

Stem Cell Therapy in Diabetes: Prospects and Challenges

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Abstract: Diabetes mellitus has a serious impact on patients' health and quality of life. Chronic hyperglycemia can lead to a series of acute and chronic complications, such as diabetic foot, diabetic nephropathy, diabetic retinopathy, diabetic neuropathy and cardiovascular disease. In addition, diabetes disrupts the pre-existing organized capacity for wound healing and impedes wound healing. Traditional ways of treating diabetes, such as oral hypoglycemic agents and insulin injections. Although these methods are effective, there is no rooted cure and there is a burden of life and risk of hypoglycemia. With the gradual maturation of stem cell technology, treating diabetes with stem cells has become a possibility. This review summarizes the results of 2024 and selected 2025. The article also details the research and clinical application of stem cells in diabetes resulting in non-healing wounds and diabetic foot. It can be seen that the technology of stem cell therapy for diabetes is maturing and being widely used.

Keywords: Stem cell, diabetes, wound healing, diabetic foot ulcers

1. Introduction

Diabetes is a prevalent and expensive chronic disease worldwide. It is estimated that the number of patients will reach 578 million globally in 2030 and exceed 700 million in 2045, with more than 5 million deaths due to diabetes each year [1]. Traditional therapies (e.g., insulin injections) are able to control the symptoms but are unable to reverse pancreatic islet β -cell damage or stop the progression of the disease. From stem cell differentiation for islet cell transplantation to combination therapies in integrative medicine, several clinical research milestones have been reached in recent years, opening up a new avenue for a functional cure for diabetes. The regenerative and immunomodulatory capabilities of stem cells, as well as the absence of immune rejection and fewer ethical issues when used in autologous disease treatment, make stem cell therapy for diabetes both promising and challenging. Currently, bone marrow mesenchymal stem cells (MSC), adipose mesenchymal stem cells, satellite cells, tendon stem/progenitor cells, and stem cells are being used to treat diabetes [2].

This paper reviews the mechanisms, clinical advances and challenges of stem cell therapy. This study aims to explore the potential of stem cell therapy in the treatment of diabetes, providing theoretical support and practical guidance for seeking functional cure options.

2. Mechanisms of stem cell therapy in diabetes mellitus

The core mechanism of stem cell therapy for diabetes can be summarized into three major directions: cell replacement, microenvironmental repair and immune regulation, which can achieve disease alleviation by replacing damaged β -cells, remodeling the immune microenvironment and promoting

tissue repair. This is based on three properties of stem cells: they have self-renewal capacity, multidirectional differentiation potential, and low immunogenicity. Their self-renewal capacity provides the basis for their use in diabetes treatment, ensuring that a sufficient number of stem cells are available to play a role in the therapeutic process. Its multidirectional differentiation potential is one of the important features that distinguish it from other somatic cells. It can be differentiated into pancreatic β -cells or cells with the function of pancreatic β -cells so as to replenish missing or damaged pancreatic β -cells and treat diabetes mellitus. The most researched cells are mesenchymal stem cells (MSCs). MSCs are weakly immunogenic due to low expression of major histocompatibility complex class II proteins and lack of the co-stimulatory molecules CD80 and CD86. This low immunogenicity means that MSCs can be used for xenotransplantation [3]. This low immunogenicity allows for increased safety of stem cell therapy.

3. Progress of clinical research on stem cell therapy for diabetes

As of today, there have been many studies on stem cell therapy for diabetes around the world.

3.1. Diabetic wound healing

Diabetes impedes wound healing, prompting researchers to explore the use of adipose-derived mesenchymal stem cells (ADSCs) that overexpress acidic fibroblast growth factor (aFGF). These modified ADSCs can produce various growth factors, including vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and basic fibroblast growth factor (bFGF), which promote the restoration of blood supply to the wound and improve graft survival. In addition, ADSCs not only enhanced the migration and proliferation of fibroblasts, but also inhibited collagen deposition and α -SMA expression in proliferative scar fibroblasts, which was beneficial to the healing of wounds caused by burns and ulcers. A single dose of aFGF-ADSCs comprehensively improved all aspects of wound repair in diabetic rats, providing a potential new approach for the treatment of chronic diabetic wounds [4]. A bioactive and degradable bioengineered micro-porous collagen-based three-dimensional scaffold (CTS) encapsulated with adipose mesenchymal stem cells (ASCs)-derived exosomes. This combination had an even greater impact on improving diabetic wound healing. This effectiveness is attributed to the biochemical composition and three-dimensional microporous structure of CTS, which are conducive to cell infiltration, adhesion, migration, and angiogenesis. In addition, ASC-derived exosomes act as key growth factors by preventing excessive inflammation and stimulating local cell differentiation, collagen synthesis and angiogenesis [1]. Stem cell vesicle-based phototheranostics (EVs@NBS-PB), represent a novel approach that combines a type I pro-photosensitizer (NBS-PB) encapsulated within umbilical cord mesenchymal stem cell vesicles (UC-EVs). This innovative combination enables imaging-guided, efficient anti-infection strategies and modulates the microenvironment to promote chronic wound healing [5]. The engineering of MSCs with ANG1 provides substantial additional benefits to the healing of diabetic foot wounds [6]. In antler stem cells (ASCs), the primary polyphenol in green tea, epigallocatechin gallate (EGCG). A gelatin/sodium alginate-based composite hydrogel, combining adipose stem cell-conditioned medium (ASC-CM) and epigallocatechin gallate (EGCG), referred to as CEGA, shows promise as a potential alternative therapy for diabetic wounds. CEGA significantly promotes the proliferation of human umbilical vein endothelial cells (HUVECs), L929 fibroblasts, and mouse monocyte macrophage leukemia cells (RAW264.7). In addition, CEGA exhibited potent antimicrobial, antioxidant, angiogenic, and macrophage polarization-modulating properties both in vitro and in vivo [7]. Exosomes (Exo-miR-1248) from miR-1248-overexpressing adipose-derived stem cells. This combination also promotes diabetic wound healing by modulating endothelial cell function [8].

3.2. Diabetic foot ulcers (Dfu)

Autologous adipose stem cells, mesenchymal stem cells, have been shown to be effective in the treatment of diabetic foot, but the results were not as expected. Researchers found that chitosan combined with adipose-derived mesenchymal stem cell exosomes up-regulated miR-103-3p expression, which inhibited the target gene DYRK1A and its mediated phosphorylation of STAT3, and thus regulated the inflammatory microenvironment of wounds, promoted vascularization and antioxidant apoptosis. The inhibition of its target gene DYRK1A and its mediated phosphorylation of STAT3 resulted in the regulation of the inflammatory microenvironment of wounds, the promotion of angiogenesis and antioxidant apoptosis, which led to the increase of wound healing and the improvement of the pathological damage of wounds in diabetic foot ulcers [9]. Heat shock prestimulated primary rat bone marrow MSCs (BMSCs) enhanced the growth and migration of dermal fibroblasts in vitro, promoted the polarization level of macrophages in wound tissue, and enhanced the therapeutic efficacy of wound healing in a DFU rat model [10]. Fibroblasts were cultured in the ethylenediamine (EDA)-modified gellan gum (GG) hydrogel scaffolds loaded with small extracellular vesicles (sEVs) derived from adipose stem cells under pro-inflammatory cytokine conditions. GG-EDA hydrogels loaded with sEV enhance fibroblast viability in these pro-inflammatory environments while retaining the anti-inflammatory and immunomodulatory properties of their cell of origin [11]. In another approach, stem cells derived from human deciduous teeth (SHED) were loaded into CP7 hydrogel to form SHED@CP7. This combination promotes the migration of human umbilical vein endothelial cells (HUVECs), enhances angiogenesis, and facilitates the healing of diabetic foot ulcers [12].

3.3. Clinical trials and cases

The Stem Cell Research Center at Peking University and the First Central Hospital of Tianjin collaborated in 2023 to study the use of chemical reprogramming technology to induce pluripotent stem cells in order to prepare islet cells for the treatment of type 1 diabetes mellitus. The research produced ground-breaking results that garnered significant attention on a global scale. The research groups of Zhongyang Shen and Shusen Wang at the First Hospital of Tianjin and Hongkui Deng at Changping Laboratory of Peking University used chemical reprogramming technology to transform patients' own somatic cells into induced pluripotent stem cells (iPSCs), and directed differentiation of the iPSCs into functional pancreatic islet β -cells, and transplanted islets into the subsheath of the rectus abdominis muscle, which was a less invasive transplantation and easy to follow up on in the long term. The patient had an 11-year history of type 1 diabetes mellitus and underwent the procedure on 6/25/2023. The patient was completely weaned from insulin injection therapy 75 days after transplantation. All safety and effectiveness clinical objectives were satisfied, the patient exhibited no symptoms of transplant-related abnormalities, and at one year, the patient's glycemic control status was stable, with a satisfactory glycemic TIR without exogenous insulin and a glycated hemoglobin of about 5%. This technology has achieved a functional clinical cure for type 1 diabetes mellitus [13].

4. Challenges and prospects

Cell therapy for diabetes still faces many technical challenges that limit the ability of stem cell therapy to move from laboratory research to widespread clinical application.

First, stem cells are difficult to obtain. For example, although embryonic stem cells have strong differentiation potential, the process of obtaining them is ethically controversial and their sources are limited. Adult stem cells, such as bone marrow mesenchymal stem cells and adipose mesenchymal stem cells, are less ethically controversial, but are less abundant in the body and require invasive procedures to obtain them. The collection of MSCs from bone marrow requires bone marrow

aspiration, which brings more pain to the patients and the amount of collection is limited. Adipose MSCs are less invasive than bone marrow MSCs, but the process of isolation and purification is more complex and requires a higher level of technology and specialized equipment. Although induced pluripotent stem cells (iPSCs) have solved some of the ethical and sourcing problems, the induction process is less efficient and more costly, and there are risks of genetic mutation.

Additionally, there are some safety risks associated with the application of stem cells to clinical settings. For instance, stem cells may self-renew and differentiate in several directions. However, when they are influenced by their internal and external surroundings, they may also proliferate and differentiate abnormally, which can lead to the development of tumors.

Therefore, there is still a lot of research space for stem cell therapy. Future studies can use imaging technologies in conjunction with gene editing, 3D printing, and novel biomaterials to reliably and precisely track the quantity of cells and the location of stem cell migration into the body. It is hoped to bring about a technological breakthrough and promote the gradual popularization of stem cell therapy in clinical applications.

5. Conclusion

This paper reviews the stem cell therapy as a promising approach to treating diabetes mellitus and discusses the mechanisms through which stem cells can alleviate the disease. Recent clinical advancements, particularly in diabetic wound healing and diabetic foot ulcers, are highlighted, illustrating the potential of various stem cell types, such as adipose-derived and bone marrow mesenchymal stem cells, in promoting tissue repair and restoring function.

However, there is still a lot of room for this study. For instance, it selected some of the stem cell therapies in 2024 and 2025 but did not fully cover the results of stem cells.

Looking ahead, future research directions should focus on enhancing the efficiency of stem cell isolation and differentiation techniques, as well as improving safety through advanced gene editing and biomaterial applications. Also, there will be more cases of stem cell therapy technology into the clinic.

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