

A Literature Review of Recent Advances in Cell Therapy for Diabetes Mellitus

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Abstract. With the rising global prevalence of obesity and population aging, the number of patients with diabetes mellitus, a common chronic metabolic disorder, keeps rising and imposes mounting pressure on clinical medical services. Although current pharmacological interventions and insulin replacement therapy can effectively control blood glucose levels, they cannot fundamentally repair the functional defects of pancreatic islet β -cells, nor can they cure the disease. Under these circumstances, cell-based therapy has gradually become a research hotspot in the field of biomedical science in recent years, as it can substitute for islet function and thereby achieve long-term glycemic regulation. This article summarizes the clinical development, technical principles, and experimental results of various approaches, and compares the advantages and disadvantages of different methods. Meanwhile, this paper discusses the shortcomings of cell therapy at the present stage. On this basis, the future development trends of diabetes cell therapy are predicted, providing a reference for subsequent research and clinical translation.

Keywords: diabetes mellitus, cell therapy, stem cells, islet transplantation

1. Introduction

With the rapid development of the global economy, profound changes have taken place in people's living standards and lifestyles, and the aging of the population has been intensifying. Diabetes mellitus ranks third among chronic noncommunicable diseases threatening human health and life quality, only behind cardiovascular-cerebrovascular illnesses and malignant tumors. The pathogenesis of diabetes is complex, mainly involving impaired islet cell function, absolute or relative insufficiency of insulin secretion, and reduced peripheral tissue sensitivity to insulin. Long-term poor glycemic control can lead to metabolic disorders in multiple organs, including microvascular and macrovascular complications, such as diabetic nephropathy, diabetic retinopathy, and diabetic neuropathy. This not only increases the risk of disability and mortality among patients, but also imposes enormous pressure on society, families, and the healthcare system.

From an epidemiological perspective, the global incidence of diabetes is continuously increasing, with a trend toward younger onset ages and broader population distribution. According to statistics from the International Diabetes Federation, the number of adult diabetic patients worldwide has exceeded 500 million, with China ranking first in the number of diabetic patients, affecting not only middle-aged and elderly people but also young adults. However, a large number of diabetic patients

are either not detected early or remain undiagnosed, resulting in delayed intervention, missed therapeutic opportunities, and greatly increased treatment difficulty. From a clinical treatment standpoint, current interventions for diabetes mainly focus on glycemic control, using oral hypoglycemic agents, subcutaneous insulin injections, and novel antidiabetic drugs (GLP-1 receptor agonists, SGLT-2 inhibitors). These treatments can temporarily control blood glucose and alleviate acute hyperglycemic symptoms, but they cannot fundamentally reverse the apoptosis and functional decline of pancreatic β -cells, nor can they prevent the onset and progression of diabetic complications. Long-term medication use brings side effects such as hypoglycemic risk, abnormal weight gain, gastrointestinal discomfort, and increased hepatic and renal burden. For patients with pre-existing vascular damage or organ impairment, conventional therapies fail to achieve long-term improvement in prognosis.

Given the unsatisfactory efficacy of traditional treatments and the ever-increasing disease burden, stem cell-based therapy has emerged as a new research direction in recent years, with the potential to fundamentally restore islet function and rebuild the body's autonomous glucose regulatory capacity. Cell therapy focuses on cell replacement, tissue repair, and functional reconstruction, transplanting functional islet cells, stem cells, and their differentiated products to supplement or repair damaged islet tissue, thereby restoring physiological insulin secretion in response to glucose stimulation. This provides a novel approach for long-term stable glycemic control and even a functional cure of diabetes. Compared with conventional drugs, cell therapy has advantages such as longer duration of action, mechanism-based improvement of pathological changes, and synergistic protective effects on complications, and is becoming an important research direction in regenerative medicine and metabolic disease fields.

Based on relevant domestic and international literature published in the past five years, this paper systematically reviews the main technical routes, mechanisms of action, research progress, existing problems, and development trends of diabetes cell therapy, aiming to provide a relatively comprehensive reference for basic research, clinical translation, and broader application of cell-based diabetes treatments.

2. Main technical approaches of diabetes cell therapy

2.1. Islet cell transplantation

Islet cell transplantation is a regenerative medicine treatment for type 1 diabetes and some severe cases of type 2 diabetes. Human pluripotent stem cells possess unlimited proliferative capacity and the potential to differentiate into any cell type in the human body. Through directed differentiation technology, large numbers of human islet cells can be cultured in vitro for cell replacement therapy of diabetes [1]. The islet is an endocrine tissue within the pancreas, and its β -cells are the only cells that secrete insulin and regulate blood glucose. Type 1 diabetes arises from immune-mediated autoimmune destruction of pancreatic β -cells, which causes absolute insulin insufficiency and necessitates lifelong exogenous insulin supplementation.

Islet cell transplantation involves infusing healthy islet cells into the patient's liver via the portal vein, reconstructing physiological insulin secretory function and treating diabetes caused by islet failure. This therapeutic modality is indicated not only for type 1 and type 2 diabetes but also for brittle diabetes (namely unstable diabetes), a subtype marked by drastic glycemic swings and recurrent shifts between severe hypoglycemia and hyperglycemia. Such clinical manifestations are prevalent in patients with long-standing type 1 diabetes and occasionally observed in individuals with type 2 diabetes accompanied by severely impaired islet function. Its main pathological basis

involves absolute endogenous insulin deficiency, impaired glucagon counterregulation, autonomic neuropathy, malabsorption, and psychosocial factors [2].

2.2. Stem cell therapy

2.2.1. Induced pluripotent stem cells (iPSCs)

Induced pluripotent stem cells (iPSCs) represent an important tool for wound repair. Derived from somatic cell reprogramming, iPSCs exhibit unlimited proliferative potential and multidirectional differentiation capacity. They can be efficiently differentiated into functional β -cells free of ethical concerns, rendering them a leading research hotspot in diabetic regenerative medicine. Multiple studies have shown that iPSC-derived β -cells can effectively control blood glucose in animal models. Autologous cell replacement therapy offers a novel wound-healing approach for diabetic ulcers [3].

On the other hand, iPSCs can also be used to treat diabetic vasculopathy. Diabetic vasculopathy (DA) is the most serious complication of diabetes mellitus, affecting vital target organs such as the heart, kidneys, and retina through microvascular (retinal, renal) and macrovascular (cardiovascular) pathways, potentially leading to life-threatening or disabling outcomes. Even when insulin and oral hypoglycemic agents control blood glucose, they have limited effects on pathological processes such as vascular dysfunction, oxidative stress, and chronic inflammation. Mesenchymal stem cell-derived exosomes (MSC-Exo) can carry bioactive molecules such as non-coding RNAs (ncRNAs) and proteins to regulate target cell functions, demonstrating promising therapeutic effects in DA treatment, including vascular repair, inflammation reduction, and improvement of endothelial function [4].

In addition, exosomes from adipose-derived mesenchymal stem cells can promote autophagy in vascular endothelial cells under high-glucose conditions, reduce oxidative stress, protect DNA, proteins, and lipids from oxidative damage, and maintain endothelial health, functional integrity, and vascular youthfulness, ultimately achieving and preserving telomere health, reducing oxidative injury, and suppressing the senescence-associated secretory phenotype (SASP) [5].

2.2.2. Mesenchymal stem cells (MSCs)

Diabetic vasculopathy is the most common and severe complication of diabetes and a major cause of blindness, renal failure, myocardial infarction, and lower-limb amputation. Prolonged high-glucose environments damage vascular endothelial cells, inducing oxidative stress, inflammatory activation, reduced autophagy, mitochondrial dysfunction, and accelerated cellular senescence, leading to disruption of the endothelial barrier. These pathological changes further impair vascular vasodilation capacity and elevate the risk of thrombosis in diabetic patients. Traditional insulin and hypoglycemic agents cannot reverse established endothelial dysfunction and pathological progression. Therefore, it is necessary to find therapeutic approaches that can simultaneously protect the endothelium and repair vascular damage.

Mesenchymal stem cells (MSCs) derived from bone marrow, adipose tissue, umbilical cord, placenta, and other tissues have characteristics such as wide availability, easy isolation and culture, low immunogenicity, and safety, making them applicable to various diseases. MSCs do not mainly act through differentiation into pancreatic β -cells, but primarily through paracrine mechanisms, secreting abundant cytokines, growth factors, and exosomes to regulate the immune microenvironment, inhibit inflammation, promote angiogenesis, reduce oxidative stress, and

enhance autophagy, thereby protecting and repairing the vascular endothelium. In recent years, MSC-derived exosomes (MSC-Exo), as novel cell-free therapeutic agents, have effectively circumvented the limitations of cell transplantation, including immune rejection, tumorigenic risks and ethical dilemmas, emerging as a cutting-edge research focus for diabetic vasculopathy treatment.

Zhou Huiju et al. proposed that MSC-Exo can carry multiple bioactive substances such as non-coding RNAs (ncRNAs) and proteins, target damaged vascular endothelium, and regulate multiple signaling pathways to improve endothelial function, reduce chronic inflammation, decrease oxidative stress, and maintain cellular homeostasis, showing promising therapeutic effects in both microvascular and macrovascular diabetic complications. Exosomes can be efficiently taken up by endothelial cells and stably deliver bioactive substances to cells, thereby continuously ameliorating high-glucose-induced cellular damage, providing a safe and effective novel therapeutic approach for diabetic nephropathy, retinopathy, cardiovascular lesions, and other complications [4].

2.3. Gene editing and engineered cells

With the rapid advancement of gene editing technologies, the CRISPR-Cas9 system has been continuously improved, enabling targeted knockout, insertion, or modification of cells to address issues such as immune rejection, short cell survival, and functional instability in traditional cell therapies.

In diabetes treatment, gene editing is mainly used in the construction of engineered stem cells to improve therapeutic outcomes. On one hand, knocking out human leukocyte antigen (HLA) class I and class II genes can significantly reduce cellular immunogenicity and minimize post-transplant rejection, potentially enabling off-the-shelf universal cell products that do not require strict donor-recipient matching. In 2025, Reichman et al. published the results of phase III clinical trial in the New England Journal of Medicine, showing that stem cell-derived islets (Zimislecel/VX880) from patients, prepared with gene-editing technology, could replace the recipients' own islets and survive long-term in the recipients while maintaining insulin-secreting function without the need for potent immunosuppressants, achieving an insulin independence rate of 83% at 1 year [6].

3. Differences in therapeutic efficacy among different strategies

Currently, the main technical routes for diabetes cell therapy include islet transplantation, stem cell therapy (iPSC/MSC), and gene-edited engineered cell therapy. These therapeutic strategies differ substantially in terms of onset velocity, therapeutic potency, durable efficacy, and applicable patient populations.

In particular, after the standardized use of the classic Edmonton protocol, the postoperative insulin withdrawal rate in type 1 diabetic patients has significantly increased. A multicenter clinical study showed that among patients receiving islet transplantation, approximately 70%-80% achieved complete insulin independence within 6 months post-surgery, with markedly reduced glycemic fluctuations, a decrease in severe hypoglycemic events to less than one-tenth of the pre-transplant level, and greatly improved quality of life.

iPSC-derived β -cells feature unlimited cellular sources, robust differentiation potential, and physiological functions highly similar to native islets, rendering them a leading candidate for the functional cure of diabetes. Vertex Pharmaceuticals (2025) reported phase 1/2 clinical trial results of their iPSC-derived islet cell therapy (VX880/Zimislecel), demonstrating that in patients with severe type 1 diabetes, 83% (10 out of 12) achieved complete withdrawal of exogenous insulin 12 months

after the first infusion, with $HbA1c \leq 7.0\%$. Meanwhile, the team of Deng Hongkui at Peking University (2024) published findings in Cell showing that chemically reprogrammed iPSC-derived islet transplantation enabled insulin independence for over 1 year in type 1 diabetic patients without severe hypoglycemic events [7].

4. Safety controversies and clinical translation barriers

Safety is a prerequisite for the transition of diabetes cell therapy from laboratory to large-scale clinical application. Distinct cell therapeutic strategies exhibit unique safety vulnerabilities and still confront multiple unresolved challenges and academic controversies. The major safety risk of islet transplantation is long-term use of immunosuppressants. Although immunosuppressants reduce the risk of rejection, they also increase the risks of infection, hepatic and renal injury, hypertension, hyperlipidemia, and tumorigenesis, especially affecting long-term survivors. A 10-year study showed that among patients receiving islet transplantation, about 30% developed severe complications due to immunosuppressant side effects, and 15% developed new-onset tumors [8].

Most relevant studies remain confined to preclinical laboratory stages. High manufacturing costs, insufficient scalable production systems and the absence of standardized quality control criteria greatly restrict clinical translation. Long-term therapeutic data are lacking, and there is a shortage of large-sample clinical studies, especially for technologies such as gene-edited cells, where data from only one or two phase 1/2 clinical trials are available.. Moreover, there are no unified standards for cell sources, differentiation protocols, or transplantation methods, with different teams using different cell origins and induction schemes. Furthermore, immune rejection and safety issues have not been fully resolved. After allogeneic islet or stem cell transplantation, the host immune system's rejection of the graft remains a major factor affecting long-term graft survival. Finally, the high cost makes widespread adoption difficult, with a single treatment costing hundreds of thousands of yuan, far beyond the affordability of ordinary patients.

Future development should focus on improving cell maturation, reducing immune rejection, developing universal cell products, and achieving low-cost large-scale production. Meanwhile, the integration of biomaterials, artificial intelligence and other interdisciplinary technologies will further promote the clinical translation of diabetic cell therapy, ultimately facilitating the realization of a functional cure for diabetes.

5. Conclusion

This article systematically reviews the three main technical routes of diabetes cell therapy: islet cell transplantation, stem cell therapy (including induced pluripotent stem cells and mesenchymal stem cells), and gene-edited engineered cell therapy. Studies have shown that when conventional therapies fail to achieve a curative effect, cell therapy has gradually become a key research direction in the diabetes field. Transplantation of functional islet cells or stem cell-derived β -cells to supplement and repair impaired pancreatic islet tissue enables patients to restore endogenous insulin secretory capacity. This approach not only provides more stable glycemic control but also reduces the adverse effects associated with long-term medication use, thus representing an important strategy for achieving "functional cure" of diabetes.

The limitations of this article are mainly reflected in the following aspects: first, due to the quantity and quality of available literature, the long-term efficacy and safety assessments of various techniques are insufficient; second, there are few direct comparative analyses among different technical routes, making it difficult to draw clear conclusions on superiority; third, the review of

emerging technologies such as the combined application of gene editing and biomaterials is not sufficiently in-depth. Future research should focus on establishing standardized cell preparation and quality control systems, conducting large-scale, multi-center long-term clinical trials, developing low-cost, universal cell products, and promoting the clinical translation of diabetes cell therapy with the aid of interdisciplinary technologies such as biomaterials and artificial intelligence, ultimately achieving a functional cure of diabetes.

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