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Stem Cell Therapy in Diabetes Mellitus

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Abstract

The loss of pancreatic cells characterizes type 1 diabetes mellitus (T1DM), the most prevalent chronic autoimmune illness in young individuals. As a result, the body lacks insulin and becomes hyperglycemic. Exogenous insulin cannot replace the endogenous insulin secreted by a healthy pancreas through administration or injection. For restoring the normal regulation of blood glucose in T1DM patients, pancreas and islet transplantation have shown promise. The broad use of these techniques is hindered by a significant shortage of pancreases and islets obtained from human organ donors, transplantation-related difficulties, a high cost, and limited procedural accessibility. There have been initiatives to handle the rising number of T1DM patients. With stem cell therapy, T1DM patients have a high probability of recovery. There have been advancements in stem cell-based therapies for T1DM with the development of research on stem cell treatment for a variety of disorders.

Keywords: *type 1 diabetes, stem cells, pancreatic beta-cells.*

Introduction

A series of long-term metabolic diseases known as diabetes mellitus (DM) are defined by hyperglycemia brought on by insufficient or resistant insulin production. Type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes, and monogenic diabetes are the four primary subtypes of DM. Due to the complete insufficiency of endogenous insulin brought on by the autoimmune death of pancreatic cells, patients with T1DM require daily insulin injections. Thus, insulin-dependent DM is another name for type 1 diabetes. Patients with type 2 diabetes who are not responding well to oral medicines may require exogenous insulin injections. Without proper care, diabetes can lead to several complications. Hypoglycemia, diabetic ketoacidosis, or hyperosmolar nonketotic coma are examples of acute consequences (HHNC). Cardiovascular disease, diabetic nephropathy, and diabetic retinopathy are examples of long-term consequences [1]. Drugs and exogenous insulin delivery can treat hyperglycemia, but they are unable to physiologically control blood sugar levels. In order to effectively cure diabetes, patients' insulin production and glucose-dependent insulin secretion control should both be restored (Fig. 1). For T1DM patients with inadequate glycemic control, clinical pancreas or islet transplantation has been suggested as a viable therapeutic alternative. However, a significant obstacle to clinical islet transplantation continues to be the global paucity of pancreas donors. Since human pluripotent stem cells (hPSCs) were expected to be used in regenerative medicine, extensive research was done on the in vitro creation of IPCs or islet organoids. Human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs), adult stem cells, and differentiated cells from mature tissues that can be transdifferentiated into IPCs are the main sources for the production of IPCs or islet organoids in vitro.

General Overview

Type 1 diabetes (T1D) is characterised primarily by the pathological loss of insulin-producing cells [2, 3]. Multiple daily exogenous insulin injections or continuous insulin infusion through a pump can lower blood glucose levels. Exogenous insulin cannot control hepatic glucose levels because it does not pass into the liver, which causes unstable glycemic

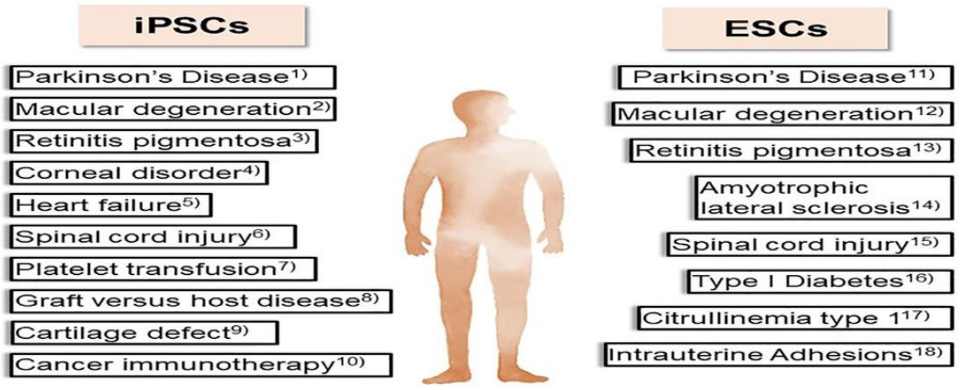

Fig 1: Clinical Trials for Cell Therapies Using PSCs Shownare clinical trials that use hiPSC or hESC and are found in UMIN Clinical Trials Registry (https://www.umin.ac.jp/ctr/index.htm) or ClinicalTrials.gov (https://clinicaltrials.gov/ct2/home) as of September, 2020

control in T1D patients [4]. In T1D patients, poor glycemic management results in long-term problems. To compensate for cell function and regulate blood glucose levels, sensor-augmented insulin pump therapy and pancreas or islet transplantation therapy may be effective options [5]. Although a pancreas transplant offers a high rate of blood glucose homeostasis and insulin withdrawal, it necessitates a technically challenging procedure and may result in a number of postoperative problems, including portal vein thrombosis [6]. The quality of life is also improved by pancreas transplantation, although there are few available donors and immunosuppressive medication is necessary [7]. According to reports, T1D patients who received islet transplants from brain-dead donors together with steroid-free immunosuppressive therapy were able to stop taking insulin [8]. Islet transplantation appears to reduce hypoglycemia episodes and improve glycemic control in T1D patients when compared to insulin injection therapy [9]. Compared to pancreatic transplantation, islet transplantation carries a decreased risk of surgical complications, although multiple transplantations are sometimes necessary to permit discontinuation of insulin therapy [10]. Thus, the lack of available donors, immunosuppressive medication, and graft rejection are issues with both pancreatic and islet transplantation. A therapeutic approach for creating pancreatic islet-like cells from human pluripotent stem cells (hPSCs), including induced pluripotent stem cells (iPSCs) or embryonic stem cells (ESCs), and using them for transplantation can be taken into consideration as a way to deal with the donor shortage. Over the past 15 years, basic techniques for causing human stem cells to differentiate into pancreatic endocrine cells, which are produced during embryogenesis from the conversion of definitive endoderm to pancreatic endoderm, have been established. This has allowed a yield of 20–40% insulin-positive pancreatic islet-like cells [11–16]. Co-culture models, such as the co-culture of islet cells and endothelial cells, should be taken into consideration since islet cells have a three-dimensional (3D) shape and interact with surrounding cells in vivo [17–19]. Pseudo-islets, which are made up of PP, PP, PP, and PP cells, are artificial pancreatic islets that have been created in vitro using a variety of techniques [20, 21]. To make it easier to identify cells that make insulin, Micallef et al. created a human embryonic stem cell reporter that encodes green fluorescent protein (GFP) at the INS locus [22]. Islet organoids created from human pluripotent stem cells (hPSCs) are depicted in Figure 1. In diabetic animals, the transplantation of pseudo-islets produced from stem cells may enhance insulin secretion [23]. It is still not entirely known, nevertheless, how the immune response and modifications to cell function develop after the transplantation of islet cells produced from stem cells. Additionally, the affordability of stem cell therapy for beta cells or pseudo-islets in comparison to traditional diabetic treatment must be taken into account.

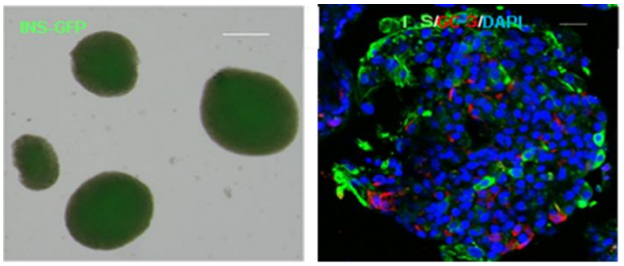

Figure 2: Pancreatic islets made from human pluripotent stem cells (hPSCs). Live-cell imaging of pancreatic islet organoids produced from hPSCs (left) and immunofluorescence (right). The insulin promoter controls the expression of GFP. Antibodies to DAPI, glucagon, and insulin are used to stain cells (blue). 20 m is represented by the scale bars in both panels.

Autoimmune Responses in Stem Cell Therapy for T1D

Autologous transplantation of pancreatic islet-like cells derived from human pluripotent stem cells (hPSCs) has the potential to control blood sugar

levels without the risk of immunological rejection. Due to the fact that the iPSCs were generated by the patients themselves, it is believed that autologous transplantation of iPSCs does not result in graft rejection. In actuality, autologous transplantation of skin, bone marrow, endothelium, or neuronal cells produced from mouse iPSCs or monkey iPSCs did not elicit immunological responses [24–26]. The autologous transplantation of mouse iPSC-derived teratoma into the subcutaneous region revealed graft rejection, according to Zhao et al. [27]. According to this study, iPSC differentiation could lead to aberrant gene expression that could lead to a T-cell-dependent immunological response upon autologous transplantation. T1D recipients may experience an autoimmune reaction from autoreactive T cells to transplanted islet cells. This chapter will go over possible autoimmune reactions that can happen when islet-like cells produced from stem cells are transplanted (SC-islets). In diabetic mice, the transplantation of pancreatic islets made from hPSCs reduced hyperglycemia [28]. As a result, autologous transplantation of iPSCs is thought to be beneficial, but it takes a lot of time and money to cultivate the cells and encourage their maturation into cells that produce insulin. Banks of iPSCs from different HLA are being created for allogeneic transplantation [29]. For T1D patients to avoid autoimmune reactions against transplanted SC-islets, an encapsulating device is particularly helpful [30]. These encapsulating devices might be better transplanted subcutaneously since hPSCs have a risk of carcinogenesis, such as teratoma. According to studies, epigenetic regulatory alterations brought on by inadequate reprogramming of somatic cells promote cancer [31, 32]. It has been shown that lysine-specific demethylase 1 (LSD1), a histone demethylase, can be pharmacologically inhibited to stop the development of teratomas from iPSCs transplanted into immunocompromised mice [33]. Immune reactions are triggered by the human leukocyte antigen (HLA), which differentiates foreign antigens [34, 35]. Antigen-presenting cells, such as dendritic cells that express HLA class II, present the antigen to helper T cells, which then trigger the onset of immune responses that are specific to the antigen. The haplotype created by the DR and DQ genes is involved in the illness susceptibility of T1D, and the class II gene has the highest association with the condition [36, 37]. Because mesenchymal stem cells (MSCs) do not express HLA class II antigens, transplantation therapy employing MSCs has also been demonstrated to be beneficial [38]. Despite the infiltration of immune cells into the peritoneal cavity and left kidney capsule following local transplantation, MSC-derived insulin-producing islet-like cells improved glycemic control in diabetic STZ-treated mice [39]. Clinical research revealed that MSC transplantation enhanced T1D patients' glycemic control [40]. However, to date, no clinical trials have looked at the use of SC-islet cells derived from iPSCs, ESCs, or MSCs. For SC-islet cell transplants, graft rejection avoidance is a crucial concern. In an autologous transplantation trial, mouse-PSC-derived islet cells were injected into the kidney capsule of mice with STZ-induced diabetes, according to Yamaguchi et al. [41]. In that file, SC islets have been generated by injecting mouse % into Pdx-1-deficient rat blastocysts, and the SC islets contained endothelial cells from rat foundations. As a result, immunosuppressive therapy became necessary during the first five days following transplantation. Even after the withdrawal of immunosuppressive drugs, SC islets continuously progressed blood glucose tiers inside the normal range in diabetic mice for 370 days. But whether the autologous transplantation of iPSC-derived islets from patients with T1D can cause graft rejection remains uncertain. Leite et al. performed an in vitro experiment in which SC-islet cells from T1D subjects or non-diabetes subjects were co-cultured with autologous immune cells, and they suggested that endoplasmic reticulum pressure triggered an immune reaction in SC-islet cells from each T1D donor and non-diabetes subject, indicating that immune responses can also occur with autologous transplants [42]. This study further demonstrated that T cell activation is limited to the autologous transplant of SC-islet cells that have been enriched in -cells and does not happen in SC-islet cells that are not enriched in -cells; however, the mechanism of -cell-specific T cell activation is not fully known. Clarifying the differences between SC-islet cells from T1D donors and those from people without diabetes is crucial when thinking about stem cell therapy for T1D patients. As far as increases in interleukin-1 (IL-1), tumour necrosis factor (TNF), or interferon (INF) levels in response to cytokine-induced stress go, Millman et al. found no differences between T1D and non-diabetes SCislet cells [43]. According to reports, SC-islet cells from T1D and T2D patients secreted insulin at levels comparable to those of non-diabetic individuals [44]. When inflammatory cytokines (TNF-, IL-1, and IFN-) were administered to SC-islet cells from patients with fulminant T1D and healthy subjects, Hosokawa et al. found that the fulminant T1D patients' SC-islet cells were more likely to undergo apoptosis [45]. The differential expression of immune response-related

genes in SC-islet cells from fulminant T1D donors and control people suggests that aberrant immunoregulation in fulminant T1D cells may speed up cell death and disease progression. Therefore, it is currently difficult to draw any conclusions about the characteristics of SC islet cells from T1D sufferers. The risk of graft rejection should be taken into account even when SC-islet cells from T1D patients are autologously transplanted. Approaches for gene modification may be helpful for shielding SC-islet cells from immunological reactions. In immunocompromised mice, engraftment and hematopoiesis were enhanced by HLA-A deletion in hematopoietic stem cells [46]. Targets for T1D treatment include immunomodulatory proteins, including CTLA4 and PD-L1, which are cytotoxic T lymphocyte-associated proteins. Immune checkpoint drugs, which block these proteins, cause T cells to become activated and have an anticancer effect. T1D development, however, has apparently been linked to the use of immune checkpoint inhibitors as a side effect [47]. The adeno-associated virus's overexpression of PD-L1 and CTLA4Ig in mouse pancreatic -cells retained the -cell mass and shielded NOD animals against the onset of T1D [48]. Treatment for autoimmune disease may benefit from a strategy that focuses on immune cells. According to a recent study, regulatory T cells (Tregs) in experimental autoimmune encephalitis (EAE) mice—a model of autoimmunity disease that displays aberrant Treg function—had higher levels of mitochondrial reactive oxygen species (mtROS) [49]. Scavenging mtROS in Tregs reduced the autoimmune responses in EAE mice [49]. According to Joshi et al.'s research, T1D-derived iPSC-derived macrophages preferentially delivered a pro-insulin peptide to islet-infiltrating T cells separated from the same donor, which resulted in T cell activation [50]. Anti-HLA-DQ antibodies selectively prevented this T cell activation. According to these results, research concentrating on T1D patients' immune cells as well as their pancreatic cells will be crucial for advancing iPSC-based diabetic therapy techniques.

Challenges of Pluripotent Stem Cell-Based Cell Therapy

Human pluripotent stem cells, such as induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs), provide previously unheard-of possibilities for cell therapy against incurable illnesses and wounds. Clinical experiments are already using both ESCs and iPSCs. However, their fundamental characteristics of tumorigenicity, immunogenicity, and heterogeneity continue to pose practical challenges that restrict their usage. Here, I summarize 20 years of research that has focused on resolving these three issues. The promise of PSCs is currently expected to be realized at a level that has never been higher. For many more patients to have access to PSC technology, there are a number of obstacles that must be overcome. I want to concentrate on the three main issues in this perspective: tumorigenicity, immunogenicity, and heterogeneity. By addressing these issues and suggesting potential solutions, I intend to hasten the development of cell treatments employing hPSCs.

Tumorigenicity

The ability of PSCs to reproduce indefinitely has allowed us to prepare billions of different kinds of human cells for transplantation, which is a significant benefit. This trait, meanwhile, has a downside since if cells continue to divide even after transplanting, they could form tumors. There are three possible tumorigenic situations. First, teratomas or tumours may form as a result of improper patterning if undifferentiated and/or immature cells are left in the final cell products that have been differentiated from human PSCs. Second, if reprogramming factors are still present in the iPS cells, they might encourage the growth of tumours. Third, genetic changes that occurred during PSC in vitro culture could be the source of tumorigenicity.

Teratoma and Other Tumors Due to Incorrect Patterning

The most critical issue with hiPSC and hESC cell transplantation is the development of teratomas. Teratoma development could be caused by even a small number of residual PSCs. Additionally, lineage-specific ll Cell Stem Cell 27, October 1, 2020 Elsevier, Inc., 523 stem cells may cause cancer as a result of improper or insufficient patterning if they are present in the transplant. For instance, patterning toward the cortex in the nervous system results in a highly proliferative cell that can create "neural rosettes," which, if injected in vivo, proliferate in a tumor-like manner [51]. As a result, scientists working on hPSC-based cell therapies have been putting a lot of time and effort into developing strategies that could stop teratomas and other tumours from developing as a result of improper patterning.

Tumorigenicity Caused by Reprogramming Factors

This risk only applies to iPSCs. All four reprogramming factors have been linked to tumorigenicity, particularly c-Myc, one of the most frequently mutated genes in human malignancies and frequently acting as a driving mutation. In fact, we

have demonstrated that the four reprogramming factors were transfected into iPSCs to produce tumor-prone chimeric mice [52]. In these tumours, we found that the c-Myc retrovirus had reactivated. Such tumours were not seen in chimeric mice created from iPSCs that were not activated by the cMyc retrovirus. Additional factors, such as a dominant-negative mutant of p53, are occasionally used in addition to the original four reprogramming factors to improve reprogramming efficiency [53]. EBNA1 is employed to sustain episomal expression of the reprogramming components in iPSCs produced using plasmids [54]. Given EBNA1's well-established roles in cancer, this is cause for concern. The incorporation of these cancer-causing transgenes in hiPSC intended for use in clinical cell treatments should therefore be carefully avoided.

Tumorigenicity Caused by Genetic Abnormalities

HiPSCs, hESCs, and any other cells that are grown in vitro before being transplanted all have this risk. Genetic modifications, such as chromosomal abnormalities, copy number variation, and single nucleotide mutations, are inexorably brought on by cell culture for in vitro expansion. Cells with abnormalities such as chromosomal deletion, duplication, or rearrangement are typically removed for use in cell treatments and other downstream applications. Chromosomal abnormalities were traditionally evaluated by karyotyping. Chromosome duplications 1, 12, 17, and 20 have frequently been observed in hESCs and hiPSCs following prolonged growth [55]. Such chromosomal defects in PSC lines prevent them from being used in cell therapy applications. Subcloning may be used in some circumstances to choose cells free of anomalies.

Heterogeneity

PSCs have both pluripotency and limitless proliferative capacity. Each PSC line is different from the others, though. The morphology, growth curve, gene expression, and tendency for differentiating into multiple cell lineages are all unique to each line. This "heterogeneity" presents a challenge for subsequent uses, such as cell treatments.

Immune regulation in human T1DM stem cell therapy

For the therapy of T1DM, ESC/iPS-derived cells have been suggested as a viable source of replacement cells. However, the widespread use of cell replacement therapy for T1DM continues to face significant challenges from both the alloimmune and autoimmune reactions. Despite significant advancements in encapsulation technology, there are still difficulties in getting transplanted hPSC-derived pancreatic progenitors, or cells, to graft. If the encapsulating system is removed, the immune system of the receiver will undoubtedly kill the engraftments. It seems hopeful to modify these encapsulated cells in certain ways to thwart autoimmune attacks. HLA mismatching is the primary molecular mechanism of immune rejection in allo- or xenografts [56]. Studies have shown that removing HLA-A genes from hematopoietic stem cells by means of zinc-finger nucleases may improve donor compatibility [57, 58]. Similar to this, deleting HLA-A and HLA-B biallelically or knocking out the 2-microglobulin (B2M) gene, which eliminates all HLA class I molecules, left one allele of HLA-C in place, allowing the hPSC grafts to resist T and NK cell attack [59]. Other Stem Cell Research & Therapy (2020) 11:275 Page 9 of 13 Chen et al., Stem Cell Research & Therapy (2020) 11:275 Page 9 of 13 Protocols for immunosuppressive effects have been reported, including the targeted overexpression of PDL1-CTLA4Ig in cells, which successfully prevented the onset of T1DM and allo-islet rejection, subsequently enhancing the survival of the cell mass [60]. Therefore, using hPSCs to modulate the immune system may be a viable way to address the problems caused by engraft rejection.

Pancreatic Stem Cell Therapy and Automated Insulin Delivery System Comparison

T1D is defined by lifelong insulin injections due to chronic hyperglycemia brought on by insulin insufficiency resulting from the loss of pancreatic -cells, primarily by autoimmune processes [61]. Currently, insulin pumps aid in better controlling blood glucose levels. A blood glucose level of 70-180 mg/dL for at least 70% of the day has been proposed as a goal range for glycemic control (time in range, or TIR) in people with T1D or T2D in general [62]. Better blood glucose level maintenance has been achieved with the use of continuous glucose monitoring (CGM) or flush glucose monitoring (FGM) and insulin pumps with a Predictive Low Glucose Suspend (PLGS) feature [63, 64]. Since the amount of insulin may be changed based on the CGM value, Sensor Augmented Pump (SAP) therapy, which combines CGM and an insulin pump, is regarded as an artificial pancreas [65]. In order to achieve the objective of diabetes therapy without the need for insulin injections, cell replacement therapy is also anticipated to be a promising treatment for T1D. Pancreas, islet, or SC-islet cell transplantation is included in cell replacement. In this chapter, we'll contrast the use of an artificial pancreas and the

transplantation of SC-islet cells (Table 1).

Table 1: Comparison of automated insulin administration systems and the implantation of SC-islet cell

	SC-Islet Cells Transplantation	Automated Insulin Delivery Systems
Advantages	*Free from insulin injection* *Improved time-in- range*	*No immunosuppression* *Improved time-in-range*
Disadvantages	*Risk of immunosuppression* *Risk of cancerization* *Risk of insulin insufficiency* *Risk of re- transplantation*	*Complicated maintenance* *Adjustment of dose according to diet* *Risk of hypoglycemia,* *DKA or HHS Local skin troubles*

At the conclusion of our evaluation of the literature, we want to underline the importance of continuing our current initiative to offer up-to-date reviews on illnesses and drug chemistry that benefit people all around the world [66–101].

Conclusions and perspectives

A promising possible therapeutic approach for treating diabetes, particularly T1DM, is stem cell-based therapy. As indicated in this review, significant developments in the study of the hPSC-derived IPCs have increased the likelihood that T1DM patients may once again have insulin secretion that is responsive to glucose. But the clinical trial outcomes of stem cell treatments for T1DM are still unsatisfactory, and there are still a lot of unanswered questions and technical challenges to be overcome. The four main issues are as follows: (1) how to develop more developed, functional hPSCs in vitro; (2) how to increase the effectiveness of IPC differentiation from hPSCs; (3) how to safeguard implanted IPCs from autoimmune attack; (4) how to produce enough of the desired cell types for clinical transplantation; and (5) how to completely establish insulin independence. Despite these challenges, the most cutting-edge method for treating type 1 diabetes is the use of stem cell-based therapy.

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