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Review

Stem Cell Therapy for Diabetes Treatment

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ABSTRACT

Diabetes mellitus (DM) is a widespread metabolic disease characterized by the disruption of blood glucose regulation, primarily caused by dysfunctional pancreatic beta (β)-cells. For the repair of β-cells, alternative approaches such as embryonic stem cells, mesenchymal stem cells, and induced pluripotent stem cells (iPSCs) are on the agenda due to the limitations of factors such as donor deficiency in islet cell transplantation treatment. It is aimed to produce real β-cells with the contributions of stem cell-based clinical studies conducted in recent years. In this chapter, stem cell transplantation is considered an alternative stem cell-based therapy in diabetes for insulin independence through various means such as β-cell differentiation and β-cell repair. Current and traditional treatment methods applied in Type 1 diabetes and Type 2 diabetes are not sufficient to prevent the devastating damage of microvascular and macrovascular complications. For this reason, promising stem cell approaches have been discussed in DM as well as its complications. This chapter focuses on the curative potential of cells with excellent differentiation ability, such as embryonic, adult, and iPSCs, in DM and its complications, which despite the discovery of insulin remain fatal.

Keywords: Beta cells, diabetes mellitus, stem cells, stem cell therapy, embryonic stem cell.

Glucose in the blood is regulated by beta (β)-cells secreted by the pancreas. Insulin plays a crucial role as a primary regulator of homeostasis since no other hormone is capable of reducing blood glucose levels. Diabetes mellitus (DM) is characterized by β-cell function loss, which leads to elevated blood glucose levels. The insulin-releasing pancreatic β-cells are destroyed or rendered ineffective, leading to DM. It is a metabolic condition that has spread worldwide. According to projections, it is estimated to reach 552 million cases in 2030.[1] There are two primary types: type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). The pathophysiology of T2DM comprises the development of resistance in insulin target tissues followed by β-cell malfunction due to a mix of genetic and environmental factors, in contrast to T1DM, which is defined by β-cell death leading to autoimmune dysfunction.[2] Monogenic diabetes, a less frequent form of the disease, is caused by a particular gene mutation that affects pancreas development and β-cell function.[3]

The literature demonstrates the availability of a range of therapeutic strategies for the management of diabetes. The most popular techniques include diet restriction, oral antidiabetic drugs, and insulin.[4-6]

One promising treatment is the exchange of β-cells via transplantation of islets of Langerhans, yet unfortunately, the lack of donors is the primary cause of its underuse. For this approach, human pluripotent stem cells (PSCs), such as embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), are a crucial supply of β-cells. With further studies, we have come remarkably close to the original form. However, the challenges of producing a fully mature β-cell remain.[7] This has the potential to be a real cure for T1DM and possibly T2DM and MD. Islet cell transplantation (ICT) has been associated with less progression of microvascular complications such as diabetic nephropathy (DNP), diabetic neuropathy (DN), diabetic retinopathy (DR), and others.[8] In different research with a three-year follow-up, ICT was superior

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to intensive medical therapy in terms of improving hemoglobin A1c and slowing the progression of DR.[9] Despite its ability to save lives, insulin often does not halt the development of end-stage microvascular complications in patients, thus, patients still face diabetes fatal consequences despite the development of insulin. Stem cell-based alternative therapy has eventually become a candidate for high interest over injected insulin as an important approach for diabetes treatment. Nonetheless, further research is needed to overcome various clinical challenges, such as donor shortages, and to determine its feasibility.

THE RELATIONSHIP BETWEEN STEM CELLS AND DIABETES

Transplantation of insulin-producing cells has enabled stem cell repair of pancreatic β-cells.[10,11] Under the normal conditions and signaling, stem cells have the astounding ability to self-renew and differentiate into specialized cells such as lymphocytes, hepatocytes, leukocytes, erythrocytes, myocytes, nerve cells, and muscle cells.[12]

As cell sources, stem cells are typically classified as ESCs or adult stem cells (ASCs). While ASCs are rare stem cells found in almost all major organs that are referred to as multipotent cells due to their limited ability to differentiate, ESCs -also known as PSCs- on the other hand, are differentiated from the embryo's inner cell mass and have the ability to differentiate into various germ cell line.[13]

Adult stem cells are commonly found in medical applications. For instance, for the successful treatment of leukemia and other hematological tumors, bone marrow transplantation employs hematopoietic stem cells (HSCs) from donor marrow. In a similar manner to HCSs, ASCs not only can multiply but also differentiate into various blood cells, whereas mesenchymal stem cells (MSCs) promote the formation of fat, bone, and cartilage.[14,15] In recent years, remarkable progress has been made in the generation of functional β-cells from human stem cell populations. This strategy describes the path that PSCs take during embryogenesis, from definitive endoderm formation to pancreatic endoderm, endocrine progenitors, and ultimately islets of Langerhans.

Ethical concerns make investigating the prospect of regenerating insulin-secreting cells problematic.[16-18]

Scientists are attempting to employ several types of stem cells to treat a wide range of medical ailments.[19] Despite these advances, more than 400 million people with diabetes worldwide continue to suffer from catastrophic consequences such as DNP, DN, and DR.[20]

Diabetes occurs when the pancreatic cells responsible for insulin secretion become dysfunctional or produce insufficient insulin, the body does not respond to the produced insulin, and glucose builds up in the blood. As a result of this inability to manage glucose, diabetes-related micro-, and macrovascular effects occur. Thirst, polyphagia, weight changes, polyuria, and blurred vision are common symptoms of diabetes. In advanced cases, hyperglycemia with ketoacidosis is likely to occur.[21-24]

PLURIPOTENT STEM CELLS AND DIABETES

Scientists highly value the pluripotent state of ESCs, and it is for that, that they are being studied for their use in a variety of medical conditions, including diabetes.[25] Through differentiation and established development, ESCs are viewed as a great source for the production of islet cells capable of producing insulin. Although challenging when considered, it is possible that ESCs might be made to differentiate into pancreatic islet cells, which then could be transplanted into the area of concern in diabetic patients, thus preventing β-cell deficiency. In the past, mouse ESCs (mESCs) have been used for this approach. Researchers have generated replicas from genetically altered and drug-selected mESCs that can secrete insulin. Following monitoring, these cells were implanted into diabetic mice and improved hyperglycemia.[26–31] Aside from mESCs, another group utilized human ESCs (hESCs) for the same purpose.[32,33]

Cells co-expressing pancreatic and duodenal homeobox 1 (PDX1) and NK6 homeobox protein 1 (NKX6.1) in the developing human embryo show multipotent pancreatic bud and stem progenitors that subsequently produce insulin-secreting β-cells.[34]

Key transcription factors (TFs) are highly expressed in pancreatic progenitor cells and β-cells involved in insulin secretion. Co-expression of PDX1 and NKX6.1 has been shown to be essential for the production of mono-hormonal, glucose-sensitive β-cells.[35,36]

Specifically, NKX6.1 is a crucial marker regulating β-cell maturation and functionality.[35,37] Researchers have reported varying degrees of success with regard to ESCs and islet generation. As a result, many issues have been encountered, including cell homogeneity,

immaturity of differentiated cells, low numbers of cells that produce insulin, and inadequate insulin sensitivity to glucose.[30,32,33,38,39] On the other hand, as neither C-peptide nor intracellular insulin is produced after the cells are cultivated in an insulin-free medium, several research groups claim that these cells are not insulin-producing cells at all.[40-42]

The first cell line to be used for *in vitro* produce β-cells were ESC cells. A procedure has been created by one group to transform mESCs into definitive, completely pure, endodermal cell lines.[16] It demonstrated the production of pancreatic endocrine hormone-producing cells containing insulin and C-peptide.[43] As a result, they were able to produce insulin from these cells in the human islet interval, yet were unable to produce it in response to glucose. Later on, this response was achieved by a different group. Pluripotent stem cells have been proven to have drawbacks, including a significant risk of tumorigenesis, immunological rejection, and ethical controversies.[18,44-46] These considerations explain the reason why the clinical use of ESCs is still unclear. Numerous molecular similarities are shared between iPSCs and ESCs. Therefore, by obtaining specific iPSCs from diabetics, the ethical and immunological rejection concerns and moral questions associated with ESC transplantation have not emerged.[47-54] These findings might make iPSCs a promising choice for cellular replacement therapy in T1DM in the future.

STEM CELL TREATMENT FOR T2DM

Type 2 diabetes mellitus is characterized by insulin resistance and reduced insulin secretion. Treatment includes diet, oral antidiabetics, and the use of external insulin.[55-64] Patients with T2DM who regularly take insulin eventually acquire insulin resistance, and existing therapies do not completely solve this issue.[65] Although transplanting pancreatic islet cells is seen to be a viable strategy, obstacles like a paucity of donors and ethical concerns have limited its use. In order to increase the lowered insulin levels in patients, stem cells such BMSCs, ADSCs, ESCs, and iPSCs can develop into beta- and comparable cells capable of producing insulin.[45,66]

Patients with T2DM who received a combination of intrapancreatic bone marrow infusion and hyperbaric oxygen therapy experienced improvements in glycemic control and C-peptide levels as well as a reduction in their need for insulin.[67] After receiving a BMSCs injection, T2DM patients improved in the same way.[68]

In rats with high-fat diet-induced T2DM, BM-MSC transplantation activated insulin receptor substrate, and reduced hyperglycemia. It was discovered that glucose transporter type 4 (GLUT4) translocation and expression had increased.[69]

Mesenchymal stem cells have demonstrated therapeutic effects on islet cell recovery and glycemic control in animal models. Clinical practice has been affected by these findings. The literature contains clinical research on MSC therapy in T2DM patients.[70-78] Nevertheless, there is still a long way to go for a definitive and routine approach to stem cell-based treatment of T2DM.

Recent research has demonstrated that VEGF is crucial to the development of vascular damage in DR and has suggested that blocking VEGF is a useful strategy for managing the condition. The reduction of VEGF production by MSC injection in a hypoxic environment by the reductase enzyme inhibitor atorvastatin has been proven.[79-85] Moreover, studies indicate that BM-HSCs provide better visual activity.[86]

Epithelial progenitor cells (EPCs) generated from mouse BM-MSCs and human MSCs have been demonstrated in animal models to stimulate neovascularization and enhance DR.[87-89]

Patients with T1DM and T2DM may develop foot ulcers and require amputations as a result of DN, one of the most prevalent consequences of DM. When hyperglycemia rises over time, DN develops into a chronic condition.[90,91] Among the reasons linked to the occurrence of DN are dysregulated glucose levels, metabolic variables, oxidative stress, elevated glycolysis hemoglobin levels, and poor blood velocity due to free radical buildup.[91,92] Besides, prolonged elevated blood glucose levels also promote the creation of advanced glycation end products (AGEs), which, after binding to their receptors, start an inflammatory reaction and enhance oxidative stress, which further causes Schwann cells to deteriorate. Subsequently, any oxidation-mediated loss of function in these cells, which govern nerve regeneration as well as neuron insulation, increases DN in diabetes patients.[93-98]

Diabetic nephropathy, a microvascular complication of DM, is one of the most common causes of end-stage chronic kidney disease and is associated with high mortality.[99-101] Matrix molecule-producing podocytes in the glomerular basal membrane are damaged in DNP, resulting in proteinuria, fibrosis, and renal failure. Self-regeneration of damaged

podocytes is limited, and the proteinuria condition worsens due to the negative effect on the glomerular barrier.[102]

Proteinuria, fibrosis, and dysfunction of proximal tubular epithelial cells (PTECs) together with increased tubulointerstitial inflammation are all signs of decreased renal function.[103] The negative features of PTECs, such as inflammation, are increased by prolonged hyperglycemia, AGEs, and glycated albumin.[104]

The renin-angiotensin system activation, synthesis of different growth factors, and excessive cytokine production are only a few of the several routes whereby AGEs are hypothesized to be implicated in the pathophysiology of DNP.[105] By preventing the production of pro-inflammatory cytokines, blocking inducible nitric oxide synthase, and encouraging parenchymal cell proliferation, MSCs can improve renal healing.[106,107] To simulate DNP characteristics, iPSCs were developed into podocytes in many studies.[108,109]

The paracrine action of renal trophic factors released by MSCs in DNP was the subject of one investigation. Animals with diabetes brought on by a high-fat diet and streptozotocin received MSCs. It was found that both therapies had ameliorative effects.[110] A significant decrease in blood glucose levels was observed in MSC-treated diabetic mice. Furthermore, albuminuria was reduced, and glomeruli were histologically normal in these animals. On the other hand, in diabetic mice without MSC treatment, glomerular enlargement was found to be present. Thus, MSC administration appeared to prevent the regeneration of beta-pancreatic islets and kidney damage in diabetic animals. According to the results of the study, MSC transplantation is recommended as a treatment for T1DM.[111] In addition to that, by reducing podocyte loss and promoting the release of bone morphogenetic protein-7, MSCs reduced fibrosis and glomerulosclerosis. They thereby contributed to the regeneration and protection of DNP.[112]

The injection of BM-MSC enhanced renal function and controlled the levels of insulin, heme oxygenase-1, AGEs, and glucose in the blood.[113] The results of the research show that stem cell-based treatments, such as MSCs, are successful in treating DNP, despite their limitations due to the consequences mentioned previously.

POTENTIAL OF STEM CELLS: THEIR IMPACT ON MACROVASCULAR AND BEYOND

Atherosclerosis is a macrovascular condition that is common in DM patients. Stroke, myocardial infarction, and vascular disease are among the risks that have been linked to persistently elevated blood sugar levels.[114,115] Depletion EPCs and the presence of cells like CD133 and CD34 are reliable indicators of arterial disease. Moreover, reduced EPC numbers have been identified as a potential new indicator of peripheral artery disease in DM.[116–118]

Vascular stem cells, which may identify EPCs, are being researched as a potential therapy for the macrovascular problems of diabetes. In one study, it was demonstrated that vascular progenitor cells developed from human vascular smooth muscle cells into vascular networks.[119] *In vivo* testing of EPCs' capacity to create vascular networks was successful. The same CD133+ subset from which mesenchymal progenitor cells (MPCs) are produced may also be a candidate for this vascular job.[120,121] Intravenous injection of MPCs slowed cardiac remodeling and enhanced myocardial function in a diabetic animal investigation employing a cardiomyopathy model, with a substantial increase in matrix metalloproteinase (MMP)-2 activity and a decrease in MMP-9.[122]

Considering in terms of long-term implications in DM, chronic hyperglycemia is known to cause endothelial dysfunction, subsequently causing issues including vascular network damage in the target organs. The ability of progenitor cells from diabetic animals to restore vascular homeostasis has been demonstrated in various experiments.[123,124] This finding implies that the number of stem cells decreases with the formation of a deficit of major stem cells in diabetes. The use of these formerly mentioned two stem cells to correct vascular dysfunction and restore vascular function still requires further research before a clear prescription can be made. Nonetheless, the use of stem cells to treat macrovascular problems appears promising.

In conclusion, diabetes is a metabolic condition that is widespread across the world. Due to damage to the pancreas' β-cells, it is characterized by insulin loss and impaired insulin sensitivity. Diabetes and its consequences continue to endanger human life despite the discovery of insulin. Although ICT has been tested by researchers as an alternate therapy, the lack of donors still poses problems in practice. Furthermore, the first stem cells employed in the stem

cell strategy for diabetes were ESCs. Yet, iPSCs have emerged as a substitute due to issues including tumor risk as well as ethical questions. Mesenchymal stem cells and BM-HSCs have also been alternative sources for β-cells. Induced pluripotent stem cells regulate glucose by developing into beta-cell-like cells, according to animal model research. We covered the microvascular and macrovascular effects of diabetes in this chapter, as well as prospective therapeutic strategies using the current stem cell paradigm. Mesenchymal and HSCs have been demonstrated to aid in retinal healing in DR by differentiating into ocular cells. Similarly, stem cell applications for DNP, DR, and atherogenic illnesses brought on by endothelial dysfunction caused by diabetes are being studied. Given intercellular communication, heterogeneity, tumor risk, and ethical considerations, cells with this remarkable capacity for differentiation are likely candidates to be used in the development of future standard operating procedures to treat diabetes and its complications by substituting insulin, which has no lasting effects.

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