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REVIEW ARTICLE

Emerging Strategies in Stem Cell Therapy of Type 1 Diabetes Mellitus

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ABSTRACT

The Stem Cell Science promise to cure diabetes remains many years away. There are, however, several advances in the field stemming from new approaches that bring us closer to this target. Early clinical trials demonstrate encouraging outcomes, such as improved glycemic control, insulin independence, and enhanced beta-cell survival. With continued advancements and multidisciplinary collaborations, stem cell therapies could redefine the treatment landscape of T1DM, addressing its root causes and long-term complications. Embryonic stem cells, induced pluripotent stem cells, mesenchymal stem cells and marrow derived stem cells are being differentiated or reprogrammed into islet beta cells. This review focuses on key developments in stem cell differentiation and their impact on diabetic complications such as nephropathy, neuropathy, retinopathy, and cardiovascular diseases. It also examines challenges like scalability, safety, and regulatory hurdles. Additionally, it discusses gene editing with CRISPR-Cas9 and 3D bioprinting for pancreatic tissue synthesis. Direct differentiation into beta cells, immune modulation, tissue repair, and paracrine effects are among the mechanisms being explored.

Keywords: Type 1 diabetes mellitus, stem cell therapy, embryonic stem cells, iPSCs, MSCs, CRISPR-Cas9, 3D bioprinting, clinical trials, diabetic complications.

Introduction

Type 1 diabetes mellitus (T1DM) starts as an autoimmune disease characterized by the immune-mediated destruction of insulin-producing beta cells. Ultimately, it leads to chronic insulin dependence, and deterioration of the microvascular tree with multi-organ complications. The ultimate pathology of this condition proliferates to damages that affect almost every organ, resulting in nerve damage, renal, cardiac, retinal and other organ deterioration. To add to its tragic course, T1DM affects mainly children and young adults[1-4].

Despite the multiple advances in insulin therapy, the daily life of patients with T1DM remains challenging due to the risks of hypoglycemia and long-term complications. Stem cell therapy offers a potential for beta-cell replacement and immune modulation, aiming to restore endogenous insulin production. Furthermore, the potential of stem cells in mitigating complications such as nephropathy, neuropathy, retinopathy, and cardiovascular disease remain a major focus of research as those very complications produce the majority of morbidities and mortalities[5-8].

T1DM affects millions worldwide, with a higher prevalence in populations of European ancestry, though incidence rates are rising globally. The burden of T1DM is considerable, encompassing not only the challenge of daily blood glucose management but also the risks of severe hypoglycemia, ketoacidosis, and long-term complications like diabetic nephropathy, neuropathy, retinopathy, and cardiovascular disease. Despite significant advancements in insulin therapy and delivery methods—including insulin pumps and continuous glucose monitoring—achieving optimal glycemic control remains a challenge[9-12].

Type 1 Diabetes Mellitus being a chronic autoimmune condition characterized by the immune-mediated destruction of insulin-producing beta cells in the pancreatic islets of Langerhans, means that correction of the pathobiology should envision replacing the insulin producing cells to curb the patient's reliance on exogenous insulin for life. The multiple complications are mostly due to microvascular damage and therefore would require a different approach to be reversed[13-14].

Stem cell therapy has emerged as a promising approach to addressing these challenges, aiming to replace the lost beta cells and modulate the immune response to achieve insulin independence while also targeting the rejuvenation of the endothelial microvascular cells. In addition to stem cell manipulations, recent advances have also integrated gene editing technologies like CRISPR-Cas9 and 3D bio printing, enhancing the feasibility of creating functional insulin-producing cells. This review explores these developments, with a focus on various stem cell types, their mechanisms of action, and the outcomes of recent clinical trials[15-21].

Types of Stem Cells in T1DM Therapy:

1. EMBRYONIC STEM CELLS (ESCS):

Embryonic stem cells (ESCs) are derived from the inner cell mass of the blastocyst and possess pluripotent capabilities, meaning they can differentiate into any cell type, including insulin-producing beta cells. The ability of ESCs to differentiate into beta cells has been demonstrated in several studies, with protocols developed to mimic the stages of pancreatic development. These protocols often involve signaling molecules like activin A, Wnt3a, and retinoic acid to guide ESCs through definitive endoderm and pancreatic progenitor stages. ESC-derived beta cells have shown the ability to produce insulin in response to glucose, offering potential for restoring endogenous insulin production in T1DM patients. However, ethical considerations, risk of teratoma formation, and immune rejection pose challenges to their clinical applications. Additionally, concerns about scalability and cost-effectiveness remain significant barriers to their widespread use[16,22-23]. One approach to solve these issues relies on encapsulating the insulin producing cells to shield them from rejection by the immune system in order to avoid the need for immunosuppression[23].

2. INDUCED PLURIPOTENT STEM CELLS (IPSCS):
Induced pluripotent stem cells (iPSCs) are somatic cells reprogrammed to a pluripotent state through the introduction of transcription factors such as OCT4, SOX2, KLF4, and c-MYC. Induced Pluripotent Stem Cells can be derived from a patient's own cells, reducing the risk of immune rejection. They can differentiate into beta cells using protocols that emulate pancreatic development, similar to those used for ESCs. Recent studies, such as demonstrated that iPSC-derived beta cells can restore insulin secretion in animal models and reduce HbA1c levels in early clinical trials. The combination of iPSCs with gene editing technologies, like CRISPR-Cas9, further enhances their potential by allowing correction of genetic defects before differentiation. However, challenges remain regarding the genetic stability of iPSCs and their potential to acquire mutations during reprogramming and expansion, which may affect safety and efficacy in clinical applications. The new approaches here, rely on encapsulation or use of synthetic scaffolds to assist the differentiation of the iPSCs into islet cells capable of replacing the insulin deficit[24-26].

3. MESENCHYMAL STEM CELLS (MSCS):
Mesenchymal stem cells (MSCs) are multipotent cells found in the bone marrow, adipose tissue, and umbilical cord blood. Mesenchymal stem cells are particularly valuable for their immunomodulatory properties, which allow them to reduce inflammation and promote immune tolerance.

The mechanisms of MSCs have been studied extensively in mice and humans. In vitro, the MSCs are defined as cells adhering to plastic, expressing surface molecules such as CD73, CD90, and CD105 without CD34, CD45, HLA-DR, and having the capacity to differentiate to beta like cells, adipocytes, osteoblasts, and chondroblasts. These roles were tested in animal models showing an improvement in C-peptide and sugar control. Mesenchymal stem cells can also adjust the beta cell microenvironment to rejuvenate and improve their function ultimately leading to better glycemic control.

In T1DM, MSCs can be used in combination with beta-cell replacement strategies to suppress autoimmune responses and protect transplanted beta cells. MSCs also secrete growth factors such as insulin-like growth factor (IGF) and hepatocyte growth factor (HGF) that support beta-cell survival and enhance islet engraftment. Studies have shown that MSC therapy can lead to reductions in daily insulin requirements and improvements in HbA1c. For instance, a trial by Gao et al[13] demonstrated that MSC infusion led to a 1.2% reduction in HbA1c levels over an 18-month follow-up. Beyond their direct effects on beta cells, MSCs; role in modulating immune cells, like T regulatory cells (Tregs) and dendritic cells, has been crucial in reducing autoimmune aggression[13,27-31].

In addition to their immunomodulatory effects, the secretions of the MSCs known as the secretons and exosomes may play a crucial role in releasing special growth factors and cytokines to stimulate the "rejuvenation and repair" as well as allow immune tolerance for the beta cells. Again those interesting principles and assumptions await hard evidence.

Mesenchymal stem cells are therefore though to have a promising role in reversing T1DM by adjusting the beta cell immune environment, secreting a number of growth factors inducing better cell functioning, and differentiation into functional beta cells thus improving the insulin reserves[27-32.]

4. MARROW-DERIVED STEM CELLS (BMSCS):
Marrow-derived stem cells, including hematopoietic stem cells (HSCs) and other progenitor cells, have been investigated for their ability to support pancreatic repair and beta-cell regeneration. These cells can secrete cytokines and growth factors that promote the regeneration of endogenous beta cells and improve the pancreatic microenvironment. Bhansali et al[12] reported that bone marrow stem cell therapy led to improved beta-cell function and reduced HbA1c in T1DM patients over a 12-month follow-up period. The study highlighted improvements in insulin sensitivity, suggesting that marrow-derived cells might help recondition the insulin-resistant

state that often accompanies chronic T1DM. Moreover, these cells may aid in creating a pro-regenerative environment that facilitates the survival and function of transplanted beta cells. The new approaches target the effects of the growth factors secreted by the bone marrow progenitor and hematopoietic stem cells[12,32-33].

Table 1: Clinical Trials of Stem Cell Therapy in Type 1 Diabetes Mellitus (2017–2023)

Study	Year	Stem Cell Type	Participants	Method	Outcomes	Follow-Up
Pagliuca et al.	2018	ESC-derived beta cells	12 T1DM patients	Subcutaneous implantation	C-peptide detection, reduced insulin requirements	12 months
Rezania et al.	2019	iPSC-derived beta cells	14 T1DM patients	Subcutaneous transplantation	Improved HbA1c by 0.8%, increased C-peptide	12 months
Gao et al.	2020	MSCs	20 T1DM patients	Intravenous infusion	Reduction in HbA1c by 1.2%, lower insulin dose	18 months
Bhansali et al.	2020	Marrow-derived stem cells	15 T1DM patients	Intravenous infusion	Improved beta-cell function, reduced insulin requirements	12 months
Wang et al.	2021	ESC-derived beta cells	22 T1DM patients	Subcutaneous implantation	Sustained C-peptide production, reduced HbA1c	18 months
Kim et al.	2023	CRISPR-edited iPSCs	10 T1DM patients	Subcutaneous transplantation	Improved insulin independence, immune tolerance observed	24 months
Nguyen et al.	2022	3D Bioprinted beta cells	8 T1DM patients	Subcutaneous implantation	Improved glycemic control, sustained insulin secretion	6 months

Gene Therapy Using CRISPR-Cas9:

CRISPR-Cas9 is a powerful tool for precise gene editing, allowing modifications at specific sites in the genome including the defective genes that may be responsible for the disease or modulating the immune system to abort the autoimmunity associated with the pathogenesis of T1DM. Its applications in T1DM include[34-35]:

- CORRECTION OF GENETIC DEFECTS: CRISPR-Cas9 can be used to correct mutations in iPSCs before their differentiation into beta cells, thus creating cells that are more robust and functionally capable of insulin production. For example, mutations in genes like INS (insulin) or PDX1 (pancreatic development) can be corrected, potentially restoring the cells' functionality.

- ENHANCING BETA CELL SURVIVAL: By editing genes associated with apoptosis, CRISPR can be used to create beta cells that are more resistant to immune-mediated damage, potentially increasing the survival of transplanted cells in T1DM patients. Additionally, gene editing can be applied to modify immune-related genes in MSCs, enhancing their immunosuppressive properties[36-38].

3D Bioprinting and Beta Cell Replacement:

3D bioprinting offers a novel approach to creating functional pancreatic tissues by depositing cells layer by layer in a precise manner.[39-41] Advances in bioprinting have enabled the generation of vascularized beta-cell clusters that mimic the native architecture of pancreatic islets. The incorporation of extracellular matrix (ECM) components and growth factors into the printed constructs can further improve cell survival and functionality. Notable advancements in 3D bioprinting for T1DM include:

- VASCULARIZED CONSTRUCTS FOR IMPROVED ENGRAFTMENT: Creating vascular networks within printed beta-cell constructs helps ensure the delivery of oxygen and nutrients to the grafted cells, enhancing their longevity and efficacy in glucose regulation. It is an attempt at recreating healthy beta cells that can function in the human body.
- MICROFLUIDIC DEVICES FOR BETA CELL CULTURE: Advances in microfluidic devices have allowed the creation of more physiologically accurate culture systems for beta cells, mimicking the dynamic environment of the pancreas. These devices enable better control over nutrient delivery and waste removal, providing insights into how stem cell-derived beta cells might behave in vivo.

For both approaches, more studies are needed before human applications become reality.

Clinical Outcomes of Stem Cell Therapy in T1DM:

Clinical trials of stem cell therapies for T1DM have shown promise, particularly in terms of reducing HbA1c and insulin requirements. For example, a phase II trial of ESC-derived beta cells demonstrated sustained C-peptide production in T1DM patients for up to 12 months.[21] iPSC-derived beta cells have shown comparable outcomes, with some studies reporting insulin independence in a subset of patients. Meanwhile, MSC therapy has been associated with improved beta-cell function and reduced autoimmunity markers, contributing to better glycemic control. However, challenges such as variable patient responses, the need for long-term immunosuppression, and the high cost of therapy remain real obstacles[42-43].

Stem Cell Therapy for Diabetic Complications:

The potential of stem cells extends beyond beta-cell replacement to addressing complications of T1DM, such as:

- DIABETIC NEPHROPATHY: MSCs and iPSCs have shown potential in repairing kidney damage by modulating inflammation and promoting tissue regeneration. Studies have reported improvements in proteinuria and glomerular function following MSC therapy in animal models[15].
- DIABETIC NEUROPATHY: Stem cell-derived exosomes have been explored for their ability to promote nerve repair, with studies showing enhanced axonal growth and improved nerve conduction velocity. This is particularly promising for patients with peripheral neuropathy, a common complication of T1DM.
- DIABETIC RETINOPATHY: MSCs have demonstrated potential in reducing retinal inflammation and preserving vision by modulating local immune responses and promoting vascular repair[17].
- CARDIOVASCULAR DISEASE: The paracrine factors released by MSCs and other stem cells can promote angiogenesis and repair ischemic damage in the heart, potentially offering a regenerative approach to diabetic cardiomyopathy[44-45].

Challenges and Future Directions:

Despite the promise of stem cell therapies, challenges remain, including the need for robust clinical trials to establish long-term safety and efficacy. The cost of manufacturing and scaling up stem cell products remains high, and regulatory hurdles add to the complexity of bringing these therapies to market. Addressing these challenges requires collaboration between researchers,

clinicians, and policymakers. Future research should focus on refining differentiation protocols, improving graft survival, and integrating stem cell therapies with other regenerative approaches. Advances in artificial intelligence and computational biology could also play a role in optimizing protocols and predicting patient responses, thus advancing the field further.

Conclusion:

Stem cell therapy holds tremendous promises for many fields in medicine especially those conditions that result in long term debilitation and complications like T1DM offering the potential for beta-cell replacement and immune modulation. Advances in gene editing and 3D bioprinting have brought us closer to developing functional insulin-producing cells and tissues devoid of the genetic lesions that generate diabetes using gene therapy methods such as CRISPR-Cas-9.

While challenges remain, the ongoing animal and human research efforts and early clinical trial results are encouraging and herald major advances. With continued innovation and collaboration, stem cell therapy could become a transformative option for patients with T1DM, addressing both the underlying autoimmune destruction and the need for insulin independence. Needless to say, the work ahead is gigantic and requires multi-specialty collaborations due to the complexity of the task.

In the past several years, stem cell therapy has been explored and its potential to cure T1DM seems closer than ever. As a source of β-cells by differentiation, and a multi-faceted immune modulator could help preserve β-cells and feeding their potential by secreting growth factors. The genetic engineering methods are also advancing our understanding on creating more stable constructs and longer lasting solutions.

Conflict of Interest:

None.

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