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Research Article

The Therapeutic Potential of Stem Cells in Diabetes Management: A Comprehensive Review

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Abstract:

Stem cells are a category of cells that facilitate the developing of organs and systems inside the body. When given particular stimuli, they may differentiate into different types of cells and have the unusual capacity to continuously self-renew. In the fields of tissue repair and regenerative medicine, stem cells are being thoroughly researched. They have enormous potential for use in congenital malformations, age-related illnesses, traumas, and neurodegenerative diseases. Furthermore, because cancer stem cells are linked to malignancies, studying stem cells is crucial for cancer research. The capacity of stem cells to differentiate into distinct cell subsets, or potency, can be used to categorize them. The aim of this research is to give an overview of adult and embryonic biology. For medical professionals working in this area, this provides an overview of stem cells and their potential therapeutic uses. Treatments based on stem cells are now a practical means of repairing damaged tissue, producing more insulin, and reducing the effects of diabetes. With an emphasis on the various types of stem cells used in diabetes treatment and the fundamental processes through which they mediate their therapeutic effects, this review explores the development of stem cell research. This study aims to give a comprehensive knowledge of stem cells' function in diabetes therapy and their potential to enhance patient outcomes in the future.

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Introduction

Diabetes mellitus is a chronic metabolic condition characterized by hyperglycemia caused by either insulin resistance or insufficient insulin production [1]. Pancreatic β-cells play an important role in maintaining blood glucose balance due to their extraordinary ability to produce and release insulin in response to changes in blood glucose levels [2]. Diabetes mellitus, a group of metabolic illnesses marked by chronically high blood glucose levels, is caused by a decrease in β-cell function. Because insulin is the only hormone capable of reducing blood glucose, its release into the bloodstream must be rigorously controlled in order to maintain glucose levels within a normal physiological range and avoid hypoglycemia or hyperglycemia. [3].

Chronic hyperglycemia caused by diabetes mellitus is one of the leading causes of chronic organ damage, including the kidneys, heart, vascular system, and eyes [4]. As the illness worsens, the amount of hyperglycemia may change. Weight loss, exercise, and oral antidiabetic medicines are common treatment options for diabetics with remaining endogenous insulin production. These therapies can have serious repercussions, including cardiovascular disease, neuropathy, nephropathy, and retinopathy [5]. Traditional therapeutic techniques, including as insulin medication and lifestyle changes, have limits, particularly in the late stages of the illness. As a result, there is increased interest in alternate techniques, such as using stem cells to treat diabetes [6].

Stem cells are undifferentiated cells that can self-renew and specialize into a wide range of cell types. A recent study found that these cells may replenish pancreatic β-cells, which create insulin in the pancreas. The application of stem cell technology to diabetes therapy is a substantial and novel advance in medical research. Offering viable treatments for reversing or controlling the condition [7]. Adult pancreatic stem cells have been difficult to identify, despite the fact that new ß-cells are produced throughout adult. Pluripotent adult stem cells' capacity to proliferate and differentiate, whether from Although being investigated, bone marrow or non-pancreatic tissue resident SP cells have not yet produced insulin-producing tissue. On the other hand, adult pancreatic tissues have been used to create insulin-producing cells in vitro. We have been studying the concept that the functional source for new ß-cells in the adult pancreas are mature duct epithelial cells that have regressed or lost their mature character after replication. [8].

Historical Background of Stem Cells

Early in the 20th century, scientists discovered undifferentiated cells with the ability to self-renew and specialize into several lineages, which gave rise to the concept of stem cells [9]. However, the full potential of stem cells was not realized until the 1960s [10]. Tests carried out in 1961 by Canadian researchers Ernest McCulloch and James Till proved the presence of hematopoietic stem cells, which may differentiate into any kind of blood cell. This discovery made it easier to investigate stem cells in regenerative medicine research [11]. the creation of induced pluripotent stem cells (iPSCs) and the identification of embryonic stem cells (ESCs) in 1981 [12]. revolutionized the field in 2006 [13]. The discovery of pluripotent stem cells in the 1990s sped up the advancement in stem cell research [14].

Human embryonic stem cells (ESCs) may develop into every type of cell in the body, as demonstrated by James Thomson and his team's successful isolation of ESCs from blastocysts in 1998. This finding sparked a great deal of interest in stem cell therapy for a variety of illnesses, including diabetes [15]. The first preclinical studies on employing ESC-derived β-cells to treat diabetes were conducted in the 2000s, marking an expansion in stem cell research. Another

significant development in stem cell research occurred in the early 2000s with the introduction of induced pluripotent stem cells (iPSCs) [16]. Human ESCs were successfully differentiated into insulin-producing cells for the first time in 2014 [17]. In the 2020s, there have been accounts of people achieving insulin independence following stem cell transplantation, and clinical studies have progressed. These adult somatic cell-derived cells are just as pluripotent as ESCs, but they don't have the moral dilemmas associated with embryonic tissue. Since then, research on stem cells has expanded dramatically, and new findings support the potential of stem cells in the treatment of diabetes [18].

Applications of Stem Cells in Medicine

The promise of stem cells in regenerative medicine, where they may be employed to repair damaged or diseased tissues, has sparked widespread attention. [19]. Their ability to differentiate into several cell types gives them promising candidates for treating a variety of ailments, including neurological disorders, heart disease, and autoimmune diseases [20]. Stem cells can help repair or replace damaged tissues. For example, stem cells may be able to help regenerate cardiac tissue that has been damaged by a heart attack [21Similarly, stem cell treatment is being investigated as a possible option for spinal cord injuries, as it has the potential to restore damaged neural cells and aid to mobility recovery. Bone marrow stem cells, a kind of adult stem cell, have been effectively employed to treat blood illnesses such as leukemia and lymphoma by stem cell transplantation. This is a long-standing technique that has saved many lives [22].

Researchers are looking at how stem cells might cure neurological disorders including Parkinson's disease and Alzheimer's disease. The aim is that stem cells will rebuild damaged neurons and restore function [23]. Scientists are exploring the possibility of using stem cells to grow entire organs for transplantation. While this is still in its early stages, progress is being made, and lab-grown tissues and organs may become a reality in the not-too-distant future [24]. Stem cells allow researchers to create disease models for testing new drugs. By generating cells that mimic diseases, scientists can more efficiently test how drugs will interact with those conditions, potentially speeding up the drug development process [25]. In the field of diabetes, stem cells hold significant promise for restoring insulin-producing β-cells within the pancreatic tissue. [26]. As the main cell type involved in insulin secretion, the regeneration of β-cells could provide a cure or significant improvement in the management of both type 1 and type 2 diabetes. Moreover, stem cells can also play a role in the immune system, offering therapeutic benefits for autoimmune related diabetes, such as type 1 diabetes. Besides diabetes, stem cells for their application in treating conditions such as Parkinson’s disease, spinal cord injuries, myocardial infarction, and liver cirrhosis. Stem cell-based medicines have shown encouraging outcomes in preclinical investigations, and several have advanced to clinical trials, demonstrating stem cells' promise as a transformational tool in modern medicine [27].

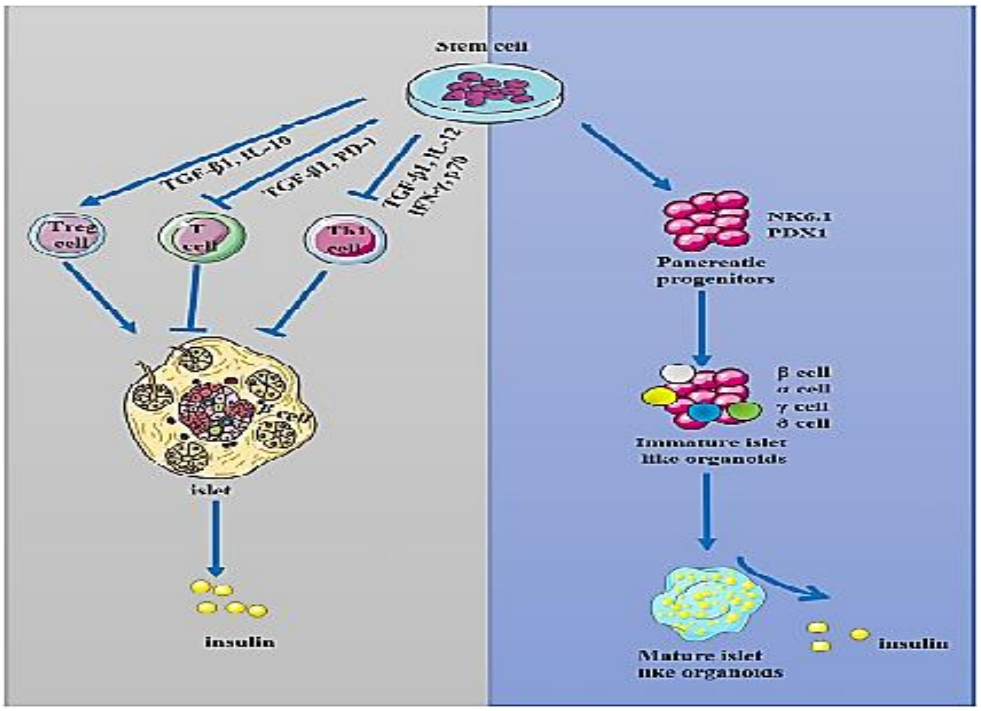

Figure 1: The potential role of stem cells in the management of diabetes mellitus is shown [28].

Types of Stem Cells Used in Diabetes Treatment

Several types of stem cell types have been explored for their therapeutic potential in addressing diabetes, which are categorized into five primary groups based on their origin, potential, and developmental stage, including:

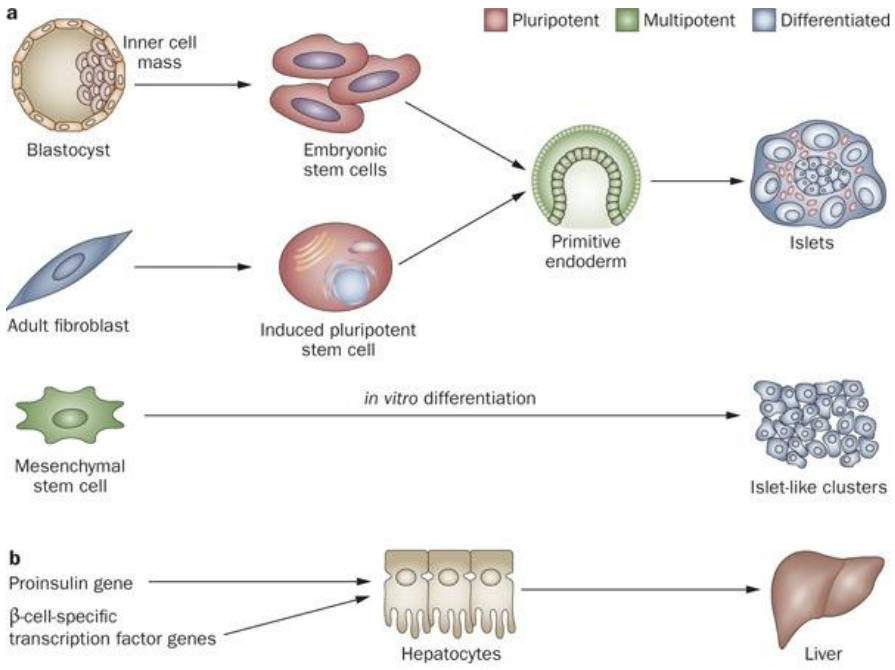

Figure 2: Stem cell and gene therapies for diabetes mellitus [29].

Embryonic Stem Cells (ESCs): These pluripotent cells originate in early-stage embryos and can develop into any cell type. ESCs are intensively explored for their potential to repair β-cells in animal models of diabetes. However, its utilization poses ethical difficulties because embryos are destroyed during the extraction process [30]. ESCs may differentiate into cells from all three germ layers and proliferate indefinitely while maintaining their pluripotency. Because human ESCs can stay in culture for extended periods of time and differentiate into any desired target cell type, they are a viable cell source for regenerative medicine to treat a range of disorders, including diabetes, Parkinson's disease, and spinal cord injury [31]. Even while ESCs may produce functioning cells and organs, transplanting them is still susceptible to allograft rejection, much like traditional donor organ transplants. Embryonic stem cells (ESCs) are pluripotent cells that may develop into any type of cell, including pancreatic endocrine β-cells, because they make up the blastocyst. The literature has published several protocols that outline the steps necessary to produce a stable somatic cell type. The use of human embryos is prohibited in many countries due to ethical concerns, which is a significant difficulty with this research line [32].

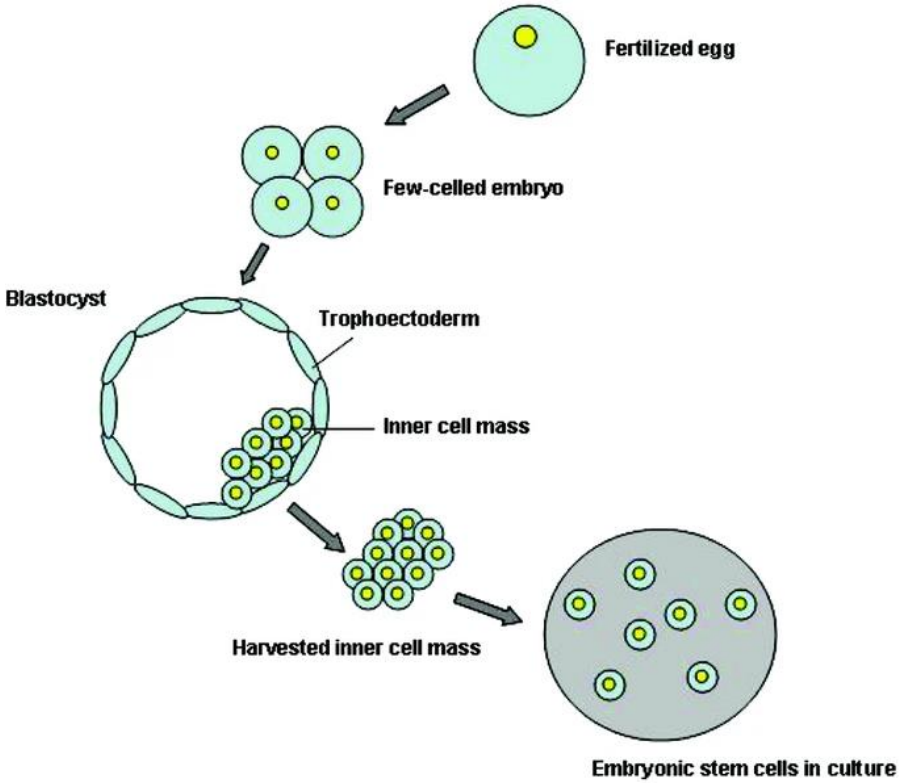

Figure 3: Generation of human embryonic stem cells [33].

Induced Pluripotent Stem Cells (iPSCs): are adult somatic cells that have been reprogrammed to exhibit characteristics similar to those of embryonic cells. Yamanaka made the initial discovery that, by starting with differentiated somatic cells (fibroblasts, blood cells, etc.) [34]. Although this approach may seem simple in theory, it is actually very complex and costly, depending on the maturation techniques. iPSCs have demonstrated great potential in generating insulin-producing β-cells and Restoring normal blood glucose levels in diabetic animal models. iPSCs are generated by reprogramming somatic cells, such peripheral blood mononuclear cells or dermal fibroblasts, into a pluripotent state by improved expression of a predetermined set of transcription factors. [35]. provides a viable alternative to ESCs due to their ability to be generated from a patient's own cells, which lowers the likelihood of immune rejection. Additionally, the intrinsic autologous property of iPSCs offers distinct immunological benefits over other cell types in the context of therapeutic applications [36].

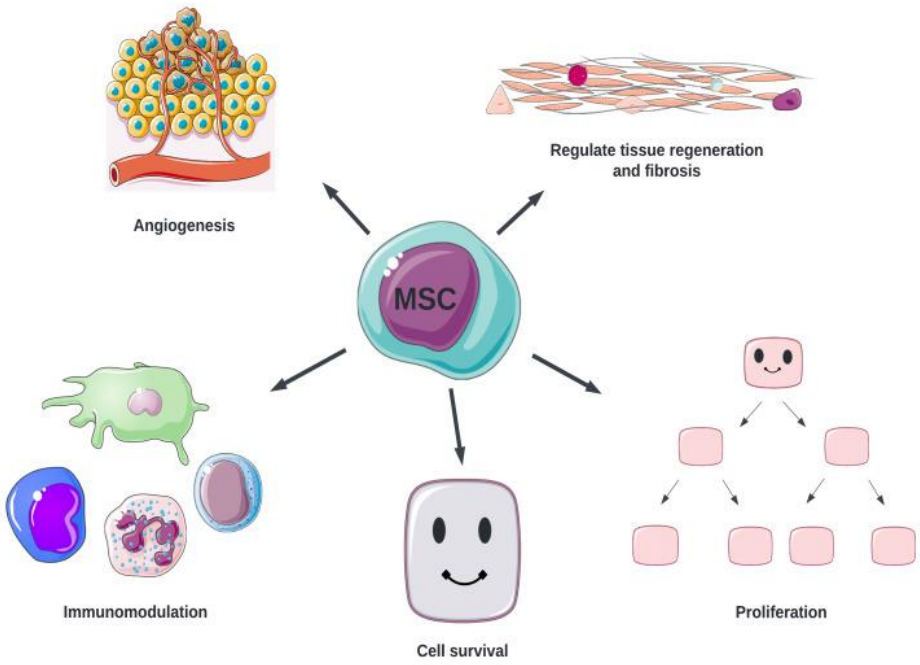

Figure 4: A variety of mechanisms has been uncovered that are involved in the regulation of T1D by MSCs [37].

Mesenchymal Stem Cells (MSCs): These multipotent stem cells, also known as stromal cells, are adult mesoderm-derived cells that can be used in nations where using ESCs is illegal. They are derived from a range of tissue sources, including bone marrow, adipose tissue, postnatal umbilical cord Wharton Jelly (WJ), the placenta, and additional sources. Although the potential for transdifferentiation into other tissue types exists across various tissues, such as bone marrow and adipose tissue, they are primarily oriented toward the generation of mesodermal tissues/organs, with a particular focus on bone, cartilage, and heart cells. They have the potential to develop into multiple cell lineages, including insulin-secreting cells. [38[. In animal models of type 2 diabetes, MSCs have been demonstrated to decrease inflammation and increase insulin sensitivity. The idea that MSCs develop into cells that produce insulin has been examined in earlier research [39]. The discovery that differentiating MSCs and the development of other cell types, such neurons, show increased production of insulin and other pancreatic transcription factors served as part of the basis for this [40]. In vitro studies of glucose-stimulated insulin secretion, as well as in vivo assessments of glucose tolerance in mice, have been employed to examine the functional capacity of insulin-producing cells derived from MSCs [41]. As an alternative to MSCs, MSC-Exos has emerged as a novel tissue regeneration technique (Figure 5).

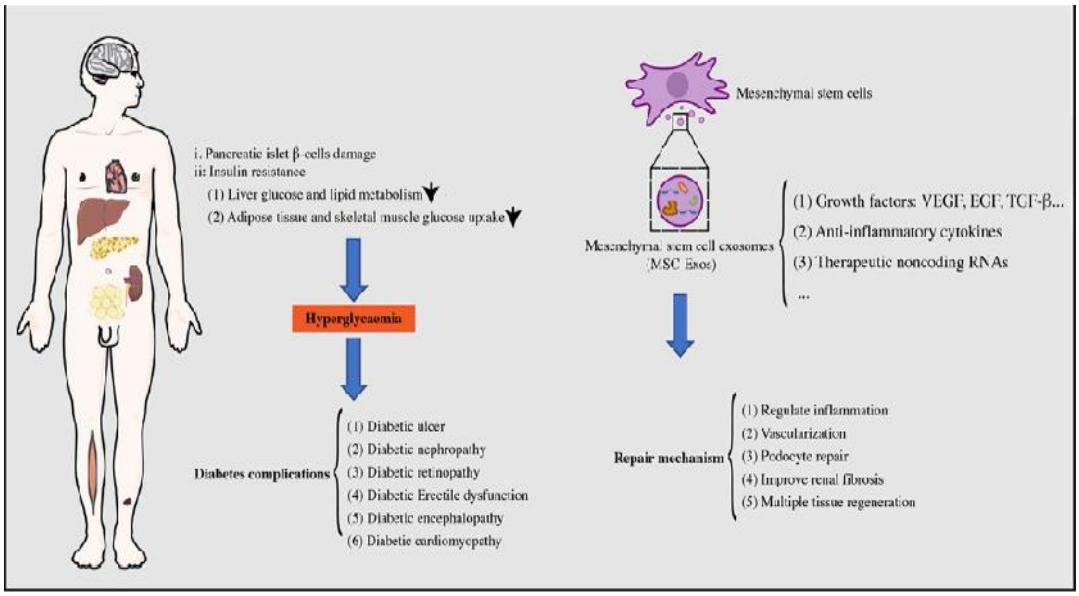

Figure 5: consequences of diabetes and the repair of mesenchymal stem cell exosomes [42].

Pancreatic Progenitor Cells: These cells are derived from the pancreas and have the ability to differentiate into insulin-producing β-cells. Researchers are investigating methods to expand and transplant these cells into The potential of human embryonic stem cells (hESCs), which are pluripotent cells extracted from the blastocyst's inner cell mass (ICM), to restore pancreatic function in diabetics is being studied [43].

They are capable of producing all three cell lineages, are genomically stable, and can self-renew. By overexpressing certain transcription factors, somatic cells can be transformed into induced pluripotent stem cells (iPSCs). There are still concerns regarding their genetic stability despite their capacity for differentiation and self-renewal [44]. hESCs and iPSCs retain pluripotency during proliferation, fulfilling the need for a limitless cell source for treatment. as a promising substitute for hESCs, their efficiency in generating mature pancreatic endocrine cells remains inferior to that achieved with hESC-derived therapies [45]. In 2015, the inaugural T1D patient in Edmonton received a transplant of hESC-based pancreatic progenitor cells. These cells are anticipated to mature into functional insulin-producing cells following transplantation, as evidenced by earlier research conducted on surrogate animal models, utilizing an encapsulation system known as PEC-Encap (VC-01) [46]. During the initial transplantation process, 40 million pancreatic progenitor cells were distributed among two subcutaneously implanted encapsulation devices in the abdomen and six smaller subcutaneously implanted devices in the arm, which served as sentinel implants to be removed at different times to evaluate cell survival and differentiation. This encapsulation technology was created to protect pancreatic progenitor cells from immune-mediated attacks, reducing both autoimmune and allogeneic reactions, and thereby eliminating the need for immunosuppressive treatment [47]. Without developing into pancreatic progenitors, the goal of deploying undifferentiated MSCs is to maintain islet survival and function (Figure 6).

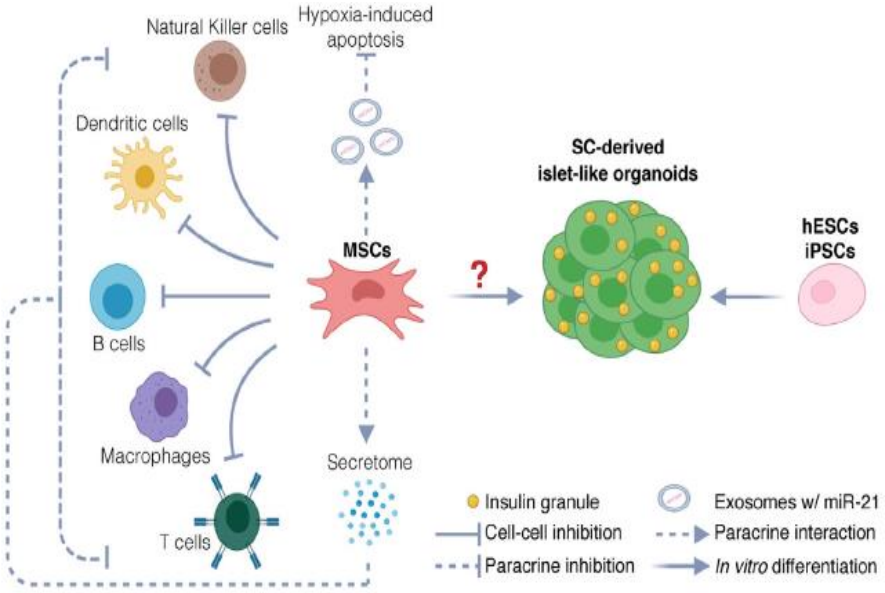

Figure 6: shows potential treatment processes. Potential pathways include endogenous islet protection and b-cell mass restoration. MSCs might preserve endogenous b cells by modulating their immune response and inhibiting hypoxia-induced death [47].

Endothelial Progenitor Cells (EPCs): These cells contribute to blood vessel formation and have been explored for their role in improving pancreatic islet function. EPCs may also promote the regeneration of damaged pancreatic vasculature, which is necessary for β-cell activity. (EPCs) are circulating bone marrow derived cells that were initially reported by Asahara et al. [48]. EPCs can migrate to areas of tissue injury or ischemia and help with wound healing, postnatal vasculogenesis, and blood vessel reendothelialization [49]. While EPCs can integrate into newly emerging vessels, their availability of humoral factors at the tissue injury site is likely more essential, as it may attract accessory cells, facilitate vascular remodeling, and trigger prosurvival responses. Bone marrow-derived endothelial progenitor cells (EPCs) have been identified as native cell populations involved in endothelial restoration and neoangiogenesis [50].

Originally separated from a subset of circulating CD34+ mononuclear cells, these EPCs exhibit the capacity to develop into endothelial cells (ECs) under in vitro conditions and incorporate into newly established vascular structures upon transplantation in ischemic animal models. Due to the limited abundance of CD34+ cells in peripheral circulation, the majority of research examining EPC functions has relied on cells generated through the culture of peripheral blood mononuclear cells in endothelial-selective media for 4–7 days. These cells, largely originating from myeloid hematopoietic lineages, were labeled as "Early EPCs," with minimal expression of stem or progenitor-cell markers [51]. Formerly classified as early EPCs, this diverse cell population, predominantly derived from myeloid hematopoietic precursors, has been demonstrated to facilitate angiogenesis and enhance vascular healing across multiple experimental settings [52].

Mechanisms of Stem Cell Action in Diabetes

Stem cells treat diabetes through numerous ways, including:

Regeneration of β-cells: Stem cells can differentiate into insulin-producing β-cells, thereby replenishing the lost or damaged β-cell population in diabetic patients. This regeneration helps restore normal insulin secretion, improving blood glucose control, In addition to IPC differentiation, By releasing growth factors and cytokines, MSCs aid in the recovery of endogenous pancreatic islet β-cells. Si et al. report that in a diabetic rat model, the infusion of MSCs led to significant regeneration of endogenous β-cells. Furthermore, increased levels of phosphorylated insulin receptor substrate 1 (IRS-1), protein kinase B (Akt), and GLUT4 in insulin-target organs demonstrated that MSC therapy markedly increased insulin sensitivity. Insulin resistance is thought to be caused by deficiencies in the expression of each of these [53].

Immune Modulation: In type 1 diabetes, an autoimmune response destroys β-cells. Stem cells, particularly MSCs, can modulate the immune system by reducing inflammation and promoting immune tolerance, thereby preventing further destruction of β-cells, MSCs have the ability to protect endogenous pancreatic islet β-cells by immunoregulation in addition to regenerating them [54]. MSCs exhibit immunoregulatory properties that include the suppression of T cell activation in response to mitogens and antigens, the inhibition of dendritic cell differentiation, and the attenuation of B cell proliferation in a dose-dependent fashion [55]. MSCs are thought to primarily exert their antidiabetic benefits through this immunomodulatory function. In people with type 1 diabetes mellitus (T1DM), MSCs may stop the autoimmune-induced death of the pancreatic β-cells that produce insulin by regulating the immune system.

Improvement of Insulin Sensitivity: Stem cells have been shown to improve insulin sensitivity in type 2 diabetes, where insulin resistance is a key feature. By promoting the regeneration of pancreatic cells and improving insulin receptor function, stem cells can enhance glucose uptake and metabolism [56].

Angiogenesis: The survival and functionality of transplanted β-cells depend on the development of new blood vessels, called angiogenesis. EPCs in particular have the ability to stimulate angiogenesis, which can improve β-cell activity and the vascularization of pancreatic islets [57].

Anti-inflammatory Effects: Diabetes, especially type 2, is characterized by chronic inflammation. By releasing anti-inflammatory cytokines, stem cells might lessen inflammation, perhaps reducing insulin resistance and enhancing metabolic processes [58].

Preclinical and Clinical Research on Stem Cell Therapy for Diabetes

Strong evidence supporting the use of stem cell treatments in the treatment of diabetes has been presented by preclinical research. It has been shown that stem cells can repair β-cells, restore insulin production, and enhance glycemic control in animal models of type 1 and type 2 diabetes. For instance, research employing ESCs and iPSCs has demonstrated notable improvements in glucose homeostasis in diabetic mice [59].

The safety and effectiveness of stem cell treatments in humans have been assessed in a number of clinical studies. Autologous MSCs have been employed in several type 2 diabetes treatments, with encouraging outcomes in terms of lowering HbA1c levels and increasing insulin sensitivity. The transplantation of β-cell precursors or pancreatic progenitor cells produced from stem cells has been the subject of several investigations. While early results are encouraging, many challenges remain in terms of cell survival, engraftment, and long-term efficacy [60].

Advantages and Challenges of Stem Cell Therapy

Advantages:

Possibility of Disease Modification: Rather than only treating the symptoms of diabetes, stem cell therapy aims to restore endogenous insulin production. Preconditioning human AD-MSCs with increasing doses of the iron chelator deferoxamine increased hypoxia-inducible factor 1 alpha levels, which in turn led to the upregulation of pro-angiogenic and neuroprotective molecules, indicating the viability of using MSCs to treat diabetic neuropathy [61].

On the other hand, Chilean study on diabetic nephropathy revealed that in low-dose STZ-induced diabetic mice, intravenously administered BM-MSCs improved insulin production, stimulated pancreatic islet regeneration, and restored normal blood glucose levels. When MSCs were administered to diabetic mice, regenerative pathways were restored, renal proliferation rates were boosted, anti-inflammatory cytokine levels were raised, and renal apoptosis and macrophage infiltration were decreased.

Regarding diabetic retinopathy, MSC treatment successfully preserved retinal ganglion cells, improving disease outcomes [62]. While lowering oxidative stress in the retina, donor cells localized to the vitreous cavity and considerably raised intraocular concentrations of important neurotrophic factors, including nerve growth factor, basic fibroblast growth factor, and glial cell line-derived neurotrophic factor, without differentiating into neural or perivascular-like phenotypes. Furthermore, in diabetic nephropathy models, MSC treatment significantly improved kidney function in diabetes-induced mice, as demonstrated by increased renal proliferative indices, decreased renal apoptotic indices, and the restoration of pro-regenerative and anti-inflammatory factors [63]. Notably, intravenous infusion of BM-MSCs had no significant impact on diabetic obesity-induced mouse models. Reduced Dependence on Exogenous Insulin: Successful stem cell treatment may remove or greatly reduce the requirement for insulin injections [64].

Challenges:

Ethical Concerns: The use of ESCs raises ethical issues, particularly related to the destruction of embryos. The use of ESCs raises ethical concerns due to their derivation from embryos, which involves destroying the embryo. This has led to debates about the moral status of embryos and whether their use in research is justifiable. The Solutions is Use of iPSCs provide an ethically superior alternative because they do not require embryos for derivation. Global Regulatory Framework: Standardizing ethical guidelines across countries for stem cell research will reduce inconsistencies and streamline research efforts [65].

Immune Rejection: Even with autologous stem cells, immune rejection remains a concern, particularly with large-scale transplantations. When stem cells are derived from donors (e.g., ESCs or iPSCs from other individuals), immune rejection is a significant concern. The immune system may recognize foreign cells as invaders, leading to their destruction unless immune suppression strategies are employed. One of the most obstacles to implementation of stem cell β-cells is the possibility in immunological rejection resulting from human leukocyte antigen (HLA) mismatch. At present, patients must rely on immunosuppressive medications to counteract allograft rejection, which may cause adverse effects varying from minor issues such as diarrhea, and acne to more critical concerns like increased susceptibility to severe infections and cancer [13]. Using patient-specific iPSC derivatives might help overcome the problem of allograft rejection and guarantee full HLA matching. However, creating such customized cells for every patient would be very expensive and resource-intensive, and it is not expected that this would be a widely used treatment for diabetes very soon. Using iPSCs produced from the patient's own cells can reduce immunological rejection, as the cells are genetically identical to the recipient.

Capsulation of Stem Cells: Encapsulating stem cells in a biocompatible material

Cell Differentiation and Integration: Ensuring that stem cells properly differentiate into functional β-cells and integrate into the pancreatic environment remains a major challenge. Risk of Tumor Formation: Pluripotent stem cells carry a risk of forming teratomas if not fully differentiated before transplantation. As a result of methodologies and technological advancements have been developed to guarantee the safe use of human ESCs and iPSCs in therapeutic contexts. For starters, transferring just developed cells can avoid cancer. Recent differentiation regimens include approaches such as endocrine cell particular to develop more mature functioning β-cells while reducing the amount of undifferentiated progenitor cells [67].

Cost and Scalability: Stem cell therapies are expensive to produce, and scaling up production for widespread clinical use presents significant logistical and economic challenges [68].

prevents direct contact with the immune system, reducing the risk of rejection [66].

Conclusion

Stem cell therapy has emerged as a highly promising approach for the treatment of diabetes, providing innovative strategies for the regeneration of insulin-producing β-cells, enhancement of insulin sensitivity, and modulation of immune responses. Despite notable advancements achieved in both preclinical studies and clinical trials, significant challenges persist concerning safety, therapeutic efficacy, and the scalability of these interventions. Continued exploration into the fields of stem cell biology, gene-editing technologies, and tissue engineering demonstrates immense potential for addressing these limitations. Such research endeavors are paving the way toward the development of curative therapies for diabetes, with the capacity to profoundly impact the lives of millions of individuals globally. As scientific understanding and technological capabilities continue to evolve, the future of stem cell-based therapies in diabetes management appears exceptionally promising.

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