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Development History and Feasibility Analysis of Mesenchymal Stem Cell Therapy for Type 2 Diabetes Mellitus

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Abstract. Type 2 diabetes mellitus (T2DM) has become a major global public health burden, and existing drugs cannot reverse the progressive failure of pancreatic β-cell function. Mesenchymal stem cells (MSCs), by virtue of their immunomodulatory, anti-inflammatory, and tissue-repair properties, offer a new strategy for the causal treatment of T2DM. This article reviews the development history and mechanisms of action of MSC therapy for T2DM, including restoration of insulin-resistance signaling pathways, reversal of β-cell dedifferentiation, suppression of chronic low-grade inflammation, and exosome-mediated paracrine effects; summarizes evidence from preclinical animal studies and recent representative clinical studies, analyzing safety and efficacy; and discusses translational bottlenecks such as cellular heterogeneity, low homing efficiency, and the lack of standardization, together with countermeasures including genetic modification, patient stratification, and exosome engineering. Current evidence indicates that MSC therapy for T2DM is safe and feasible, with glucose-lowering and organ-protective potential; however, complete remission rates are low and therapeutic responses are highly heterogeneous, and routine clinical application still requires high-quality evidence-based support and standardized systems.

Keywords: Type 2 diabetes mellitus, Mesenchymal stem cell, Exosome

1. Introduction

The 11th edition of the IDF Diabetes Atlas, published by the International Diabetes Federation (IDF), estimates that approximately 589 million people aged 20–79 worldwide had diabetes in 2024 (a prevalence of 11.1%), a figure projected to rise to 853 million by 2050; diabetes-related health expenditure exceeded 1 trillion US dollars in 2024, and approximately 3.4 million people died from diabetes [1]. More than 90% of these cases are type 2 diabetes mellitus (T2DM), whose core pathology is peripheral insulin resistance (IR) superimposed on progressive failure of pancreatic β-cell function. Existing therapies—including metformin, GLP-1 receptor agonists, and SGLT2 inhibitors—can only control blood glucose and delay complications; they cannot reverse β-cell failure.

Mesenchymal stem cells (MSCs) are a class of adult stem cells with self-renewal capacity and multidirectional differentiation potential; they combine immunomodulatory, anti-inflammatory, and tissue-repair properties, theoretically matching the multi-faceted pathological demands of T2DM.

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MSCs can be obtained from bone marrow, adipose tissue, umbilical cord, and other tissues; among these, umbilical cord-derived MSCs, with their strong proliferative capacity, low immunogenicity, and freedom from ethical controversy, are currently the mainstream choice in clinical trials [2]. Their therapeutic principle does not rely on a single target but on the synergy of multiple pathways: repairing insulin signaling, protecting and regenerating β cells, remodeling an anti-inflammatory immune microenvironment, and secreting exosomes. It should be noted, however, that a high-glucose microenvironment damages the function of MSCs themselves: in diabetic model mice, bone marrow MSCs show reduced numbers, diminished proliferation and survival, and markedly impaired regenerative capacity [3]. and high glucose can also induce premature senescence and apoptosis of MSCs, suggesting hidden risks of autologous transplantation and the greater feasibility of allogeneic umbilical cord-derived cells [4].

Since MSCs were first used in diabetes research, the field has progressed from basic mechanistic exploration to clinical translation: numerous animal studies have confirmed the glucose-lowering and organ-protective effects of MSCs and their exosomes; a randomized, double-blind, placebo-controlled phase II trial completed in 2022 provided high-quality evidence-based support for their efficacy ; Nevertheless, MSC therapy still faces bottlenecks such as cellular heterogeneity, low homing efficiency, and the absence of manufacturing standardization, with limited complete remission rates; overall, the field is at a critical stage of transition from clinical trials to routine application.

Focusing on the use of MSCs in the treatment of T2DM, this article systematically reviews their development history and biological basis, provides an in-depth analysis of their multi-target mechanisms of action, summarizes representative evidence from preclinical and clinical studies, and analyzes current challenges and feasible optimization strategies. Through this review, we aim to provide a relatively complete reference framework for understanding the current research status and translational prospects of MSC therapy for T2DM, and to offer a basis for selecting future research directions and designing clinical protocols.

2. Mechanisms of action of MSCs

2.1. Ameliorating peripheral IR

Insulin exerts its glucose-lowering effect through a precise intracellular signaling chain: after insulin binds to its membrane receptor, the receptor tyrosine kinase undergoes autophosphorylation and then phosphorylates insulin receptor substrate-1 (IRS-1); IRS-1 recruits and activates phosphatidylinositol 3-kinase (PI3K), which catalyzes the production of the second messenger PIP3, thereby activating protein kinase Akt and ultimately driving translocation of the glucose transporter GLUT4 from intracellular vesicles to the cell membrane, allowing glucose uptake into skeletal muscle and adipose cells [5]. The core pathology of T2DM lies in the "severing" of this pathway: chronic hyperglycemia and free fatty acids activate protein kinase C (PKC) and c-Jun N-terminal kinase (JNK), causing aberrant phosphorylation of IRS-1 at serine 307; this "erroneous phosphorylation" suppresses normal tyrosine-phosphorylation signal transmission, preventing GLUT4 from reaching the membrane and leaving glucose trapped outside the cell [5]. Following MSC infusion, phosphorylation levels of IRS-1 and Akt are restored and GLUT4 expression is upregulated in muscle, liver, and adipose tissue—effectively reconnecting this signaling chain [6]; in the liver, MSCs simultaneously suppress FOXO1-mediated expression of gluconeogenic genes and reduce endogenous glucose output, improving blood glucose from both the "uptake" and "production" sides.

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2.2. Protecting and regenerating β cells

The traditional view held that β cells are lost in large numbers through apoptosis in advanced T2DM, but recent studies have revised this understanding: a considerable proportion of β cells are not dead but have "dedifferentiated" under glucotoxic and lipotoxic stress—that is, they revert to a progenitor-like state that no longer secretes insulin and lose their identity markers, a functionally reversible "dormancy" rather than irreversible demise [7]. MSCs act precisely on this link: in co-culture systems of human T2DM islets, MSCs secrete interleukin-1 receptor antagonist (IL-1Ra) to block IL-1β-mediated inflammatory injury of β cells, causing dedifferentiated cells to re-express insulin and restoring glucose-stimulated secretory function [7]; animal experiments have also observed that MSCs can promote transdifferentiation of islet α cells into β cells and inhibit β-cell apoptosis, expanding the functional β-cell pool from multiple sources [6]. In addition, cytokines secreted by MSCs can improve the local microcirculation of islets, providing nutritional support for β-cell repair and functional recovery.

2.3. Suppressing chronic low-grade inflammation

T2DM is essentially a state of metabolic, chronic low-grade inflammation. One of its molecular starting points is the NLRP3 inflammasome: persistent hyperglycemia overloads the mitochondrial electron transport chain and generates reactive oxygen species (ROS); ROS promote the binding of thioredoxin-interacting protein (TXNIP) to NLRP3 and the assembly of the inflammasome, which in turn activates caspase-1, cleaving pro-IL-1β and pro-IL-18 into mature pro-inflammatory factors and triggering pyroptosis, directly injuring β cells; IL-1β also aggravates serine phosphorylation of IRS-1 via the JNK pathway, coupling inflammation and IR into a vicious cycle [8]. MSC intervention is systemic: first, through the COX-2/PGE2 and IL-6/IL-4Rα pathways, MSCs promote polarization of macrophages in adipose and islet tissues from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, downregulating TNF-α, IL-6, and IL-1β while elevating IL-10 [8]; second, they increase the number of regulatory T cells (Tregs) and restore the Th17/Treg immune balance, reshaping an anti-inflammatory microenvironment at the level of adaptive immunity [9]; third, through factors such as TSG-6, they inhibit NF-κB activation, blocking the "priming" signal of NLRP3 at its source [10]. The multi-node, interlinked pro-inflammatory network is thereby interrupted.

2.4. paracrine effects of exosomes

A growing body of evidence indicates that the therapeutic efficacy of MSCs depends not on engraftment of the cells themselves, but on the exosomes they secrete—lipid bilayer vesicles 30–150 nm in diameter that carry miRNA and other bioactive substances and can be taken up by β cells, hepatocytes, and adipocytes [11]. The specific "cargo" has been identified one by one: miR-21 promotes β-cell survival by inhibiting PTEN and thereby activating the Akt pathway; miR-146a targets inflammatory signaling to alleviate islet inflammation; and miR-125b-5p improves β-cell function by inhibiting the JNK pathway [10]. As a "cell-free therapy," exosomes circumvent the embolism and tumorigenicity risks of live-cell infusion, and systematic reviews have confirmed that they can lower blood glucose and reverse histopathological damage to islets [11]. Compared with living cells, exosomes are more stable, easier to store and transport, and less immunogenic, and they can be engineered to load specific miRNAs for "customized" therapy.

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3. Preclinical studies

Animal studies have generally confirmed the glucose-lowering and organ-protective effects of MSCs and their exosomes in T2DM models. In streptozotocin (STZ)-induced diabetic models and spontaneous T2DM models such as db/db mice, MSC infusion significantly reduces fasting blood glucose and glycated hemoglobin, improves glucose tolerance and insulin sensitivity, and alleviates islet inflammation and β-cell apoptosis; their effects extend beyond the islets themselves to target organs of diabetic complications such as nephropathy, cardiomyopathy, and fatty liver, demonstrating multi-organ protective value [12]. Regarding administration routes, a 2025 rat study systematically compared the efficacy of human umbilical cord MSCs infused via four routes—local pancreatic, tail vein, intraperitoneal, and dorsal pancreatic artery; all groups significantly lowered HbA1c and improved lipid profiles and liver and kidney function within 2–4 weeks, with the tail-vein route showing the best efficacy, indicating that the administration route is a key process parameter requiring optimization [13]. Regarding potentiation strategies, preconditioning with hypoxia, cytokines, or growth factors can partially restore the function of diabetes-impaired MSCs [4]; combination of MSCs with drugs such as liraglutide or metformin, as well as co-delivery approaches such as hydrogel encapsulation, can further enhance efficacy [9]. Regarding dose exploration, most studies show dose-dependent efficacy, but the benefit plateaus beyond a threshold, suggesting the existence of an optimal dose window; some studies have also observed the potential of MSC exosomes in ameliorating complications such as impaired diabetic wound healing and neuropathy.

From a translational perspective, the significance of preclinical research lies not only in validating efficacy but also in providing key parameters for clinical protocol design: it defines preliminary safety windows for cell source, dose, administration route, and treatment course; reveals the dependence of efficacy on the microenvironment and preconditioning processes; and provides proof of concept for the feasibility of cell-free preparations such as exosomes. It is fair to say that without systematic animal experimental evidence, dose selection, dosing regimens, and endpoint design in subsequent clinical trials would lack a foundation.

However, it must also be recognized that STZ-induced or db/db mouse models cannot fully reproduce the chronic, multifactorial course of human T2DM, and extrapolation of animal results to the clinic has obvious limitations. Further analysis shows that such limitations manifest at three levels: first, the pathogenesis of model animals is relatively simple and cannot reproduce the heterogeneity of human T2DM, in which genetics, obesity, and lifestyle factors are interwoven; second, animal experiments involve short treatment courses and small sample sizes, preventing assessment of the long-term safety of MSCs and the pattern of efficacy attenuation; third, cross-species immunological differences mean that the survival and immunogenicity of allogeneic MSCs in animals differ from those in humans. Therefore, positive results from animal studies should be regarded as "feasibility signals" rather than "efficacy guarantees," and their extrapolation must be verified by rigorously designed clinical trials.

4. Clinical studies: analysis of representative cases

In recent years, several high-quality clinical studies have been published, providing human-level evidence-based support for the efficacy and safety of MSC therapy for T2DM. Taken together, these studies yield the central argument of this section: MSC therapy for T2DM is generally safe and can tangibly improve glycemic control and islet function, but the magnitude of benefit is limited and

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there are marked individual differences. This argument is substantiated below through four representative studies.

In 2022, Zang and colleagues from the Chinese PLA General Hospital reported a single-center, double-blind, placebo-controlled phase II randomized controlled trial: 91 patients with T2DM were enrolled and received three intravenous infusions of umbilical cord MSCs with 48 weeks of follow-up; 20% of patients in the MSC group achieved the primary endpoint of HbA1c <7.0% with an insulin dose reduction of ≥50% (versus 4.55% in the placebo group), mean HbA1c decreased by 1.31% (versus 0.63% in the control group), 13.5% of patients were able to discontinue insulin completely for a period of time, and no serious transplant-related adverse events occurred [2].

In 2023, Zang's team further published a post hoc analysis based on continuous glucose monitoring (CGM): at 9 weeks after treatment, the rate of achieving the target for glucose time in range (TIR) reached 59.5% in the MSC group, significantly higher than 27.8% in the placebo group, suggesting that MSCs not only lower average blood glucose but also reduce glycemic variability and improve glucose quality [14].

In 2024, Zhao Jian and colleagues from the same team reported a post hoc analysis of patients with T2DM complicated by non-alcoholic fatty liver disease (NAFLD): in the UC-MSC group, fasting blood glucose decreased from 8.33 mmol/L to 7.46 mmol/L at week 9; the rate of achieving the HbA1c target at week 48 was 48.5% (versus 12.5% in the control group); the reversal rate of fatty liver on hepatic ultrasound at week 20 reached 45.5% (versus 18.75% in the control group); and triglycerides and total cholesterol remained consistently better than baseline, suggesting additional benefits of MSCs for diabetes complicated by fatty liver [15].

In 2025, Chin and colleagues in Malaysia reported a real-world retrospective registry study: among 218 T2DM patients who received intravenous allogeneic umbilical cord MSCs, HbA1c decreased from 7.77% to 7.52% at 6 months ($p<0.001$), HOMA-IR improved significantly, hs-CRP decreased significantly at 12 months in the high-inflammation subgroup, renal function indices improved in patients with early chronic kidney disease, and no adverse reactions occurred throughout the study [16]. In the same year, a meta-analysis by Kashbour and colleagues pooling 13 RCTs with 507 patients showed that at 12 months, HbA1c in the MSC group decreased by an additional 0.72 percentage points compared with the control group, fasting C-peptide increased by 0.24 ng/mL, and no serious adverse events or deaths were reported [17].

A cross-sectional comparison of the above studies reveals the following: first, the levels of evidence form a complementary pattern of "randomized controlled trials—post hoc analyses—real-world registries," in which RCTs confirm the causality of efficacy while real-world data suggest the accessibility of efficacy in broader populations; second, the magnitude of glucose lowering is similar across studies (HbA1c reductions of approximately 0.3–1.3 percentage points), but complete remission rates are low, efficacy partially attenuates over time, and the characteristics of responders remain unclear; third, all studies consistently report a favorable safety profile, with no serious transplant-related adverse events. Overall, MSCs are safe and effectively lower blood glucose, but individual heterogeneity is large and efficacy is not yet stable; future efforts need to improve response rates through patient stratification and process optimization. It is noteworthy that studies with better efficacy mostly employed umbilical cord-derived cells and multiple intravenous infusion regimens, suggesting that cell source and dosing regimen may be key variables affecting response.

5. Challenges and prospects

MSCs face multiple challenges in translation to clinical application: (1) inconsistent efficacy among cells from different tissue sources, donors, and production batches; (2) low homing efficiency—after

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intravenous infusion, most cells are trapped in pulmonary capillaries, and the proportion truly reaching target tissues is only in the single-digit percentage range [18]; (3) the absence of unified standards for cell manufacturing processes, dosage, administration routes, and treatment courses; and (4) unresolved technical difficulties with exosomes, including large-scale purification, quality control, and storage stability; in addition, there are issues of regulatory approval and ethical norms for stem cell products [19].

To address these bottlenecks, future breakthrough directions include the following. First, genetic modification can be used to overexpress homing molecules such as CXCR4: as the receptor of SDF-1, CXCR4 and SDF-1 together form the "SDF-1/CXCR4 axis," which is the core navigational mechanism guiding the directional migration and homing of stem cells to injured tissues; overexpressing CXCR4 through genetic modification can rebuild the homing capacity of mesenchymal stem cells and improve their efficiency in reaching target tissues such as the pancreas, thereby enhancing their therapeutic effect on type 2 diabetes. Cell-surface engineering can likewise enhance the targeted engraftment of MSCs [18] and increase homing rates. Second, targeted delivery devices and biomaterial carriers can be developed to improve local retention and survival, and unified cell manufacturing and quality-control systems can be established to promote standardization. Third, patients can be stratified based on baseline β-cell function, disease duration, and inflammatory phenotype; the latest post hoc analysis has preliminarily confirmed that sex and baseline C-peptide levels can serve as predictors of efficacy [20]. Fourth, the engineering of cell-free preparations such as exosomes can be advanced, for example by loading specific miRNAs into MSC extracellular vesicles via electroporation to enhance their therapeutic potency [11]. These strategies are expected to improve the controllability, reproducibility, and clinical translation success rate of MSC therapy for T2DM. At the same time, establishing a full-chain regulatory and ethical framework covering donor screening, cell manufacturing, release testing, and long-term follow-up is also a prerequisite for routine clinical application.

6. Conclusion

This article has systematically reviewed the development history and mechanisms of action of mesenchymal stem cells (MSCs) in the treatment of type 2 diabetes mellitus, analyzing their molecular and cellular basis from four aspects—ameliorating peripheral IR, protecting and regenerating β cells, suppressing chronic low-grade inflammation, and exosome-mediated paracrine effects—and summarizing evidence from preclinical animal experiments and representative clinical studies. The analysis shows that MSC therapy for T2DM is generally safe and can tangibly improve glycemic control and islet function, providing a new path for the causal treatment of diabetes that differs from conventional glucose-lowering drugs; it also indicates that cell source, administration route, and patient baseline characteristics are key variables affecting efficacy, providing a reference for protocol design and patient stratification in subsequent clinical trials. It should be noted that the clinical studies on which this article relies have small sample sizes and limited follow-up durations, and there is marked heterogeneity among studies, so extrapolation of the conclusions should be made with caution. In the future, with the conduct of large-scale, long-term randomized controlled trials and the maturation of optimization strategies such as genetic modification and exosome engineering, MSCs are expected to become an important component of the comprehensive treatment system for T2DM.

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