

New Advances in the Treatment of Diabetic Wounds

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Abstract: Diabetic wound is one of the common complications of diabetes, characterized by high incidence, difficulty in repair, prolonged healing, etc., which seriously affects patients' quality of life and threatens human health. Due to the lack of effective treatment strategies, the clinical efficacy of diabetic wound treatment is limited. In recent years, with the in-depth research on the healing process and molecular biology basis of diabetic wounds, a series of innovative treatment methods have gradually emerged. This article reviews the recent advances in the treatment of diabetic wounds, including stem cell therapy/exosome therapy, nanotechnology, and hydrogel dressings responsive to the microenvironment.

Keywords: Diabetic Wounds; Stem Cells; Nanofibers; Microenvironment-responsive Hydrogels.

1. Introduction

Diabetic wounds are a prevalent complication of diabetes. Over the past few years, extensive research has been conducted on the healing process and molecular biology underlying diabetic wounds, leading to the development of several innovative treatment methods. This article aims to provide a comprehensive overview of the recent hot research on diabetic wound healing[1]. Diabetes is characterized by elevated blood glucose levels, which, as the disease progresses, can result in significant damage to the heart, blood vessels, eyes, kidneys, and nerves. These detrimental effects give rise to a range of complications, including cardiovascular and cerebrovascular diseases, diabetic nephropathy, diabetic retinopathy, diabetic foot ulcers, and other vascular complications. Notably, vascular complications are regarded as among the most severe consequences of diabetes[2]. The current consensus on the treatment of diabetic wounds is through comprehensive multidisciplinary therapy. Early detection, timely treatment, debridement, and infection control are crucial. Clinical treatment modalities mainly include surgical debridement, hyperbaric oxygen therapy, negative pressure wound therapy, skin grafting, and flap repair of wounds. However, currently, the effectiveness of methods for treating diabetic wounds remains limited, necessitating continuous exploration of more effective treatment approaches. In recent years, with in-depth research into the healing process and molecular biology of diabetic wounds, a series of innovative treatment methods have emerged. This article provides an overview of research hotspots in diabetic wound management, including stem cell therapy, stem cell-derived exosome therapy, nanofiber materials, and hydrogels responsive to the wound microenvironment.

2. Stem Cell/Stem Cell-Derived Exosome Therapy

2.1. Stem Cell Therapy

Stem cells are undifferentiated cells capable of self-renewal and differentiation into various mature cell types with diverse proliferative and differentiation capacities. They

undergo cell division to renew themselves and differentiate into tissue- or organ-specific cells[3]. Previous research indicates that stem cells have potential in the treatment of diabetic wounds. They contribute to enhanced wound healing by fostering angiogenesis, mitigating inflammation, activating anti-apoptotic pathways, and remodeling the extracellular matrix [4]. In recent years, various types of stem cells have been utilized in clinical practice. Mesenchymal Stem Cells (MSCs) are abundant in diverse organs including bone marrow, adipose tissue, umbilical cord, placenta, and peripheral blood [5]. A randomized study demonstrated that local injection of umbilical cord mesenchymal stem cells (UCMSCs) around chronic wounds can facilitate wound healing [6]. Intralesional injection of UCMSCs can also increase the number of blood vessels in diabetic wounds and promote wound healing [7]. Cao et al. compared the healing effects of bone marrow mesenchymal stem cells (BMMSCs), UCMSCs and adipose tissue-derived mesenchymal stem cells (ADSCs) by local injection into diabetic wounds. The results indicated that all three types of stem cells could effectively promote the formation of new blood vessels in the wounds. Among them, adipose tissue-derived mesenchymal stem cells showed the best effect in promoting the healing of ischemic wounds and significantly promoting angiogenesis. Therefore, adipose tissue-derived mesenchymal stem cells may be ideal cells for therapeutic angiogenesis and treatment of chronic ischemic wounds [8]. In addition to the three commonly utilized types of mesenchymal stem cells, epidermal stem cells (ESCs) have emerged as a subject of investigation in the context of diabetic wounds. Yang et al. were the first to establish that the localized administration of ESCs expedites wound healing in diabetic mice via activation of the Notch signaling pathway [9].

2.2. Stem Cell-derived Exosome Therapy

According to relevant reports, adverse reactions may occur clinically during the application of stem cell therapy for treating diabetic wounds. The escalation in exudate production from diabetic wounds could potentially be attributed to the utilization of stem cell therapy[10]. Moreover, inevitable transplant complications arise in diabetic patients who undergo stem cell transplantation, encompassing symptoms such as febrile neutropenia, alopecia, and

gastrointestinal reactions[11]. Stem cell-derived exosome therapy represents a significant advancement in the treatment of diabetic wounds, offering improved efficacy and avoiding host rejection reactions. Exosomes, nanoscale membrane vesicles primarily secreted by MSCs, serve as drug and RNA carriers for treating various diseases. Exosomes encapsulate miRNAs, mRNAs, and proteins, facilitating their transfer to target cells, thereby modulating intercellular communication and fostering wound healing. Emerging studies suggest that exosomes released by diverse stem cell populations exhibit notable efficacy in enhancing the resolution of diabetic wounds. Notably, exosome-based cell-free therapy demonstrates a notably lower incidence of adverse reactions compared to conventional stem cell therapy. Consequently, the exploration of exosome-based cell-free therapy has garnered significant attention as a promising avenue for addressing diabetic wound management. The research by Tao et al. demonstrates that circ-Snhg11 within exosomes derived from Bone marrow mesenchymal stem cell exosomes (BMSC-Exos) enhances the anti-ferroptotic signaling mediated by GPX4/SLC7A11 by sequestering miR-144-3p, consequently expediting the repair and regeneration of diabetic wounds. Han et al. demonstrated that KLF3-AS1 from BMSC-Exos promotes VEGFA signaling and induces angiogenesis by inhibiting miR-383, thereby facilitating the healing of diabetic wounds in mice [12]. Wang et al.'s study demonstrates that exosomes released by hypoxic adipose-derived stem cells (ADSCs) stimulate fibroblast proliferation and migration by activating the phosphatidylinositol 3-kinase (PI3K)/Akt pathway. This stimulation leads to the enhanced release of vascular growth factors and extracellular matrix, thereby expediting the healing process of diabetic wounds[13]. Shi et al. extracted hypoxia-affected bone marrow mesenchymal stem cell-derived exosomes (hyBMSC-Exo), significantly improving the functionality of keratinocytes, including autophagy, proliferation, and migration. This effect is mediated by the transfer of miR-4645-5p via hy-BMSC-Exo, which inactivates the AKT-mTORC1 signal induced by MAPKAPK2 in keratinocytes, further activating their autophagy, proliferation, and migration, thereby promoting the healing of diabetic wounds[14]. Chen et al. found that exosomes derived from adipose-derived stem cells can restore high glucose-induced fibroblast dysfunction by inhibiting Bax/caspase 3-mediated cell apoptosis, alleviating fibroblast damage, and accelerating wound healing in diabetic mice[15].

3. Nanotechnology

Nanotechnology, particularly nanofiber materials, is experiencing rapid development in the realm of diabetic wound treatment research. Over recent years, nanofiber scaffolds have been employed across a spectrum of wound healing applications, demonstrating beneficial effects on the management of diabetic wounds. Nanofibers possess a spatial structure akin to the extracellular matrix (ECM), characterized by attributes such as high-water absorption, interconnected pores, breathability, and moisture permeability. These attributes foster an optimal milieu for wound hemostasis, the prevention of exogenous infections, the facilitation of cell migration and proliferation, cellular respiration, and exudate absorption. The distinctive physicochemical properties of nanofibers render them optimal carriers for drugs, enabling the transportation of growth factors, cytokines, anti-inflammatory and

antimicrobial agents, hypoglycemic drugs, and other bioactive substances to enhance diabetic wound healing. Anand et al. prepared a multifunctional nanofiber scaffold by loading asiaticoside (AT) onto polyvinyl alcohol (PVA)-sodium alginate (SA)-silk fibroin (SF). This scaffold exhibits low cytotoxicity and shows excellent antimicrobial activity against both Gram-positive bacteria and Gram-negative bacteria (*Pseudomonas aeruginosa* and *Staphylococcus aureus*). Additionally, it is capable of promoting cell migration and significantly enhances wound healing in diabetic rats[16]. Sanaz et al. designed a dual drug delivery micro/nanofiber core-shell system using polycaprolactone/sodium sulfated alginate-polyvinyl alcohol (PCL/SSA-PVA) as the core/shell components via emulsion electrospinning technology. This system aims to optimize the sustained delivery of copper oxide nanoparticles (CuO NPs), thereby promoting wound re-epithelialization and neovascularization, and significantly accelerating wound healing in diabetic rats [17]. Cam and colleagues improved wound healing in diabetic patients by using electrospun nanofiber scaffolds loaded with hypoglycemic drugs metformin, pioglitazone, and glimepiride[18].

Nanofiber scaffolds possess a great potential in combination with hydrogels through multiple approaches. He et al. demonstrated that short nanofibers of carboxymethylated poly(methyl methacrylate) (PMAA) were combined with carboxymethyl chitosan. The resultant mixture was further blended with aldehyde-functionalized sodium alginate to facilitate the preparation of self-healing, injectable polysaccharide hydrogels[19]. Ding et al. designed a nano-fiber hydrogel containing deferoxamine (DFO), which can provide sustained release of DFO for more than 40 days. The nano-fiber hydrogel with DFO alleviates vascular generation disorders and chronic inflammation in diabetic wounds, increases collagen deposition, and promotes wound healing[20]. Kumar et al. designed a three-layered nanofiber scaffold with antibacterial and antioxidant properties, including a top layer composed of hydrophobic sericin protein mixed with polyvinyl alcohol (PVA), a middle layer loaded with silver sulfadiazine sericin protein, and a bottom layer composed of polycaprolactone (PCL) and sericin protein. The three-layered nanofiber scaffold exhibited excellent wettability, slow in vitro degradation, controlled drug release, as well as effective antibacterial and antioxidant properties, which could protect wounds from bacterial infections and improve wound healing in a mouse model[21].

4. Water-soluble Hydrogels with a Responsive Microenvironment.

Water-soluble hydrogels equipped with a responsive microenvironment have emerged as a prominent research area within hydrogel materials for diabetic wounds. Due to the multifaceted nature of these wounds, antibiotics and other drugs are frequently employed in combination with hydrogel dressings in clinical settings, but challenges arise as these drugs are often impeded by the wound microenvironment. In response, researchers have devised responsive hydrogel dressings based on the microenvironmental characteristics of diabetic wounds, such as high levels of glucose and low pH values, or alternatively, in conjunction with external stimuli, such as light or magnetic fields. The aim is to achieve a controlled release of drugs, gel degradation, and microenvironmental enhancement for improved wound

healing. This responsive hydrogel dressing approach exhibits high potential for advancing the treatment of diabetic wounds. Guo et al. encapsulated nanoscale zinc oxide within a hydrogel to create an injectable material that responds robustly to inflammatory cues and possesses self-healing properties. This hydrogel maintains high biocompatibility and possesses effective hemostatic and angiogenic enhancing capabilities. It is particularly responsive to the acidic pH conditions prevalent in chronic wounds. Within an inflamed milieu, the hydrogel releases zinc oxide and paeoniflorin, facilitating the healing of diabetic rat wounds infected chronically by providing hemostasis, combating infection, and fostering neovascularization[22]. Wu et al. employed quaternized chitosan, polypyrrole, and polyethylene glycol as carrier materials for desferrioxamine, thereby creating a conductive, antibacterial hydrogel with pH-responsive properties. The findings of their study suggest that this hydrogel facilitates the proliferation and migration of endothelial cells by upregulating the expression of vascular endothelial growth factor (VEGF), and effectively releases desferrioxamine to augment angiogenesis[23]. Shao et al. engineered a self-healing, injectable, and adaptive multifunctional hydrogel by grafting quaternized chitosan with 3-carboxy-4-fluorophenylboronic acid groups onto polyethylene glycol hydroxyl groups via a boronate esterification reaction. This hydrogel, which encapsulates the pro-angiogenic drug deferoxamine (DFO) within DFO@G (DFO-loaded gelatin microspheres), exhibits boronate ester bonds that can adaptively interact with high glucose and hydrogen peroxide levels present in the diabetic wound microenvironment, thereby mitigating oxidative stress and enabling the early release of DFO@G during the wound healing process. Subsequently, the sustained release of DFO is realized by the hydrogel's response to the overexpressed matrix metalloproteinases in the wound. In a full-thickness diabetic wound model, the hydrogel accelerated angiogenesis by upregulating the expression of hypoxia-inducible factor-1 (HIF-1) and vascular endothelial growth factor (VEGF), which led to collagen deposition and facilitated rapid wound closure. This multifunctional hydrogel not only adaptively modifies the microenvironment to promote healing by reducing oxidative stress but also responds to matrix metalloproteinases for DFO release, indicating its potential as a therapeutic strategy for diabetic wounds[24]. Zhou Wu et al. engineered a dual-responsive, temperature-sensitive, and shape-adaptive hydrogel (CBP/GMs@Cel&INS) that exhibits glucose and MMP-9 sensitivity. This innovative hydrogel, composed of polyvinyl alcohol (PVA) and chitosan modified with phenylboronic acid (CS-BA), encapsulates insulin (INS) and gelatin microspheres incorporating celecoxib (GMs@Cel). It effectively mitigates inflammation and modulates the elevated levels of glucose and MMP-9 at the site of injury. Utilizing its thermosensitive shape-adaptive properties, the hydrogel potentially accelerates the healing process of wounds [25].

5. Summary and Prospects

The complexity of diabetic wound healing stems from prolonged hyperglycemia, oxidative stress, and neuropathy, which collectively impair cellular function and disrupt molecular homeostasis, potentially resulting in delayed or non-healing wounds. Advances in understanding the molecular underpinnings of diabetic wound healing have sparked the development of novel therapeutic strategies. Stem

cell therapy presents a promising avenue, albeit with potential complications that may limit patient acceptance. The safety, efficacy, reproducibility, mechanism of action, and biological roles of stem cell-derived exosomes in accelerating healing remain unclear. Hydrogel dressings, a burgeoning field in diabetic wound management, offer the advantage of delivering medications in response to local microenvironmental cues, positioning them as promising auxiliaries. However, the dynamic nature of the healing process necessitates vigilance, as fluctuations in factors such as glucose levels, pH, and reactive oxygen species (ROS) at the wound site could impact the healing trajectory. Low concentrations of ROS exhibit antibacterial and angiogenic properties, whereas their higher concentrations can harm cells and impede healing. Thus, the translation of responsive hydrogel dressings to clinical practice necessitates precise and timely monitoring of the diabetic wound microenvironment. Despite the promise of these treatments, their application in clinical settings is hindered by limitations that warrant further investigation. It is anticipated that more efficacious therapies for diabetic wounds will emerge in the future.

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