

## REVIEW ON STEM CELL THERAPY AS A INITIATIVE TOWARDS DIABETES MELLITUS

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### **ABSTRACT**

Diabetes mellitus affects millions of people worldwide, and is associated with serious complications that affect nearly all body systems. Because of the severity of this global health concern, there is a great deal of research being performed on alternative treatments and possible cures. Previous treatments for diabetes have included exogenous insulin injection and pancreatic islet transplantations. These treatment methods have several limitations; thus, the use of stem cells in treating diabetes is currently a significant area of research. This review outlines current research on stem cell therapy for diabetes mellitus. Numerous studies have been performed on animals using various types of stem cells, including mesenchymal stem cells and

embryonic stem cells. Moreover, results and limitations of animal studies have been confirmed in various clinical trials. Overall, stem cell treatment shows prospective advantages over insulin injections and other current treatment options, and ongoing clinical trials suggest that this therapy may be a viable treatment option for diabetics in the near future.

**KEYWORDS:** Diabetes, islets cells, embryonic stem cells, induced pluripotent stem cells, mesenchymal stem cells.

### **INTRODUCTION**

Diabetes mellitus is a group of glucose metabolism disorders characterized by high levels of blood glucose. The disease affects nearly 350 million people worldwide; this number is constantly increasing, and is expected to grow tremendously in the future. Various categories of diabetes exist: type 1 diabetes is an autoimmune disease in which the body's immune cells

attack and damage insulin-producing  $\beta$  cells in the islets of Langerhans of the pancreas, resulting in insulin secretion deficiency. Type 2 diabetes is characterized by insulin resistance at the receptor level and by hyperinsulinemia. Many obese patients are at risk for type 2 diabetes, as massive secretions of insulin not only increase insulin resistance, but also impair the  $\beta$  cell's insulin-secreting function.<sup>[1, 2]</sup>

The long-term hyperglycemia associated with diabetes has severe implications, including blood vessel and nervous system damage, vision complications, cardiovascular disease, and infection.<sup>[3,4]</sup> Considering the serious complications and enormous associated costs of diabetes, researchers are investigating possible cures.<sup>[5]</sup> Stem cells are able to replace damaged cells in the body; therefore, they offer a promising treatment to replace the non-functional insulin-producing  $\beta$  cells of the pancreas.<sup>[2, 6]</sup> The purpose of this review is to further explore the current progress of stem cell- derived  $\beta$  cells as a treatment and cure for diabetes mellitus. Though exogenous insulin therapy, the current treatment for hyperglycemia in diabetics allows patients a degree of control over their blood sugar levels, many diabetics experience the numerous complications of protein glycosylation due to chronically elevated glucose levels. Constant control over insulin administration is critical, as insulin overdose causes hypoglycemia and coma in severe cases, while insulin insufficiency leads to the damaging effects of hyperglycemia in essentially every system of the body. It is clear, therefore, that this standard therapy for diabetics fails to mimic the insulin secretion of healthy  $\beta$  cells. Hence, exogenous insulin is life saving, but not curative.<sup>[5, 7]</sup>

## ISLETS CELLS

Islets obtained from the cadavers, foetal tissue or from xeno-source: Success of Edmonton protocol.<sup>[8]</sup> Provided the proof of concept for cellular therapy to treat T1DM and current status was reviewed recently.<sup>[9,10]</sup> Islets isolated from cadavers infused in immuno-suppressed patients with diabetes through the portal vein resulted in quick and sustained insulin production.<sup>[8]</sup> However, need for alternative source of regulated insulin release is acutely felt due to scarcity of cadaveric islets. Use of foetal islets or those obtained from pigs have associated ethical and immunological concerns. In addition, use of pigs as a source of islets has associated issues like zoonoses.

### Stem cells as a source of islets

Use of stem cells including pluripotent stem cells (PSCs), multi potent adult stem cells and progenitors holds lot of promise to treat a variety of diseases. Use of medicines and

antibiotics can cure a disease whereas stem cells may be able to replace diseased cells with healthy cells and as a result the patient becomes free of the disease. Both pluripotent and adult stem cells have been used as a source for pancreatic islets. Approval given by USFDA to study the efficacy and safety of embryonic stem cells derived pancreatic progenitors in T1DM patients is a major step in the field.<sup>[11]</sup>

#### **Alternative sources of islets cells**

Due to the shortage of the donor of the islet cells there was the search for alternative sources. Several sources are suggested:

- From pigs
- Induction from human pancreatic duct cells
- Fetal pancreatic stem cells
- Induction of insulin producing B cells and each one has its own benefits and downsides.

#### **EMBRYONIC AND INDUCED PLURIPOTENT STEM CELLS**

It has already been shown that human embryonic stem cells (ESCs) can be directed to become fully mature beta cells. This feat was accomplished by Novocell, Inc. (now ViaCyte, Inc.) by exploiting what was known about embryonic development and progress made with mouse ESCs.<sup>[12]</sup> A stepwise approach was used to direct human ESCs towards islet cells, in which culture conditions were coupled with sequential addition of growth and differentiation factors that were able to drive ESC differentiation to definitive endoderm, gut-tube endoderm, pancreas and then islet cells. It was possible to generate cells in vitro that had characteristics of islet cells but were not fully mature. However, after immature precursor cells were transplanted into immunodeficient mice, maturation progressed to produce beta cells that were convincingly normal with regard to multiple characteristics. Importantly, these cells could make and store fully formed insulin, release insulin in response to a glucose stimulation, and could cure diabetes in mice. However, much further research is needed before this advance can be brought to clinical application. For example, there is concern that these populations of precursor cells might contain cells that will form teratomas. A current strategy involves transplanting cells within a planar macroencapsulation immunoprotective device that is transplanted under the skin.<sup>[13]</sup> In addition, investigators are working to obtain full maturation invitro. To find better ways to direct the development of ESCs into mature beta cells, there has been some success using a high-throughput screening approach to identify compounds that promote differentiation.<sup>[14]</sup>

Efforts to direct the differentiation of iPS cells to mature islet cells are also progressing but have not yet had the success of ESCs.<sup>[15]</sup> There are concerns about the epigenetic changes in these cells and this is undergoing intense investigation. For example, there are now genome-wide reference maps of DNA methylation and gene expression for 20 human ESC lines and 12 human iPS cell lines.<sup>[16]</sup> Such analyses make it possible to better understand the uniqueness of individual cell lines. Similar genome-wide mapping of epigenetic marks has been carried out in mouse ESCs.<sup>[17]</sup> Studies also indicate that microRNAs promise to play important roles for understanding iPS cells, as evidenced by the demonstration that knockdown of three microRNAs interfered with reprogramming efficiency.<sup>[18]</sup>

There are many practical issues about preparing beta cells from individuals using iPS cell technology, but at some point it should be possible to produce these at a reasonable cost. One major advantage for such generated beta cells is that they would not be faced with allojection. However, in the case of type 1 diabetes, these cells would be targets for autoimmunity and it would be necessary to develop strategies to resist this immune assault. For type 2 diabetes, these cells could be transplanted into a variety of locations without concern about immune rejection.

### **MESENCHYMAL STEM CELL THERAPY**

Stem Cell therapy provide handsome alternative to islet cell transplantation in type 2 diabetic patients. Mesenchymal stem cell therapy is best among autologous adult stem cells. Mesenchymal stem cells are less pluripotent than embryonic stem cells it renders the efficiency of MSCs to be differentiated into insulin secreting stem cells. Moreover, MSCs can be isolated different sources like umbilical cord, bone marrow and pancreatic stroma. MSCs can be obtained from the patient for autologous transplant. This of course can also be the case for ESCs if reproductive cloning techniques are followed; however, autologous MSCs from diabetic patients are still remarkably different from ESCs, because of prolonged exposure to hyperglycemia. Studies in transgenic mice showed that stem cells engineered to produce insulin did much more efficiently in hyperglycemic environment. MSCs are niche cells. Their traditional role in the bone marrow is the formation of the stroma and facilitation of growth, differentiation, and engraftment of HSCs. Islets derived from human fetal pancreatic progenitor cells From 10 to 12 weeks post conception pancreas is composed of many tube like structures that are confined within loose mesenchymal.

## CONCLUSION

Both type 1 and type 2 diabetes are among the most amenable diseases for treatment. Functional restoration of existing  $\beta$ -cells, transplantation of stem cells or stem cell-derived  $\beta$ -like cells might provide new opportunities for treatment. However, the use of stem cells to generate a renewable source of  $\beta$ -cells for diabetes treatment remains challenging, largely due to safety concerns. Current differentiation protocols that use viral vectors to generate induced  $\beta$ -cells result in low numbers of functional  $\beta$ -cells, and possible unexpected genetic modifications. While BMSC transplantation could improve metabolic variables with no obvious side effects, Tang reported that long-term culture of human BMSCs raises the risk of malignant transformation post transplantation.<sup>[19]</sup> Safety issues, including sources of cells, must be carefully evaluated before clinical applications. The definition of stem cells depends on the cell surface markers, and their efficiency of differentiation greatly relies on the purity of cell source sorted by cell surface markers. Reports suggest that approximately 100,000 cells are needed for each recipient, but a low differentiation rate necessitate longer time in in vitro culture to develop adequate numbers of cells for transplantation. However, the longer culture time can increase the possibility of malignancy. Indeed, new technologies to improve differentiation efficiency are essential. Monitoring clinical trials closely will be key. Development of a transplant registry in combination with assessment and optimization of clinical protocols will help identify optimal cell types and cell surface markers for characterization, and may ultimately lead to safe, effective treatments.

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