REVIEW ARTICLE

Cell-based therapies for type 1 diabetes mellitus: Recent advances

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Abstract

Type 1 diabetes mellitus (T1DM) is caused by a selective autoimmune-mediated destruction of insulin-producing β-cells. Exogenous insulin delivery continues to be the only standard treatment method. Even though some patients accurately comply with their prescribed course of medication, transient episodes of hyperglycemia and hypoglycemia cannot be entirely avoided by this symptomatic treatment. Nowadays, with a better understanding of disease development and stratification, more personalized therapeutic approaches are emerging for T1DM. In this review, the highlights of some of the potential cell-based therapies for T1DM are summarized. Specifically, the focus is on islet transplantation approaches, the generation of insulin-producing cells from stem cells, transdifferentiation of other cell types into β-cells, discussing the role of mutagens either in preserving the β-cell mass or inducing the β-cell proliferation and a tissue engineering approach. Even though stem cell differentiated β-cells are promising, there are considerable obstacles that must be overcome before the dream of personalized T1DM therapy becomes a reality.

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Introduction

Diabetes mellitus (DM) is rising to an alarming epidemic level with morbidity and mortality due to its microvascular and microvascular complications. The increase in the prevalence of DM in most regions across the globe has been parallel to the rapid economic development due to urbanization and the adoption of modern lifestyles. Diabetes mellitus is a group of chronic metabolic disorders characterized by hyperglycemia and impaired glucose tolerance. Hyperglycaemia or increased blood glucose level is caused by abnormalities either in insulin secretion, insulin action, or both that affect carbohydrate, fat, and protein metabolic dysfunction causing multiple organ failure. The pathogenesis of DM is either due to the autoimmune-mediated destruction of insulin-producing pancreatic beta cells or defects in the insulin action pathway that result in hyperglycemia [1,2]. According to the international diabetes federation (IDF) 2022 atlas, globally around 537 million adults aged between 19-72 years are living with diabetes mellitus and it is projected to rise to 643 million by 2030 and 783 million by 2045. An estimated 240 million adults are living with undiagnosed DM and 90% of undiagnosed diabetes patients are in middle and low-income countries. IDF confirms that diabetes mellitus is one of the fastest-growing health emergencies of the current century

with a mortality of approximately 6.1 million in 2021. In India, approximately 73 million adults have diabetes and the number of undiagnosed patients is even higher. India has the highest number of type 1 diabetic patients under the age of 19. This increased number of diabetic patients causes a huge economic burden on healthcare costs [3].

Since DM is characterized by complex pathophysiology and diverse presentation, any classification of this disorder is therefore arbitrary, yet useful, and frequently impacted by the physiological parameters present at the time of assessment and diagnosis. The classification now in use is based on the pathogenesis and etiology of the disease and is helpful in determining the necessary therapy and clinical assessment of the disease. It is mainly categorized into Type 1 diabetes mellitus (T1DM), Type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM), and diabetes-induced or related with particular specific illnesses, pathologies, and/or syndromes [4]. T1DM, often referred to as insulin-dependent diabetes mellitus (IDDM), or juvenile-onset diabetes, accounts for around 5–10% of all diabetes cases. It is an autoimmune condition defined by the T-cell-mediated apoptosis of pancreatic beta-cells, which causes an insulin deficit and ultimately leads to hyperglycemia [5].

The major treatment for T1DM is intense insulin therapy administered by injection or an insulin pump. The primary therapeutic goal is to maintain tight glycaemic control to reduce the long-term micro and macrovascular consequences. Although these approaches are effective, the normalized level of HbA1c is rarely accomplished without the constant risk of hyperglycemia. The majority of T1DM transplant therapies have hence focused on islet cell or solid organ transplantation. Islet cell transplantation can be allogenic or autologous, and whole pancreas transplantation usually takes place either alone or together with a kidney. Cell-based therapy for type 1 diabetes now has more options due to the recent advancements in the area of autoimmune disorders and stem cell biology [6]. In this review, we examine the current cell-based treatment for type 1 diabetes.

Islet Transplantation

Transplantation of pancreatic islets is considered as a therapeutic option for the treatment of T1DM. The islet transplantation has successfully achieved exogenous insulin independence for several years for T1D patients. Despite its efficacy, during the 1980s, the following three severe obstacles prevented the implementation of islet transplantation as a treatment for diabetes in humans, 1) lack of an effective nontoxic immunosuppressive regimen capable of preventing alloimmune and autoimmune damage to the islet graft, 2) lack of a donor source of human pancreas, and 3) inability to reliably extract a sufficient number of viable islets from human pancreas. Only half or fewer of the roughly one million islets in an adult human pancreas are consistently successfully isolated. As a result, to provide enough isolated islets to achieve insulin independence, clinical islet transplantation frequently needs the donation of two or more donor pancreas [7-9].

New attempts at clinical islet transplantation for diabetes were made in the late 1980s and 1990s as a result of significant advancements in the field of islet isolation including the development of the collagenase perfusion followed by digestion in Ricordi chamber, dithizone staining, improvements in viability testing, etc. There had been 270 islet transplants for people with type 1 diabetes as of December 31, 1995, with a 10% overall insulin independence rate. Fourteen of the 270 patients with insulin dependence who got islet transplants achieved insulin independence for at least a year. In 2000 Shapiro et al. reported a series of seven T1D

patients who were insulin-independent following islet transplantation. The steroid-free immunosuppressive treatment employed in these patients is known as the "Edmonton protocol". It included daclizumab (an IL-2 receptor antagonist), sirolimus, and low-dose tacrolimus. The use of numerous donors (up to three donors) to give significant islet mass and the steroid-free immunosuppressive regimen appeared to be related to the success of this protocol [10-12].

As a result of the Edmonton group's success, islet transplant programs have stepped up their efforts, and new islet transplant facilities have been established. Thirty-six people with T1D underwent islet transplantation using the Edmonton procedure as part of an international multicenter trial. Among that, 21 people (58%) achieved insulin independence at some time, and 5 of them did so after two years. The outcomes confirmed that the Edmonton procedure constituted a significant advancement in the area of islet transplantation, although it was evident that there were still certain obstacles that needed to be overcome. The majority of recipients' islet function decreased or was lost over time, insulin independence was not always reached, and infusion of an islet mass bigger than predicted was necessary [13]. According to the Collaborative Islet Transplant Registry (CITR), 2007 to 2010 is known as the "new era" in islet transplantation [14]. The good news is that there has been a constant increase in islet transplantation due to the organized activity of several islet transplantation centers and networks worldwide like nPOD, HIRIN, IPITA,etc. [15].

The quick establishment of blood flow for nutrient delivery, oxygen supply, and immune regulation is a crucial factor in improving islet graft survival after transplantation. Due to an immediate blood-mediated inflammatory reaction (IBMIR) and an initial immunological response, it is estimated that 50% of the islet loss occurs in first few days of transplantation. Currently, the liver is the location of choice for islet transplantation since it requires minimal invasiveness, easy to access, and has a low risk of bleeding and thrombosis. Through portal circulation, the liver can also oxygenate the transplanted islets until revascularization [16]. Apart from the liver, researchers are now focused on the establishment of new transplantation sites for better revascularization and graft survival like an omental pouch, intramuscular, spleen, subcutaneous space, etc. [17].

Generation of Beta Cells from Stem Cells

Since the demand for endocrine replacement therapy for T1D patients has increased, there has been a lot of interest in the differentiation of stem cells into pancreatic islets or insulin-producing beta cells. Studies examining the mechanisms of islet development have influenced efforts to differentiate either of pluripotent stem cells, embryonic stem (ES) cells, induced pluripotent stem (iPS) cells, and adult stem cells into insulin-producing beta cells. To achieve progressive differentiation of the cells through specific developmental pathways, considerable work was undertaken to optimize the culture conditions, specifically the concentrations of medium components and timing of the activation or inhibition of important signaling pathways. The obtained insulin-producing cells should express certain biological markers of normal β-cells that confirm a terminal differentiation status, such as MAFA (a basic leucine zipper transcription factor expressed in mature beta cells but absent in other pancreatic cell types), NEUROD1 (a downstream factor of NGN3 expressed in most pancreatic endocrine cells, including β-cells), PDX1/NKX 6.1 (restricted co-expression in beta cells). The differentiated cells should also secrete insulin when challenged with low and high concentrations of insulin and C-peptide [18-21].

Embryonic Stem Cells

The most remarkable feature of embryonic stem cells (ESCs) is their ability to differentiate into every type of adult cell. Human ESCs were differentiated into definitive endoderm, gut-tube endoderm, pancreatic, and eventually islet cells using a stepwise method in which culture conditions were combined with the gradual addition of growth and differentiation agents [22,23]. TGF-family molecules, retinoic acid, and fibroblast growth factors (FGFs), which play important roles in directed differentiation, are used in identical amounts in protocols from various labs. The expression of stage-specific transcription factors serves to identify and validate each step, and the functionality of β-cell activity is evaluated by insulin synthesis and secretion in response to glucose. In order to reduce the culture time and increase the effectiveness of β-cell differentiation, various modifications have been made to the stepwise protocol. The differentiated beta cells' inadequate maturity is a significant limiting factor in stem cell differentiation [24,25]. Even though the molecular mechanisms underlying the functional development are still being studied, the differences between immature and mature β-cells have been identified by comparing fetal and adult islets, while mature cells have more insulin secretory granules and are more active at metabolizing glucose than immature cells. Upon maturation, β-cells also express MafA, Ucn3, and Err in addition to the β-cell markers Pdx1, Nkx6.1, and Isl1 [26,27]. Nair et al., obtained about 90% efficiency of β-cells by using cell cluster dissociation, sorting, and reaggregation processes [28]. In order to effectively differentiate ESCs into beta-cells for islet cell replacement treatment, differentiation techniques have been modified to mimic the signals the cells experience in vivo. Although there has been significant advancement in these scientific areas, there are still moral concerns about the harvesting of human embryos [29].

Induced-pluripotent stem cells

The generation of induced pluripotent stem cells (iPSCs) from adult cells provides a renewable source of pluripotent cells. Adult somatic cells can develop ESC-like properties by being treated with Yamanaka factors like OCT4, KLF4, SOX2, and MYC in ESC-like culture conditions. iPSCs can develop into cells from all three lineages and share similar morphological and transcriptomic properties as ESCs [30,31]. As a result, these cells carry the same risk of teratoma development as ESCs, but the use of iPSCs avoids ethical dilemmas because no embryos are destroyed. Similar methods to those developed for ESC differentiation can be used to differentiate iPSCs into beta-cells. However, a few studies have also asserted that iPSCs' varying epigenetic profiles and genetic instability have an impact on the requirements and effectiveness of their differentiation [32]. By modulating the cytoskeleton, Hogrebe et al., improved the efficiency of β-cell differentiation using hiPSCs and hESCs. They used Latrunculin A to depolymerize the actin network in order to specify the endocrine system because they reasoned that actin polymerization affected the specification of the endodermal lineage. In order to facilitate the development of β-cells that demonstrated GSIS that was comparable to that of human islets, they were able to maintain blood glucose levels in diabetic mice. The ability of stem cells to differentiate into beta-cells has improved, although compared to native pancreatic islets in terms of responsiveness to glucose and expression of beta-cell-specific genes is less in stem cell-derived beta cells [33].

Adult stem cells

Due to their lack of ethical issues and limitless supply, adult stem cells are the

most crucial source for cell therapy of numerous disease models. Various studies have shown that stem/progenitor cells found in bone marrow [34], adipose tissue, [21,35] liver [36], gut [37], salivary glands [38], neural tissues [39], dental pulp tissue [40], placenta [41], amnion [42], and umbilical cord [43] can be used to generate insulin-producing cells. The pancreas is a source of stem cells like duct cells, acinar cells, and stem cells with the ability to differentiate and be reprogrammed to ensure the development of insulin-producing cells. In earlier studies, human pancreatic duct cells have been shown to multiply in vitro and develop into insulin-producing cells. In addition, it was discovered that after partial pancreatectomy in diabetic mice, ductal progenitors might develop into mature ductal epithelial cells [43]. These findings indicate the existence of stem/progenitor cells in the pancreas, which may provide a prospective source of new islets.

Multi-potent mesenchymal stem cells (MSCs) are found in adult tissues and are distinguished by their capacity to self-renew and differentiate into several lineages. MSCs can be extracted from bone marrow, umbilical cord, and adipose tissue. MSCs can be expanded in vitro and, like iPSCs have the benefit of reducing the chance of immunological rejection. Additionally, MSCs generate numerous growth factors that aid the growth and survival of neighboring cells and have a low tendency to develop teratomas. Through the inhibition of IFN-γ and TNF-α and the upregulation of IL-10, they have been proven to have immunomodulatory effects also. Through the production and secretion of VEGF, HGF, IL-6, and TGF-1, MSCs also show pro-angiogenic properties [45,46]. The most studied sources of MSCs are adipose tissue and bone marrow. Extracting a sample from the bone marrow requires an intrusive, painful process, and liposuction aspiration is a common practice that enables collection of sufficient adipose tissue. The total amount of human marrow collected while under local anesthesia is no more than 40 ml. A harvest from adipose tissue, on the other hand, requires only 200 ccs of local anesthesia. Approximately 5000 adipose tissue mesenchymal stem cells can be obtained from 1 ml of adipose tissue aspirate. About 600–1000 bone marrow mesenchymal stem cells are produced from the same volume of bone marrow aspirate (BM-MSCs) [47]. These findings show that adipose tissue is a superior source of MSCs to other sources. It has been reported that human ADSCs can differentiate into insulin-producing cells in vitro under specific medium conditions and that these cells express pancreatic developmental genes like Isl-1, Ipf-1, and Ngn-3 as well as the islet hormone genes glucagon and somatostatin. In a recent study, human adipose-derived MSCs were differentiated into insulin-producing cells using growth factors like activin, FGF, and EGF. When implanted, the patients' insulin requirements dropped by 30% to 50%, and their serum C-peptide levels increased by 4 to 26 fold, indicating that differentiated ADSC transplantation may be a useful therapeutic approach for the management of diabetes [48-53].

Beta Cell Proliferation

During pancreas development, β-cell expansion occurs through proliferation upon differentiating from progenitors. In the fetal and neonatal pancreas, beta cell proliferation is important to increase cell mass, but it rapidly reduces in early adolescence and is almost limited in adulthood and this decreased proliferative capacity is inversely correlated to their functional maturation [54]. However, it is now widely accepted that in situations with high metabolic demand, such as pregnancy, obesity, or injury, adult beta cell mass may be increased by proliferation rather than by neogenesis [55]. Therefore, the expansion of existing beta cells

by inducing proliferation is considered to be a potential approach to rectorate lost beta cell volume in diabetic patients. Development of new β-cells occurs in the postnatal period, supporting the theory that signaling molecules abundant either in the intrauterine environment or circulating in young individuals could promote their expansion. In this regard, significant biochemical mechanisms have previously been identified that control the proliferation of β cells in both the early and late phases of life [56].

A network of highly coordinated cell cycle regulators control the beta cell replication and the proliferation can be induced by both intrinsic and extrinsic factors. Intrinsic factors include glucose, amino acids, insulin-like growth factors (IGF), prolactin (PRL), placental lactogen (PL), glucagon-like peptide-1 (GLP-1), growth hormone, hepatocyte growth factor (HGF), epidermal growth factors (EGF), transforming growth factor (TGF), and extracellular matrix (ECM) [57-60]. Intrinsic factors, are cyclins, cyclin-dependent kinases, and cyclin-dependent kinase inhibitors, etc [61,62]. Transforming growth factor-beta (TGF-beta), the cytokine interleukin 1-beta (IL1-beta), pancreastatin, and the diazepam binding inhibitor are all known to decrease the proliferation of beta cells in fetal rodents [63,64]. The ability of β-cells to multiply at various periods of life is correlated with the expression of these regulators. The majority of adult beta cells are in the quiescent (G0) phase of the cell cycle [65]. In response to the mitogenic signals, they enter the G1, S, G2, and M stages of the cell cycle to begin replication and these events are controlled by cyclins and cyclin dependant kinases (CDKs). Cyclin D1 and D2 have been given a key function in the positive control of beta-cell proliferation. These cyclins bind to CDK4 and in turn initiate cell cycle progression through their kinase activity. Human beta cell replication appears to be heavily reliant on the CDK4-cyclin D1 complex [66-68]. The presence of a mitogen during the G0/G1 transition, initiates a cascade of events, among them being the strong expression of cyclin D1. Along with CDK4/6 and cyclin D known as the initiator complex translocates to the nucleus and hyperphosphorylate retinoblastoma protein(Rb) which is a key regulator of β-cell proliferation. Rb inhibits transcription factors of the E2F family when it is hypophosphorylated, limiting the cell cycle's progression. In its hyperphosphorylated form, E2F is released which improves the production of genes necessary for cell cycle progression, including "later" cell cycle-promoting molecules such as cyclins E and A. Then, cyclin E-CDK2, cyclin A-CDK1, and cyclin B-CDK1 complexes come together and, in turn, promote progression into the S, G2, and M phases, respectively. Cell cycle inhibitors, which predominate cell cycle activators in human beta cells regulate the progression through the cell cycle events [69-72].

Over the last decades, a plethora of small molecules have been identified which induce β-cell proliferation like inhibitors of DYRK1A-NFAT, GSK3, and NF-κB signaling pathways, phorbol esters, dihydropyridines (DHP), and thiophene pyrimidines, etc. suggesting that these molecules have unique potential in the treatment of diabetes. Studies have shown that inhibiting the activity of the kinase DYRK1A is a novel method for enhancing the proliferation of human β-cells. In a high-throughput screening for inducers for MYC expression in HepG2 cells, Wang et al. found that a small molecule harmine has the potential to inhibit DYRK1A thus increasing β-cell proliferation. In another study, an aminopyrazine dual inhibitor of DYRK1A and GSK3 in beta cells also induces proliferation. The effects of 5-iodotubercidin (5-IT), which was once assumed to cause phenotypic activity by inhibiting adenosine kinase also act as an inhibitor of DYRK1A. The action of DYRK1A inhibitors (such as harmine, 5-IT, leucettine-41, and INDY) on human islets can be boosted by TGF inhibitors or GLP-1 agonists like exendin 4. It has also

been demonstrated that the activity of this family of chemicals involves inhibiting both DYRK1A and DYRK1B, two closely related isoforms, rather than just DYRK1A alone. Importantly, these substances have been shown to reverse glucose dysregulation in a number of mice models of diabetes, including streptozotocin-induced diabetes and in partial pancreatectomy [73-75].

Beta Cell Transdifferentiation

A differentiated cell can transform into a different type of cell through a process known as transdifferentiation or lineage reprogramming [76]. It has recently emerged as one of the promising methods to generate beta cell sources for cell replacement therapy for T1DM. Since hepatic, gastrointestinal, and pancreatic non β-cells originate from similar endodermal progenitor cells, it is possible to transdifferentiate these cells into β-cells. To achieve transdifferentiation, only a small portion of the epigenome needs to be altered due to the similarity in developmental transcription mechanisms, epigenetic landscapes, and distinct arrangement of endogenous cells. Pancreatic non-β-cells, including ductal, acinar, α and δ-cells share similar epigenetic profiles and developmental histories. MaFa and pdx1 are the major transcription factors that regulate reprogramming by interacting with other factors during transdifferentiation [77]. The transdifferentiation of β-cells from α-cells is induced by the deletion of the Aristaless-related homeobox gene (Arx) or by the overexpression of PAX4, MafA, and Pdx1 through the use of elastase 2A [78]. In another study, total in vivo ablation of β-cells in mouse models induces β-cell transdifferentiation not only from α-cells but also from ductal and acinar cells [79]. Glucagon and glucagons like peptide-1 (GLP-1), GABA, and artemisinss also induce α-cells to β-cell transdifferentiation [80,81]. Furthermore, pancreatic δ-cells can also transdifferentiate into insulin-producing cells but only in juveniles and this ability to adapt has been associated with the forkhead box O1 network [82].

Pancreatic duct cells as a potential candidate for the generation of β-cells have been proven in many studies. Islet renewal and pancreatic regeneration are expected to be accomplished by progenitor cells that express Ngn3 near or within the pancreatic duct. These cells can self-renew and differentiate and also express cytokeratin (CK)-19 [83,84]. There are studies that proved that, these CK-19-expressing cells can be differentiated into beta cells with specific growth factor supplements [85]. Lineage tracing studies also found that during postnatal development, new β-cells were budding from a new lobe of the duct. In that experiment, islet cells expressing duct-specific CAII-Cre R26R constitutively indicated that duct cells expressing CAII had transdifferentiated into acinar cells and new islets [86]. Furthermore, using GLP-1 and exendin treatment, duct cells can be differentiated into β-cells and Expression of MafA, Pdx1, and Ngn3/NeuroD can induce the transdifferentiation of adult murine pancreatic duct cells into β-cells, whereas inducing Pax6 was also necessary to transform human ductal cells into β-cells [87,88].

After islet isolation from donors, large populations of acinar cells are discarded; however, it has been proven that these cells can transdifferentiate into β-cells both in vivo and in vitro with the formation of duct cells as an intermediary step [89]. Additionally, the Meltons group showed evidence of exocrine cell reprogramming to β-cells. Elastase 2A was used as a specific stimulant of acinar cells to induce the expression of Ngn3, Pdx1, and MafA. The research confirmed the role of each gene in the transdifferentiation of exocrine cells. They suggested that the expression of Ngn3 and MafA inhibits acinar cell fate and Ngn3 promotes pancreatic

endocrine cell differentiation of α, β and δ cells. Additionally, MafA suppresses the fates of acinar and δ-cells and activates α and β cell fates. Pdx-1 also suppresses δ-cell differentiation and induces β-cell formation [90]. In another study, in vitro differentiation of mouse acinar cells was accomplished by treating the cells with nicotinamide and epidermal growth factor. According to Baeyens et al., Ngn3 expression is correlated with the JAK/STAT signal pathway during β-cell neogenesis. They showed that pancreatic acinar cells were transdifferentiated as a result of constitutive overexpression of mitogen-activated protein kinase and signal transducer and activator of transcription 3. Lentiviral gene delivery into acinar cells for 7 days resulted in an increase in the expression of specific markers such as insulin and Pdx1 [91].

Due to the proliferative capacity, the conversion of genetic factors together with small molecules targeting specific pathways could make the human liver cells an ideal source of functional insulin-producing cells due to the tissue specificity, and shared endodermal origin between hepatocytes and pancreatic cells. Pdx1 has ectopic expression in certain hepatocytes. These hepatocytes were detected close to central veins and exhibit a tendency to transdifferentiate into β-cells. Maintaining this β-cell plasticity requires the stimulation of the Wnt signaling pathway, ectopic overexpression of Pdx1 and NeuroD1, downregulation of the hepatic transcription factors HNF1 and HNF4, etc [92]. Intestinal cells have the capacity to transform into β-cells that produce insulin due to the ectopic expression of Pdx1, MafA, and Ngn3 in the intestinal crypts. Enterocytes can develop β-like properties under the control of Pdx1, MafA, and Ngn3, including the ability to convert preproinsulin into its mature form. Functional β-like cells are generated by knocking off the FoxO1 transcription factor in enteroendocrine cells. In another study, by the activation of Ngn3 and its downstream genes by GLP-1 administration increased the synthesis of insulin in developing enterocytes [93,94].

Tissue Engineering Approach for Beta Cell Regeneration

During pancreas organogenesis, tissues from several germ layers release and react to growth signals. Cells are grown as monolayers in 2D cultures during in vitro differentiation. As a result, there are no 3D interactions between cell types as they take place during islet development in vivo. In addition, the islets experience cellular stress due to the degradation of the islet microenvironment and the loss of the supporting matrix that takes place during isolation, purification, and the pretransplant culture period. Islet function and survival are compromised due to the poor microenvironment and lack of cell-cell contact. Tissue engineering, a process that combines the concepts of biology, engineering, and materials science to create biological substitutes for implantation into the body to either repair, replace, or restore tissue/organ function, has emerged as a means of overcoming the current limitations. The Edmonton technique has many drawbacks that a tissue engineering method has the ability to address, perhaps to increase the lifetime of islet transplantations. The three main elements of engineered tissues are called the tissue engineering triad: cells, scaffolds, and signaling cues. In tissue engineering, the idea of scaffolding is to at least partially mimic the functions of native ECM [95-97].

The pancreatic islets lose all of their attachments to the extracellular matrix during the isolation process. The effect of ECM–islet interactions on islet survival and function has been highlighted in a number of studies. Scaffolds are used in tissue engineering procedures for islet transplantation as a temporary ECM that provides the islets with the necessary mechanical support during transplantation. A

scaffold should be a three-dimensional, porous, and biocompatible matrix with a controlled rate of tissue creation that results in the degradation of the implanted material and its substitution by the newly created tissue [98,99]. Scaffolds made of synthetic, natural, or hybrid materials in islet transplantation have been extensively studied. Some of the synthetic polymers that are most frequently used in islet transplantation methods are polylactic acid (PLA), polyglycolic acid (PGA), polylactic-co-glycolic acid (PLGA), polyethylene glycol (PEG), and polydimethylsiloxane (PDMS), polycaprolactone. With synthetic polymers, the large-scale fabrication of 3D, biodegradable, and nonimmunogenic structures are with repeatable mechanical and physical properties. However, the hydrophobic nature of these materials limits their biocompatibility, and the generation of pro-inflammatory acidic byproducts during their decomposition limits their use. For instance, after 15 days, rat islets cultured on a porous poly(glycolic acid) (PGA) scaffold had four times insulin secretion and were two times more viable than those cultured on 2D tissue culture plates [100]. Combination of these scaffolds and islets with insulinotropic stimuli, such as glucagon-like peptide-1 (GLP-1), exendin-4 (Ex-4), or insulin-like growth factor-1 (IGF-1), as well as proangiogenic factors and cells, such as VEGF, platelet-derived growth factor (PDGF), and endothelial cells (ECs), has shown notable improvements in insulin secretion, islet survival, and engraftment. Furthermore, bioactive compounds that increase the hydrophilicity have been combined with these synthetic scaffolds in order to "functionalize" them, or increase their biocompatibility. Thus, in preclinical islet transplantation procedures, synthetic polymers coupled with various biological materials or with ECM proteins have been used successfully [52,101-104].

Polysaccharides like chitosan, alginate, and hyaluronic acid, and proteins like gelatin collagen, fibrin, silk, etc. are natural polymers with properties like low toxicity, biocompatibility, and enzymatic breakdown which are extensively used in islet tissue engineering. Furthermore, natural polymers have bioactive moieties that support the formation of cell-scaffold interactions and improve tissue functionality. There are reports suggesting that in vitro and in vivo islet transplantation experiments, chitosan has been used as a scaffold, either alone or in combination with other materials like collagen or gelatin, to protect against the immune response and to promote islet survival and function. Another polysaccharide that has occasionally been used successfully in islet transplantation is cellulose [105-107]. The use of ECM-derived proteins as a scaffold in these methods is an appropriate modification considering the effect of ECM on islet survival and function. Similarly, scaffolds for islet transplantation have been made of polypeptides, ECM-derived proteins, or polymerizable proteins like fibrin or silk has been reported. Another study from our lab reported a biomaterial scaffold made of two natural polymers gelatin and dextran dialdehyde showed better islet viability and insulin secretion than on 2D tissue culture plates [51]. Collagen, the primary structural proteins of the ECM, is the most abundant protein in mammals. When employed alone or in combination with growth factors it has increased islet survival and function both in vitro and in vivo [108]. Fibrin hydrogels are frequently employed in tissue engineering, and 3D fibrin scaffolds function as a temporary ECM, supporting long-term islet survival and function. Although fibrin can help with islet graft vascularization, it is often combined with proangiogenic growth factors, especially when islets are implanted in extrahepatic sites [109,110]. Furthermore, the bioartificial endocrine pancreas has been created using a variety of decellularised organs, including the liver, placenta, lung, and pancreas. Although biological scaffolds are more biocompatible, repeatability issues must be addressed in order to prevent batch-to-batch variability [111-114].

Generation of insulin-producing islet-like clusters (ILCs) on 3D biomaterial scaffold has been reported in various studies which have better insulin secretion when compared with insulin producing. The formed islets on the 3D scaffold system showed increased viability and insulin secretion than ILCs formed on 2D surfaces [51-53,115,116]. Another benefit of using a 3D future system is the co-culture of different cell types resembling the native pancreatic islets with ECM interaction and enhanced vasculature. One of our studies showed the advantage of co-culturing of islet cells with endothelial cells on a 3D scaffold for better islet function (unpublished data). A biomaterial-based tissue-engineered chamber filled with growth factor-matrigel has been successful in the generation of the pre-vascularized subcutaneous cavity for islet transplantation [117]. In another study, by inducing the formation of cavities with neovasculature, device-less pre-vascularization has also been shown to be effective [118]. VEGF-loaded PLCL capsule was also effective in the generation of pre-vasularised pouch for islet transplantation [119].

Immunoprotection Through Biomaterial

To achieve successful islet transplantation for T1DM, encapsulation of transplanted pancreatic construct in a protective polymeric membrane is necessary to create a barrier between the transplanted construct and the autoantibodies of the recipient's immune system and it serves as an optimal cell encapsulation device that is biocompatible, non-biodegradable and is stable. It should facilitate the mass transfer to maintain the viability and functionality of transplanted cells and also allow the transfer of insulin and glucose to maintain normoglycemia. Apart from this, it needs to have a well-controlled pore size to exclude the penetration of immune cells, autoantibodies, and pro-inflammatory cytokines [120,121]. Generally, encapsulation strategies have been divided into two groups based on the size of the encapsulating structure: microencapsulation [122-124] and macro encapsulation [125-127]. These broad categories share several considerations, such as choosing an acceptable tissue donor, preventing graft function loss due to a severe immune response, and providing proper mass transfer. One of the earliest examples of islet encapsulation for the treatment of diabetes was the xeno-transplantation of human insulinoma tissue into rats in 1933 using membranous bags [128]. However, immune-isolated islet transplantation did not become established until a series of studies in the early 1950s which evaluated the survival rates of allo-transplanted tissue in an extravascular zone with and without a cell-impermeable encapsulating membrane., Though receiving fewer nutrients, these studies showed that the non-vascularized transplanted tissue survived longer when an encapsulating membrane was used because it prevented immune cell interaction and the activation of the direct antigen presentation pathway [129-131].

In 1980, Lim and Sun performed the first experiment on islet encapsulation in alginate microspheres for β-cell replacement therapy. In an effort to reduce nutrient diffusion distance and graft empty space, conformal islet coatings have since become a viable alternative to microcapsules. The enhanced surface area to volume ratio, which is helpful for mass transfer, and ease of implantation of microencapsulation are advantages, while total graft removal and monitoring are inherent disadvantages compared to larger devices [132]. The advantages of macro encapsulation over microencapsulation include better graft monitoring and often guaranteed complete cellular retrieval upon device removal. On the other hand, it is more challenging to obtain enough mass transfer and ease of implantation for these constructions. Over the past few decades, a wide range of islet-encapsulating devices have been created. These devices comprise cylindrical, planar, and

hollow-fiber constructions. In recent years, improvements in 3D printing and microfabrication technology have also aided in the creation of increasingly complex shapes [133].

There have been numerous reports over the years regarding the macro and microencapsulation devices for islet transplantation with varying degrees of success. In our studies, we have shown that our fabricated immunoisolation macro-capsules made of PU-PVP IPN [134] could effectively encapsulate Islet-like clusters (ILC) derived from a variety of tissues [34,35,40-42,115] and reverse the diabetes of experimentally induced diabetic mice and rats. Further, a study from our lab reported a combinatorial approach of tissue engineering and macro encapsulation was more successful in the reversal of diabetes and prolonged survival of viable islets for a period of 3 months with avoidance of core necrosis in the implant. In that study, islet seeded on a biomaterial scaffold encapsulated in a nanoporous immunoprotection bag made of PU-PVP IPN [134] which was implanted in diabetic rats showed a reversal of hyperglycemia [116]. Polymer-based encapsulation devices such as those made of polycaprolactone (PCL) based nanoporous encapsulation were used as long-term immunoprotection devices. However, the small pores size and biodegradability of PCL make it less efficient for long-term clinical applications [135]. Similarly, a nanofiber-integrated cell encapsulation device (NICE device) was reported to prevent cell escape and reported to maintain normoglycemia over a longer period of time but failed to obtain controlled nanopores which are criticalin clinical islet transplantation studies [136]. In another study, when stem cell-derived beta cell encapsulated in alginate derivative hydrogel was implanted in diabetic mice achieved long-term glycemic control but was also capable of mitigating foreign body reaction [137]. Recently, we developed a nanoporous immunoisolation membrane via 3D printing using PU-PVP IPN [134] with controlled pore size. Here, we have adopted a combined approach for the development of an immunoprotective pancreatic transplantation device (IPTD) by generating mesenchymal stem cells (ADMSCs) derived islet-like clusters on a highly porous scaffold and their subsequent encapsulation in a 3D printed nanoporous immunoprotection membrane. Diabetic animals transplanted with IPTD restored normoglycemia within 14 days and maintained its normoglycemic compared to the diabetic control group and the device was also successful in alleviating FBR (expand). Upon transplantation for sixty days, its nanoporous membrane prevented the entry of immune cells thus protecting the transplanted cells inside the device. Here we developed an immunoprotective pancreatic transplantation device using an easy and scalable fabrication method as a translatable strategy for the safe delivery of stem cell derived beta cell for T1DM patients (unpublished).

Conclusion

In the last two decades, much progress has been reported in the field of cell-based treatment for diabetes. The introduction of the Edmonton protocol was the potential game changer of islet transplantation therapies. Further, lack of sufficient donor islets prompted many researchers with groundbreaking ideas of generating insulin-producing beta cells from various stem cell and progenitor sources.. Currently, clinical trials for stem cell-derived islets for T1D are underway with promising results, further promoting stem cell-derived islets as the future of T1D treatment. Maintaining the viability and functionality of transplanted cells is a major obstacle in the long run. Other well-recognized problems include hypoxia-induced cell loss and chances of undifferentiated stem cell escape. Innovative strategies like bioengineering and the development of tissue-engineered transplanta-

tion devices with a porous scaffold that mimics the 3D microenvironment of the native pancreas and its subsequent encapsulation in a nanoporous immuno-isolation membrane could be effective in addressing these challenging problems.

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