenging issue. The authors highlighted the importance of macrophage polarization in diabetic wound healing, and we strongly endorse this perspective. However, we emphasize that future research should also recognize the essential role of healthy M1 macrophages in the diabetic wound healing process.

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INTRODUCTION

Diabetes is a prevalent and significant clinical condition. By 2045, an estimated 783.2 million people worldwide will have diabetes, presenting a major public health challenge and causing a substantial societal burden[1]. Among the most common complications are wound healing disorders, particularly diabetic foot ulcers (DFU). Between 19% and 34% of diabetic patients develop foot ulcers, which are the leading cause of amputation in these individuals[2]. Alarmingly, up to 70% of patients may die within five years after amputation[3]. In underdeveloped regions, inadequate public sanitation and a lack of professional wound care exacerbate complications, leading to severe infections and poor prognoses[4]. Thus, promoting effective wound healing remains a significant challenge for the medical community.

Scientometrics (bibliometrics) has emerged as a valuable tool for analysing the impact, characteristics, and trends of research on specific topics. While it has limitations compared to traditional reviews, bibliometric analysis can reveal research trends and key points, providing constructive insights for future studies[5]. Wen *et al*[6] utilized scientometrics to offer a comprehensive overview of macrophage-related DFU research. Their study highlights the complexity of macrophage phenotypic switching in diabetic wounds and highlights the potential role of exosomes as a burgeoning area of research.

WOUND HEALING AND MACROPHAGE POLARIZATION

Wound healing is a complex and precise biological process involving interactions among various cell types and mediators. It progresses through four main stages: Haemostasis (immediately post-injury), inflammation (1-4 days), proliferation(4-21 days), and remodelling (21 days to 2 years)[7]. Compared with healthy individuals, slow wound healing is a significant feature of diabetes. The slow onset and delayed resolution of wound inflammation are major factors contributing to healing difficulties in diabetic patients. Macrophages play crucial roles in both the initiation and resolution of wound inflammation.

Macrophages exhibit notable heterogeneity and plasticity, resulting in different phenotypes depending on the microenvironment. The classical macrophage polarization model involves two opposite phenotypic states: "classically" activated M1 macrophages, which are induced by lipopolysaccharide or interferon-γ, and "alternatively" activated M2 macrophages, which are triggered by interleukin-13 (IL-13) or IL-4[8]. M1 macrophages primarily exert pro-inflammatory, anti-infection, and anti-tumour immune functions, often resulting in inflammation and autoimmune diseases. In contrast, M2 macrophages exhibit anti-inflammatory and tissue repair functions but can promote tumour progression[9]. Macrophage activation is currently believed to occur on a continuous spectrum, with M1 and M2 representing the two extremes. Macrophage polarization is dynamically reversible, meaning that M1 macrophages can switch to M2 macrophages and vice versa as microenvironmental conditions change[10].

Macrophages are involved in nearly all stages of wound healing, particularly during the inflammatory and proliferative phases. At the onset of wound inflammation, macrophages are recruited to the affected area and transform into the M1 type under the influence of pro-inflammatory factors, engulfing necrotic tissue and apoptotic neutrophils. As inflammation subsides and the proliferative phase begins, wounded macrophages predominantly polarized toward the M2 type, promoting healing through inflammation suppression, angiogenesis, re-epithelialization, and other processes [11]. Notably, the phagocytic function of M1 macrophages plays a critical role in the phenotypic transition of wounded macrophages[12]. Additionally, macrophages activated in high-glucose environments are more prone to adopt a senescent phenotype, further complicating the M1-to-M2 transition[13]. Therefore, the balance between M1 and M2 macrophage polarization is essential for the clearance of necrotic tissue, resolution of inflammation, and tissue repair in wounds. Accelerating wound healing by using drugs or immunosuppressants to polarize macrophages towards a pro-repair subtype or recruiting macrophage subpopulations prior to wound healing is a common therapeutic strategy.

IMBALANCE OF MACROPHAGE POLARIZATION IN DIABETIC WOUNDS

Diabetes is a metabolic disorder that induces low-grade systemic inflammation, significantly impacting the immune

system. Dysregulated metabolic pathways and immune abnormalities affect every stage of wound healing[14]. A key issue is the imbalance of macrophage polarization. An RNA sequencing study of wound tissues from patients with DFU and healthy subjects revealed a higher M1/M2 ratio in DFU tissues than in healthy skin[15]. High-glucose environments, hypoxia, and the formation of advanced glycation end products reduce the phagocytic activity of M1 macrophages. In the diabetic wound environment, however, M1 macrophages secrete proinflammatory cytokines such as IL-1β, IL-6, and tumor necrosis factor-α, which attract circulating monocytes to the site of inflammation and drive their differentiation into the M1 phenotype. This accumulation of M1 macrophages in chronic wounds impedes their transition to the M2 phenotype, preventing the wound from progressing from the inflammatory phase to the proliferative granulation phase. As a result, chronic inflammation persists, leading to impaired wound healing[16].

Current research has focused primarily on therapies aimed at promoting wound healing by inducing macrophage polarization towards the M2 phenotype[17,18]. For example, the topical application of a macrophage-regulating drug such as ON101 cream reduces the activity of inflammatory M1 macrophages while enhancing the M2 macrophage population through granulocyte colony-stimulating factor-mediated M2 polarization. This shift facilitates the transition of the ulcer from the inflammatory phase to the proliferative and remodelling phases, promoting wound healing[19]. However, whether these therapies can repair damaged M1 macrophages and enable their spontaneous and stable polarization toward the M2 phenotype remains an open question and requires further investigation.

EXOSOMES: A PROMISING THERAPEUTIC STRATEGY

Exosomes are extracellular vesicles containing lipids, proteins, RNA, and DNA that serve as key mediators of intercellular communication. Throughout the various stages of diabetic wound healing, exosomes regulate the functions of macrophages, endothelial cells, fibroblasts, and keratinocytes. This regulation is crucial for inhibiting excessive inflammation, promoting angiogenesis, and facilitating collagen synthesis[20].

Recent studies have highlighted the potential of exosomes to modulate macrophage phenotypes in diabetic wounds. Shi *et al*[21] discovered that hypoxic bone marrow mesenchymal stem cells-derived exosomes loaded hydrogel alleviate macrophage dysfunction by inhibiting SREBP2 activity, promoting the polarization of macrophages to the M2 phenotype, and thereby promoting diabetic wound healing. Similarly, Liu *et al*[22] reported that melatonin-stimulated mesenchymal stem cell-derived exosomes improve diabetic wound healing by targeting the phosphatase and tensin homolog/protein kinase B pathway to regulate macrophage polarization between the M1 and M2 phenotypes. Furthermore, Cheng *et al*[23] demonstrated that hypoxic human umbilical vein endothelial cells-derived exosomes enhance endothelial cell function under high-glucose conditions by increasing the expression of the long non-coding RNA HAR1B, reducing oxidative stress and inflammatory responses, and promoting KLF transcription factor 4 expression *via* interaction with the transcription factor basic helix-loop-helix family member e23; thus, these exosomes increase angiogenesis and promote the polarization of macrophages toward the M2 phenotype, ultimately accelerating diabetic wound healing.

CONCLUSION

Bibliometrics provides a comprehensive perspective on macrophage-related DFU research and facilitates interdisciplinary integration and collaboration. Macrophage phenotypic switching plays a crucial role in immune-related diseases, particularly in inflammation-driven conditions such as diabetic wounds. Most current research focuses on promoting the polarization of macrophages toward the M2 phenotype. However, the wound healing process is dynamic and complex and requires robust M1 macrophages with strong phagocytic abilities during the initial phases of healing[24]. Future research should explore the balance between M1 and M2 macrophages in wound healing. We look forward to the emergence of new therapies that can repair damaged M1 macrophages during the inflammatory phase and promote M2 macrophage polarization during the proliferative phase, resulting in sequential promotion.

In addition, natural medicines offer promising alternatives to synthetic drugs, particularly in the treatment of diabetic wounds. Unlike single-target synthetic therapies, natural medicines often provide multitarget, synergistic effects, which can increase their therapeutic potential[25]. Many natural compounds have been shown to regulate the activity of macrophages, which is key in diabetic wound healing. For example, Song *et al*[26] demonstrated that *Sanguisorba officinalis* L. promotes diabetic wound healing by inhibiting the nuclear factor-κB (NF-κB)/NOD-like receptor family pyrin domain containing 3 signalling pathway, thereby increasing the ratio of M2 to M1 macrophages. Similarly, Li *et al*[27] reported that apigenin accelerates wound healing in diabetic mice by upregulating the expression of miR-21, which inhibits the toll-like receptor 4/myeloid differentiation factor 88/NF-κB signalling axis and promotes M2 macrophage polarization. Recent advancements have also highlighted the effectiveness of hydrogels infused with natural medicines for treating diabetic wounds. For example, hydrogels containing Wormwood essential oil and Ganoderma lucidum polysaccharides have shown excellent mechanical properties, strong tissue adhesion, and notable antibacterial, anti-inflammatory, and antioxidant effects. These anti-inflammatory benefits are partly mediated by the ability of hydrogels ability to promote M2 macrophage polarization[28,29]. In the management of diabetic wounds, blood glucose control remains crucial. Natural medicines not only facilitate wound healing but also help regulate blood glucose levels, making them a promising and holistic therapeutic approach[30].

FOOTNOTES

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