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The Application and Breakthrough of Mesenchymal Stem Cells in the Treatment of Diabetes

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Abstract:

Diabetes is a widespread chronic metabolic disorder that endangers human health because of its high incidence, prolonged progression, and the severity of its complications. Blood glucose levels can be effectively managed through traditional therapies, including insulin injections and oral hypoglycemic agents.Since conventional therapies are unable to restore damaged islets or prevent the ongoing deterioration of β-cell function, patients remain reliant on lifelong medication. Over the past few years, stem cell approaches—particularly those involving mesenchymal stem cells—have drawn increasing attention as a novel therapeutic option. Given their intrinsic abilities of self-renewal, multipotent differentiation, and immunomodulation, mesenchymal stem cells have been recognized as multifunctional candidates in diabetes therapy, since they are capable not only of enhancing islet activity and preserving as well as regenerating pancreatic β-cells, but also of orchestrating immune responses, improving insulin sensitivity, and attenuating chronic complications such as nephropathy and neuropathy; moreover, accumulating evidence from preclinical research and early clinical investigations further indicates that Mesenchymal stem cell (MSC) transplantation contributes to the re-establishment of glucose homeostasis while exerting sustained protective influences through paracrine signaling and anti-inflammatory cascades. However, challenges such as low differentiation efficiency, limited cell survival in vivo, and safety concerns remain to be addressed before large-scale clinical application can be realized. Overall, MSC-based therapy represents a novel and potentially transformative approach for diabetes treatment, offering hope for achieving functional recovery beyond symptomatic control.

Keywords: Diabetes; β-cell; mesenchymal stem cells.

1. Introduction

Diabetes is becoming more common and is now one of the leading chronic health problems worldwide. Prolonged high blood sugar, which defines diabetes, causes a series of metabolic and cellular issues. The International Diabetes Federation' s Global Diabetes Atlas reports that diabetes already affects hundreds of millions of adults globally. Many cases remain undiagnosed. In several countries, over ten percent of adults are affected. Experts predict that the global prevalence of diabetes will continue to rise significantly in the coming decades [1, 2]. This growing issue harms both individual health and overall quality of life. It also creates major challenges for society, putting significant pressure on healthcare systems and increasing the need for effective and sustainable treatment options.

In China, the incidence of diabetes has risen sharply. This trend is linked to economic growth, urbanization, changes in diet, reduced physical activity, and an aging population [3]. Diabetes occurs in two main forms. Type 1 diabetes mellitus results from autoimmune destruction of β-cells. Type 2 diabetes mellitus arises from insulin resistance and β-cell dysfunction. Conventional glucose-lowering drugs, such as insulin and oral hypoglycemic agents, can effectively control blood sugar,but they cannot restore β-cell function or stop disease progression. Patient adherence and treatment optimization also reduce their clinical effectiveness. Islet transplantation may offer a potential cure, but this approach faces major barriers, including a lack of donors, immune rejection, and high costs. These challenges limit its practical use .

Researchers are mainly exploring two strategies. The first strategy is to generate insulin-producing cells from stem cells. This approach may restore natural insulin secretion and correct the loss of β-cell function [4]. The second strategy uses mesenchymal stem cells. These cells can regulate immune activity, reduce inflammation, repair the islet microenvironment, and relieve diabetic complications [5]. Preclinical and early clinical studies show encouraging results. Mesenchymal stem cells help maintain β-cell survival and improve insulin sensitivity through paracrine effects. These findings suggest their potential as a broad therapeutic option. Overall, the evidence highlights the urgent need for regenerative and long-lasting treatments. Stem cell-based interventions may represent a new and transformative strategy for future diabetes care.

2. The pathogenesis of diabetes

2.1 Type 1 Diabetes Mellitus

Type 1 diabetes is a chronic metabolic disorder caused by autoimmunity. It develops when pancreatic β-cells are selectively destroyed. This process leads to a complete lack of insulin. This autoimmune reaction causes abnormally high blood glucose levels [6]. The main clinical symptoms are frequent urination, excessive thirst, increased hunger, and unintended weight loss [7].

2.2 Type 2 Diabetes Mellitus

Type 2 diabetes mellitus accounts for most diabetes cases worldwide. It is defined by insulin resistance and progressive loss of pancreatic β-cell function [8]. At the same time, pancreatic β-cells fail to fully compensate by increasing insulin secretion. The imbalance results in persistent hyperglycemia, and β-cells can no longer maintain this high secretion, and type 2 diabetes develops [9].

3. Mesenchymal Stem Cells

3.1 The feature of Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) are adult stem cells with self-renewal ability and multilineage differentiation potential. They were found in many other tissues, such as bone marrow, adipose tissue, umbilical cord, and dental pulp [10]. MSCs show three main biological properties. First, they can differentiate into mesoderm-derived cell types, including osteocytes, chondrocytes, and adipocytes. They regulate immune responses.

3.2 The function of Mesenchymal Stem Cells

MSCs help maintain hepatic metabolic balance through several mechanisms. They reduce harmful factors such as reactive oxygen species (ROS) and damaged mitochondria, thereby restoring homeostasis [11]. MSCs improve glycemic control by upregulating glycolytic enzymes, including Glucokinase (GCK) and Lactate Dehydrogenase (L-PK), while suppressing gluconeogenic enzymes such as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and Glucose-6-phosphatase (G6Pase) [12]. MSCs promote the clearance of dysfunctional mitochondria and stimulate insulin granule production, further supporting metabolic regulation.

4. Research Progress on the Mechanism of MSC in Treating Diabetes

4.1 Therapeutic Potential of MSC-Secreted Factors in Diabetes Management

The factors secreted by mesenchymal stem cells have been shown to possess substantial therapeutic potential for

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diabetes treatment, owing to their ability to act through a network of synergistic mechanisms that simultaneously modulate immune responses, enhance β-cell function, and improve systemic metabolic homeostasis. These mechanisms include β-cell protection and regeneration mediated by hepatocyte growth factor and vascular endothelial growth factor secretion, which activate PI3K/AKT survival pathways while inhibiting caspase-3 and upregulating B-cell lymphoma 2 (Bcl-2) expression, and are further enhanced by exosomal miR-21 and miR-375, promoting β-cell proliferation and functional maturation [13].

4.2 Immunomodulatory effects of mesenchymal stem cells in diabetes treatment

They restore immune homeostasis by simultaneously suppressing overactivated immune cells while promoting regulatory immune cell proliferation [14]

MSCs exhibit distinct immunoregulatory patterns in different diabetes types: primarily targeting autoimmune responses in type 1 diabetes, while focusing on metabolic inflammation in type 2 diabetes. This multifaceted immunomodulation, operating at cellular, local, and systemic levels, positions MSCs as a promising immunotherapeutic approach for diabetes.

4.3 Differentiation of MSCs into insulin-producing β-cells

In specific circumstances, MSCs have the capacity to mature into insulin-secreting β-cells, thereby providing a potential route for the reestablishment of endogenous insulin production.Empirical evidence indicates that insulin and Wnt signaling, along with other growth factors and signaling pathways, are fundamental in the differentiation of mesenchymal stem cells into insulin-producing β-cells, thereby aiding in potential strategies for restoring endogenous insulin secretion.Insulin secretion is a capability acquired by differentiated mesenchymal stem cells, which is directly involved in blood glucose regulation and the re-establishment of glycemic homeostasis [15].

4.4 Promotion of endogenous pancreatic β-cell proliferation

Mesenchymal stem cells can be induced to differentiate into insulin-producing β-cells under defined protocols. This differentiation process is orchestrated by a complex network of growth factors and signaling pathways, with insulin and Wnt signaling playing particularly critical roles in regulating both cell differentiation and maturation [16]. Following differentiation, MSC-derived β-cells acquire the ability to secrete insulin, actively regulate blood glucose levels, and contribute to the restoration and maintenance of systemic glycemic homeostasis.

5. Mesenchymal Stem Cell Treatment of Diabetes

5.1 Mesenchymal Stem Cell Therapy for Type 1 Diabetes

In the context of type 1 diabetes mellitus management, genetic modification of mesenchymal stem cells represents a promising therapeutic strategy, potentially enhancing their functional efficacy and β-cell regeneration capacity. Using CRISPR-Cas9 gene editing, researchers can precisely regulate these critical transcription factors, thereby facilitating the differentiation of MSCs into insulin-producing β-like cells [17]. Gene editing techniques applied in MSC cultures enable the controlled expression of transcription factors, further promoting differentiation into β-cell phenotypes .

Advanced in vitro differentiation techniques, along with customized culture media and selective growth factors, facilitate the induction of MSCs to aggregate into cell clusters resembling pancreatic islets [18].

Post-differentiation, the subsequent critical step requires the implantation of the resultant cell aggregates into T1DM models. In T1DM patients, the immune system attacks and eliminates β-cells, and immunosuppressive therapy or encapsulation with biocompatible materials such as alginate or polyethylene glycol can be used to prevent immune rejection [19].

Fig.1 shows that Scientists have designed stepwise pancreatic differentiation protocols from PSCs by copying the way the pancreas normally develops in the body. In these protocols, PSCs go through several stages: they first become definitive endoderm (DE), then turn into the primitive gut tube (PG). After that, they develop into pancreatic progenitors (PP), then endocrine progenitors (EP), and finally change into hormone-expressing endocrine cells (EC). To make this process work in vitro, researchers control signaling pathways. They either turn on or block WNT, the transforming growth factor-β (TGF-β) superfamily pathways like Activin, Nodal, and Bone Morphogenic Protein (BMP), and also use retinoic acid (RA) and protein kinase C (PKC) signaling [20].

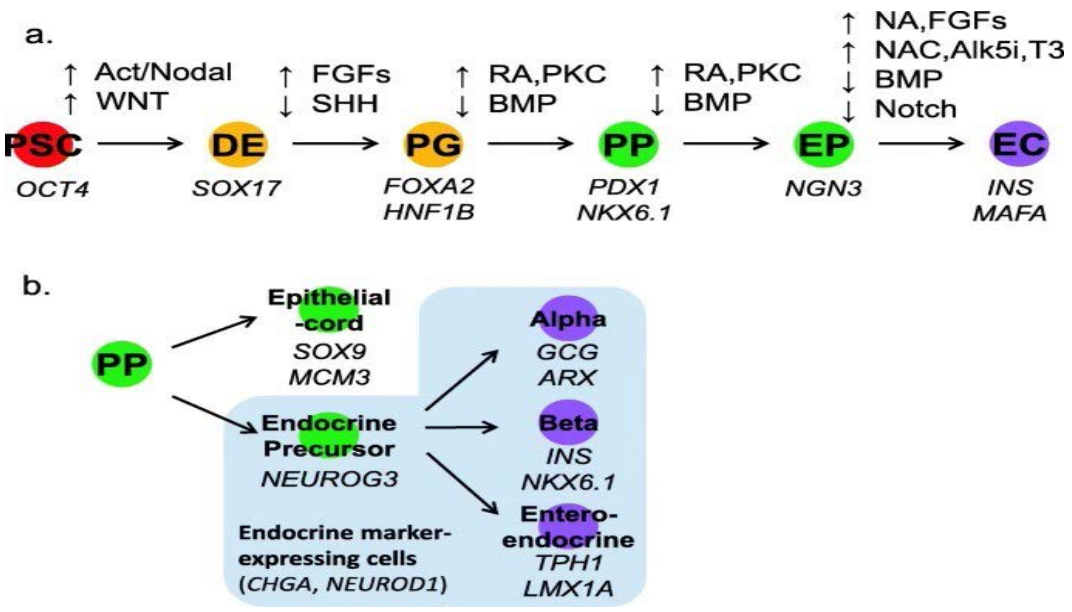

Fig.1 Growth factor-mediated and small molecule-mediated differentiation into pancreatic endocrine β-cells (a) directed differentiation of PSCs into pancreatic β-cells (b) scRNA-seq analysis reveals gene expression across distinct cell populations [20]

5.2 Mesenchymal Stem Cell Therapy for Type 2 Diabetes

Mesenchymal stem cells are recognized as a promising therapeutic modality for type 2 diabetes mellitus, owing to their ability to inhibit β-cell dedifferentiation and improve insulin secretion [21]. MSCs utilize exosome secretion of microRNAs to upregulate transcription factors, PDX1 and MAFA, thereby restoring β-cell function and supporting insulin production [22]. Additionally, MSCs exhibit immunomodulatory properties, alleviating chronic pancreatic inflammation, which in turn enhances insulin sensitivity and supports β-cell activity [23]. MSCs exhibit immunomodulatory properties, alleviating chronic pancreatic inflammation, which in turn enhances insulin sensitivity and supports β-cell activity [15].

Research indicates that MSC-derived exosomes possess the capacity to mitigate β-cell injury and enhance insulin sensitivity in diabetic animal models, suggesting potential as an alternative to conventional stem cell-based therapies [24].

5.3 Challenges in MSC-based Diabetes Therapy

Glucose-responsive insulin secretion is present in MSC-derived IPCs under laboratory conditions. however,the stability and functionality of these cells post-transplantation are still under investigation. Immune rejection, insufficient vascularization, and the intricate structure of the pancreatic microenvironment, may impede the viability and integration of these cells [25].

The ability of MSC-derived insulin-producing cells (IPCs) to maintain precise blood glucose control in vivo is still being studied. These cells show glucose-responsive insulin secretion in vitro.The in vivo environment is more complex, including blood glucose fluctuations, immune responses, and tissue-specific interactions, which may affect cell function [15].

5.4 Future Prospects

Stem cell therapy holds significant promise for diabetes treatment, particularly in generating insulin-producing cells through differentiation of mesenchymal stem cells. However, several challenges impede its clinical application. Efficient differentiation protocols for MSCs into functional IPCs are not yet fully established. Existing cell replacement therapies predominantly rely on rodent models, necessitating validation in higher-order animal models like primates. The comprehensive assessment of both the safety and long-term efficacy of MSC-derived IPC transplantation has yet to be completed.

To advance clinical translation, future research should focus on elucidating key signaling pathways regulating pancreatic development and β-cell differentiation. Identifying specific molecular markers that promote β-cell differentiation and optimizing in vitro induction protocols are crucial steps. Additionally, systematically assessing the efficacy and safety of cell reprogramming technology treatments is essential. Establishing standardized clinical application standards and regulatory frameworks will further facilitate the integration of this technology into clinical practice. These developments are expected to provide a strong ba-

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sis for the future clinical implementation of MSC-based therapies in the treatment of diabetes.

6. Conclusion

Mesenchymal stem cells show promising potential in diabetes treatment, especially in generating insulin-secreting cells through the differentiation of mesenchymal stem cells. To advance their application in diabetes therapy, future research should focus on elucidating key signaling pathways that regulate pancreatic development and β-cell differentiation, as well as improving the efficacy and safety of cell replacement therapy.

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