THERAPY OF ENDOCRINE DISEASE

Islet transplantation for type 1 diabetes: so close and yet so far away

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Abstract

Over the past decades, tremendous efforts have been made to establish pancreatic islet transplantation as a standard therapy for type 1 diabetes. Recent advances in islet transplantation have resulted in steady improvements in the 5-year insulin independence rates for diabetic patients. Here we review the key challenges encountered in the islet transplantation field which include islet source limitation, sub-optimal engraftment of islets, lack of oxygen and blood supply for transplanted islets, and immune rejection of islets. Additionally, we discuss possible solutions for these challenges.

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Introduction

Type 1 diabetes (T1D) is an autoimmune disease where the immune system destroys insulin-producing pancreatic β cells, leading to increased serum blood glucose levels. Despite tremendous efforts to tightly regulate blood glucose levels in diabetic patients by different methods of insulin therapy, pathologic processes that result in long-term complications exist (1). Another approach, transplantation of the pancreas as a pancreas-after-kidney or simultaneous pancreas–kidney transplant is used for the majority of T1D patients with end stage renal failure. Surgical complications and lifelong immunosuppression are among the major pitfalls of this treatment (2).

Pancreatic islet transplantation has been introduced as an alternative approach to transplantation of the pancreas. This procedure does not require major surgery and few complications arise. However, lifelong immunosuppression is still needed to preserve the transplanted islets. Although during the past two decades significant progress in islet transplantation conditions and outcomes has been achieved, challenges remain that hinder the use of this therapy as a widely available treatment for T1D. After reviewing the history of islet transplantation, we classify the major challenges of islet transplantation into four distinct categories relative to the transplantation time

point: islet source limitation, sub-optimal engraftment of islets, lack of oxygen and blood supply, and immune rejection (Fig. 1). We also discuss possible solutions to these challenges.

History of islet transplantation and clinical results

The first clinical allogenic islet transplantation performed by Najarian *et al.* (3) at the University of Minnesota in 1977 resulted in an unsatisfactory outcome. In 1988, while Dr Camilio Ricordi was a postdoctoral researcher in Dr Lacy's laboratory, they introduced an automated method for isolation of human pancreatic islets (4).

This research led to the first partially successful clinical islet transplantation at Washington University in 1989. By 1999, ~270 patients received transplanted islets with an estimated 1 year insulin independence rate of 10%. In 2000, a successful trial was published by Shapiro *et al.* (5). In their study, all seven patients who underwent islet transplantation at the University of Alberta achieved insulin independence. Of these, five maintained insulin independence 1 year after transplantation. This strategy, known as the Edmonton protocol, had three major differences compared to the previous transplant procedures. These differences included a shorter time between preparation of islets and transplantation, use of islets from two or three donors (~11 000 islet equivalents

Figure 1

Major challenges and possible solutions for islet transplantation. In a time-dependent manner, major challenges of islet transplantation are divided into four categories. The possible solutions to overcome each challenge are

mentioned below each category. Tx, transplantation; iPSCs, induced pluripotent stem cells; TSSCs, tissue specific stem cells; ECM, extracellular matrix. A full colour version of this figure is available at <http://dx.doi.org/10.1530/EJE-15-0094>.

Review	M Khosravi-Maharlooei, E Hajizadeh-Saffar and others	Islet transplantation for type 1 diabetes	173:5	R167
--------	---	--	-------	------

per kilogram of recipient body weight), and a steroid-free immune suppressant regimen (5). In their next year's report, it was shown that the risk-to-benefit ratio favored islet transplantation for patients with labile T1D (6). In a 5-year follow-up of 47 patients by the Edmonton group, ~10% remained insulin-free and about 80% still had positive C-peptide levels. Other advantages of islet transplantation included well-controlled HbA1c levels, reduced episodes of hypoglycemia, and diminished fluctuations in blood glucose levels (7).

Two studies by Hering *et al.* at the University of Minnesota reported promising outcomes in achieving insulin independence from a single donor. In 2004, they reported achievement of insulin independence in four out of six islet transplant recipients (8). In their next report, all eight patients who underwent islet transplantation achieved insulin independence after a single transplant; five remained insulin-free 1 year later (9). Dr Warnock's group at the University of British Columbia showed better metabolic indices and slower progression of diabetes complications after islet transplantation compared to the best medical therapy program (10, 11, 12, 13).

The last decade has shown consistent improvement in the clinical outcomes of islet transplantation. A 2012 report from the Collaborative Islet Transplant Registry (CITR) evaluated 677 islet transplant-alone and islet after-kidney recipient outcomes for the early (1999–2002), mid (2003–2006) and recent (2007–2010) transplant era. The 3-year insulin independence rate increased considerably from 27% in the early transplant era to 37% during the mid and 44% in the most recent era (14). Another analysis at CITR and the University of Minnesota reported that the 5-year insulin independence after islet transplantation for selected groups (50%) approached the clinical results of pancreas transplantation (52%) according to the Scientific Registry of Transplant Recipients (15).

Islet source limitation

The first category of islet transplantation challenges refers to donor pancreatic islet limitations as a major concern prior to transplantation. The lack of donor pancreatic islets hinders widespread application of islet transplantation as a routine therapy for T1D patients.

Pre-existing islet sources

Currently, pancreata from brain dead donors (BDDs) are the primary source of islets for transplantation. Since whole pancreas transplantation takes precedence over islet

transplantation due to the long-term results, the harvested pancreata are frequently not used for islet isolation. However, the long-term insulin independence rate after islet transplantation is approaching the outcome of whole pancreas transplantation (15). The rules for allocating harvested pancreas organs may change in the future and provide an increased source of pancreata for islet transplantation.

Non-heart-beating donors (NHBDs) may emerge as potential sources for islet isolation. Due to the potential ischemic damage to exocrine cells which may induce pancreatitis, NHBDs' pancreata are not preferred for whole pancreas transplantation. A study by Markmann *et al.* (16) has reported that the quality of ten NHBDs' pancreatic islets was proven to be similar to islets obtained from ten BDDs.

Xenogenic islets are another promising source of pre-existing islets for transplantation. Pig islets are the only source of xenogeneic islets that have been used for transplantation into humans, not only because of availability but also due to similarities in islet structure and physiology to human islets (17). Nonetheless the same challenges for allotransplantation, yet more severe, include limited engraftment and immune rejection following xenotransplantation of pig islets. Different strategies such as genetic engineering of pigs are underway to produce an ideal source of donor pigs for islet transplantation (18).

Human embryonic stem cell-derived β cells

In the future, generation of new β cells from human embryonic stem cells (hESCs) may provide an unlimited source of these cells for transplantation into T1D patients (Fig. 2). Research has made use of known developmental cues to mimic the stages of β cell development (19) and demonstrated that hESCs are capable of stepwise differentiation into definitive endoderm (DE), pancreatic progenitor (PP), endocrine progenitor, and insulin producing β -like cells (BLCs) (reviewed in (20)). The forced expression of some pancreatic transcription factors (TFs) such as *Pdx* (21), *Mafa*, *Neurod1*, *Neurog3* (22) and *Pax4* (23) in ESCs is an effective approach in this regard. Although this approach has yet to generate an efficient differentiation protocol, it provided the proof of principle for the concept of 'cell-fate engineering' towards a β cell-like state (24). The introduction of a chemical biology approach to the field of differentiation (reviewed in (25)) was a step forward in the reproduction of more efficient, universal, xeno-free, well-defined and less expensive differentiation

Figure 2

β cell sources for replacing damaged islets in type 1 diabetic (T1D) patients. Pre-existing islets can be harvested from brain dead donors (BDDs) or non-heart beating donors (NHBD) for allotransplantation and from other species for xenotransplantation. Expandable cell sources such as embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) can be differentiated into insulin producing cells (IPCs) in a stepwise manner through mimicking developmental steps that include the definitive endoderm (DE), pancreatic progenitor (PP) and

endocrine progenitor (EP) stages. Patient-specific β cell sources can be derived from the following steps: (i) trans-differentiation of adult cells toward IPCs, (ii) reprogramming to iPSCs and (iii) differentiating toward IPCs. Differentiation of tissue specific stem cells (TSSCs) is another strategy to generate patient specific β cell sources. *In vivo* conversion of other cells to β cells through delivery of pancreatic transcription factors (TFs) is the last strategy described in this figure. A full colour version of this figure is available at <http://dx.doi.org/10.1530/EJE-15-0094>.

methods. A number of these molecules such as CHIR (activator of Wnt signaling, DE stage) or SANT1 (inhibitor of Sonic hedgehog signaling, PP stage) have been routinely used in the most recent and efficient protocols (26). Attempts at producing efficient hESC-derived functional BLCs (hESC-BLCs) *in vitro* recently led both to static (27) and scalable (26) generation of hESC-BLCs with increased similarity to primary human β cells. These transplanted cells more rapidly ameliorated diabetes in diabetic mouse models compared to previous reports.

While studies on production of hESC-BLCs have continued, the immunogenicity challenge remains an important issue in the clinical application of these allogeneic cells. To overcome this problem, some groups

have introduced macroencapsulation devices as immune-isolation tools for transplantation of hESC-BLCs into mouse models (28). In another strategy, Rong *et al.* produced knock-in hESCs that constitutively expressed immunosuppressive molecules such as cytotoxic T lymphocyte antigen 4-immunoglobulin fusion protein (CTLA4-Ig) and programmed death ligand-1. They reported immune-protection of these allogeneic cells in humanized mice (29).

Recently, Szot *et al.* showed that co-stimulation blockade could induce tolerance to transplanted xeno-genetic hESC-derived pancreatic endoderm in a mouse model. This therapy led to production of islet-like structures and control of blood glucose levels.

Review	M Khosravi-Maharlooei, E Hajizadeh-Saffar and others	Islet transplantation for type 1 diabetes	173:5	R169
--------	---	--	-------	------

Co-stimulation blockade could prevent rejection of these cells by allogeneic human peripheral blood mononuclear cells in a humanized mouse model (30).

Patient-specific cell sources

Although the differentiation potential and expandability of hESCs make them a worthy cell source for islet replacement, immunological limitations exist as with other allotransplantations. Additionally, the use of human embryos to generate hESCs remains ethically controversial (31). Several approaches have been proposed to circumvent this hurdle as discussed in the following sections.

Induced pluripotent reprogramming ► Human induced pluripotent stem cells (hiPSCs) are virtually considered the ‘autologous’ equivalent of hESCs. Several groups have differentiated hiPSCs along with hESCs into insulin producing cells through identical protocols and reported comparable differentiation efficiencies (26, 32).

Theoretically, iPSCs should be tolerated by the host without an immune rejection. However, even syngeneic iPSC-derived cells were immunogenic in syngeneic hosts (33), which possibly resulted from their genetic manipulation. Epigenetic studies of produced iPSCs traced epigenetic memory or reminiscent marks, such as residual DNA methylation signatures of the starting cell types during early passages of iPSCs (34, 35) which could explain the mechanisms behind such observations. Alternative strategies such as non-integrative vectors (36), adenoviruses (37), repeated mRNA transfection (38, 39, 40), protein transduction (41), and transposon-based transgene removal (42) have been successfully applied to develop transgene-free iPSC lines. This progression towards safe iPSC generation (reviewed in (43)) offers a promising technology for medical pertinence. The cost and time needed to generate ‘custom-made’ hiPSCs is another important consideration. Establishment of ‘off-the-shelf’ hiPSCs that contain the prevalent homozygous HLA combinations has been proposed as a solution (44). Such HLA-based hiPSC banks are assumed to provide a cost-effective cell source for HLA-compatible allotransplantations which may reduce the risk of immune rejection.

Differentiation of tissue-specific stem cells ► The presence of populations of tissue-specific stem cells (TSSCs) in different organs of the human body provides another putative patient-specific cell source. As a long-known class of TSSCs, bone marrow (BM) stem cells are

currently used in medical procedures and can be harvested through existing clinical protocols for a variety of uses (45). Although a preliminary report has suggested that BM stem cells can differentiate into β -cells *in vivo* (46), further experiments have demonstrated that transplantation of BM-derived stem cells reduces hyperglycemia through an immune-modulatory effect and causes the induction of innate mechanisms of islet regeneration (47, 48). Other *in vitro* murine studies have shown that BM mesenchymal stem cells (MSCs) can be directly differentiated into insulin producing cells capable of reversing hyperglycemia after transplantation in diabetic animals (49, 50). *In vitro* generation of insulin producing cells from human BM and umbilical cord MSCs have also been reported (51, 52). However, the functionality and glucose responsiveness of these cells are unclear.

Transdifferentiation (induced lineage reprogramming) ► Transdifferentiation can be defined as direct fate switching from one somatic mature cell type to another functional mature or progenitor cell type without proceeding through a pluripotent intermediate (53). Studies of mouse gall bladder (54), human keratinocytes (55), α -TC1.6 cells (56), pancreatic islet α -cells (57), liver cells (58, 59) and skin fibroblasts (60, 61) demonstrate that non- β somatic cells may have potential as an alternative source for cell therapy in diabetes. Viral gene delivery of a triad of TFs (*Pdx1*, *Neurog3* and *Mafa*) is another effective strategy for *in situ* transdifferentiation of both pancreatic exocrine cells (62) and liver cells (63) into functional insulin secreting cells.

The clinical application of this approach faces a number of challenges such as efficiency, stability and functionality of the target cells, identification of proper induction factor(s), epigenetic memory, safety concerns, and immune rejection issues associated with genetic manipulation (reviewed in (53)).

β cell regeneration ► Restoration of the endogenous β cell mass through regeneration is an attractive alternative approach. Replication of residual β cells (64, 65, 66), re-differentiation of dedifferentiated β cells (67), neogenesis from endogenous progenitors (68, 69) and transdifferentiation from (mature) non- β cells (62, 70) are proposed mechanisms for β cell regeneration.

β cell replication is the principal mechanism by which these cells are formed in the adult pancreas under normal physiological conditions (64, 66). Approaches that promote β cell replication and/or redirect dedifferentiated

Review	M Khosravi-Maharlooei, E Hajizadeh-Saffar and others	Islet transplantation for type 1 diabetes	173:5	R170
--------	---	--	-------	------

β cells toward insulin production can present an interesting strategy to restore the endogenous β cell mass.

In addition to β cells, evidence exists for the contribution of other pancreatic cell types such as acinar cells, α cells and pancreatic Neurog3 expressing cells (68) to the formation of new β cells in different mouse models. The signals that drive the endogenous regenerative mechanisms are only marginally understood. A role for paracrine signaling from the vasculature to β cell regeneration has been hypothesized. This hypothesis is supported by clear correlation between blood vessels and β cell mass adaptation during periods of increased demand and the impact of endothelial cell-derived hepatocyte growth factor (HGF) on the β cell phenotype. In addition to the putative role of paracrine signals from the vasculature, the possibility of an endocrine trigger for β cell proliferation and regeneration has been proposed. In this regard a fat and liver derived hormone, ANGPTL8/betatrophin, was suggested as a β cell proliferation trigger (71). Although new findings about lack of efficacy of this hormone in human islet transplantation (72) and knock-out mouse models (73) contradicted its expected utility for clinical application, the proposed possibility of endocrine regulation of β cell replication might provide an alternative approach for augmenting insulin based treatment or islet transplantation in the future. Several factors have been evaluated for their ability to promote β cell regeneration. Glucagon-like peptide-1, HGF, gastrin, epidermal growth factor (EGF) and ciliary neurotrophic factor are among these factors (74). While growth factors that promote β cell proliferation can be applied when a substantial residual β cell mass remains or has been restored, factors that promote cellular reprogramming towards a β cell fate and/or reactivate endogenous β cell progenitors are of great interest for T1D and end-stage type 2 diabetes patients. To revert to the diabetic state, a combination of exogenous regenerative stimuli and adequate immunotherapy is necessary to protect newly-formed β cells from auto-immune attacks in T1D patients.

Sub-optimal engraftment of islets

Significant portions of islets are lost in the early post-transplantation period due to apoptosis induced by damage to islets during islet preparation and after transplantation. During the islet isolation process, insults such as enzymatic damage to islets, oxidative stress and detachment of islet cells from the surrounding extracellular matrix (ECM) make them prone to apoptosis. Furthermore, while islets are transplanted within the

intra-vascular space, inflammatory cytokines initiate a cascade of events that contribute to their destruction.

Improvement of pancreas procurement, islet isolation and culture techniques

The main source of islets for clinical islet transplantation is the pancreas of BDDs. Brain death causes up-regulation of pro-inflammatory cytokines in a time-dependent manner (75), hence islets are subject to different stresses during the pancreas procurement which can induce apoptosis. In the previous decades, several studies have shown that improvements in pancreas procurement, islet isolation and culture techniques result in increasing islet yield and subsequently favorable clinical outcomes. The islet isolation success rate is affected by factors such as donor characteristics, pancreas preservation, enzyme solutions, and density gradients for purification. Donor characteristics such as weight and BMI (>30) significantly affect islet yield (76, 77). Andres *et al.* (78) have claimed that a major pancreas injury which involves the main pancreatic duct during procurement is significantly associated with lower islet yield. In addition, the pancreas preservation method has undergone improvement in the past few years with the use of perfluorocarbon (PFC), which slowly releases oxygen. PFC in combination with University of Wisconsin (UW) solution is a two-layer method for pancreatic preservation during the cold ischemia time, which leads to a higher islet yield (77). In terms of enzyme solution effects in pancreas digestion and islet separation from acinar tissues (79, 80), although liberase HI has been determined to be very effective in pancreas digestion, its use in clinical islet isolation was discontinued due to the potential risk of bovine spongiform encephalopathy transmission (79, 80). Therefore, enzyme formulation has shifted to collagenase blend products such as a mixture of good manufacturing practice (GMP) grade collagenase and neutral protease (79, 80). The enzymes mixture and the controlled delivery of enzyme solutions into the main pancreatic duct facilitated the digestion of acinar tissue and their dispersement without islet damage (79, 81, 82).

Considering the importance of islet purification in their functionality, a number of studies have focused on improvements in islet purification methods. These methods include PentaStarch, which enters pancreatic acinar tissue and alters its density, a Biocoll-based gradient, and a COBE 2991 cell separator machine to increase post-purification islet yield (79, 80, 83). In addition, culturing the isolated, purified islets for

Review	M Khosravi-Maharlooei, E Hajizadeh-Saffar and others	Islet transplantation for type 1 diabetes	173:5	R171
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12–72 h causes enhancement of their purity and provides adequate time to obtain the data from islet viability assays as an important parameter in engraftment outcomes (80).

Due to the toxic nature of pancreatic acinar cells, it has been shown that islet loss after culture is higher in impure islet preparations. Supplementation of α -1 anti-trypsin (A1AT) into the culture medium maintains islet cell mass and functional integrity (84). By the same mechanism, Pefabloc as a serine protease inhibitor, can inhibit serine proteases that affect islets during the isolation procedure (85). Supplementation of human islet culture medium with glial cell line-derived neurotrophic factor (GDNF) has been shown to improve human islet survival and post-transplantation function in diabetic mice (86). In addition, treatment of islets prior to transplantation by heparin and fusion proteins such as soluble TNF- α , which inhibit the inflammatory response, can improve engraftment and islet survival (79, 87, 88). The presence of human recombinant prolactin in islet culture medium improves human β cell survival (89).

Although early islet survival has been improved by the mentioned modifications, most patients require more than one islet infusion from multiple donors in order to achieve insulin independency and a functional graft over a 2–3 year period after transplantation (90). In 2014, Shapiro group *et al.* reported a significant association between single-donor islet transplantation and long-term insulin independence with older age and lower insulin requirements prior to transplantation (76). Moreover, higher weight and BMI of the donor resulted in a higher isolated islet mass and significant association with single-donor transplantation (76). The effectiveness of pre-transplant administration of insulin and heparin has been shown on achievement of insulin independence in single-donor islet transplantation (76).

Prevention of apoptosis, reduction of the effects of inflammatory cytokines and oxidative damage

Both intrinsic and extrinsic pathways are involved in the induction of islet apoptosis after transplantation (91). Different strategies are used to block these two pathways or the final common pathway to prevent islet apoptosis.

Several inflammatory cytokines exert detrimental effects on islets after transplantation which lead to apoptosis and death; the most important are IL1 β , TNF- α and IFN- γ (92). Over-expression of IL1 receptor antagonist in islets (93), inhibition of TF NF- κ B which mediates the detrimental effects of these cytokines on islets (94), inhibition of toll-like receptor 4 and blockade of high

mobility group box 1 (HMGB1) with anti-HMGB1 mAb (95) are among the strategies used to inhibit inflammatory cytokines. There is decreased expression of anti-oxidants in pancreatic islets in comparison to most other tissues. Therefore, islets are sensitive to free oxygen radicals produced during the islet isolation process and after transplantation. According to research, over-expression of antioxidants such as manganese superoxide dismutase (SOD) (96) and metallothionein (97) in islets or systemic administration of antioxidants such as catalytic antioxidant redox modulator (98) protect the islets from oxidative damage. Inhibitors of inducible nitric oxide synthase are effective in protecting islets during the early post-transplantation period (99).

Prevention of anoikis

Interaction of islets with the ECM provides important survival signals that have been disrupted by enzymatic digestion of the ECM during the islet isolation process. This leads to an integrin-mediated islet cell death or anoikis (100). Integrins, located on the surface of pancreatic cells, normally bind to specific sequences of ECM proteins. Some synthetic peptide epitopes have been identified that mimic the effect of ECM proteins by binding to the integrins. Arginine-glycine-aspartic acid is the most extensively studied epitope which reduces the apoptosis rate of islets (101). Transplantation of islets in a fibroblast populated collagen matrix is also used to prevent anoikis in which fibroblasts produce fibronectin and growth factors to enhance viability and functionality of the islets (102).

Attenuating the instant blood-mediated inflammatory reaction

Islets are injected into the portal vein to reach the liver as the standard site for islet transplantation. When islets are in close contact with blood, an instant blood-mediated inflammatory reaction (IBMIR) occurs through activation of coagulation and the complement system. Platelets attach to the islet surface and leukocytes enter the islet. Finally, by formation of a clot around the islet and infiltration of different leukocyte subtypes, mainly polymorphonuclears, the integrity of the islet is disrupted (103).

Different strategies to attenuate IBMIR include inhibitors of complement and coagulation systems, coating the islet surface, and development of composite islet-endothelial cell grafts (103).

Review	M Khosravi-Maharlooei, E Hajizadeh-Saffar and others	Islet transplantation for type 1 diabetes	173:5	R172
---------------	---	--	--------------	-------------

Tissue factor and macrophage chemoattractant protein (MCP-1) are among the most important mediators of IBMIR. Although culturing islets before transplantation enhances tissue factor expression in them (104), addition of nicotinamide to the culture medium significantly reduces tissue factor and MCP-1 expression (105). Islets treated with anti-tissue factor blocking antibody along with i.v. administration of this antibody to recipients after transplantation result in improved transplantation outcomes (106). These inhibitors of the coagulation cascade have been administered in order to attenuate IBMIR: (i) melagatran as a thrombin inhibitor (107), (ii) activated protein C (APC) as an anticoagulant enzyme (108) and (iii) tirofiban as a platelet glycoprotein IIb-IIIa inhibitor (109). Thrombomodulin is a proteoglycan produced by endothelial cells that induces activated protein C generation. Liposomal formulation of thrombomodulin (lipo-TM) leads to improved engraftment of islets and transplantation outcomes in the murine model (110, 111).

Retrospective evaluation of islet transplant recipients has shown that peri-transplant infusion of heparin is a significant factor associated with insulin independence and greater indices of islet engraftment (112). Low-molecular weight dextran sulfate (LMW-DS), a heparin-like anticoagulant and anti-complement agent, is an alternative to reduce IBMIR (113).

Bioengineering of the islet surface through attachment of heparin (87) and thrombomodulin (114) is an efficient technique to decrease IBMIR without increasing the risk of bleeding. Immobilization of soluble complement receptor 1 (sCR1), as a complement inhibitor on the islet surface through application of different bioengineering methods, decreases activation of the complement system that consequently leads to decreased IBMIR (115, 116). Endothelial cells prevent blood clotting, thus their co-transplantation with islets in composites has also been evaluated and proven to be an efficient strategy to attenuate IBMIR (117).

Sites of transplantation

Infusion through the portal vein is a commonly used method of islet transplantation where islets easily access oxygen and nutrients at this site. Drawbacks, however, include activation of the complement and coagulation system (IBMIR), surgical side effects such as intra-abdominal hemorrhage and portal vein thrombosis, and lack of a safe way to detect early graft rejection. BM (29) and the striated muscle, brachioradialis, (30) are

alternative sites that have been tested successfully in human trials.

Lack of blood supply and oxygen delivery

Pancreatic islets are highly vascularized micro-organs with a dense network of capillaries. Despite the high demand of blood supply for intra-islet secretory cells there is a lag phase of up to 14 days for re-establishment of intra-graft blood perfusion which can contribute to a tremendous loss of functional islet mass in the early post-transplantation days. Furthermore, providing oxygen solely by gradient-driven passive diffusion during isolation and early post-transplantation can result in decreasing oxygen pressure in islets radially from the periphery to the core. In hypoxic conditions, β -cell mitochondrial oxidative pathways are compromised due to alterations in gene expression induced by activation of hypoxia-inducible factor (HIF-1 α) which leads to changes from aerobic glucose metabolism to anaerobic glycolysis and nuclear pyknosis (118).

Enhancement of islet vasculature

The most prevalent strategies that enhance vascularization include the use of angiogenic growth factors, helper cells and the ECM components which we briefly discuss. Secretion of pro-angiogenic factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGFs), HGF, EGF and matrix metalloproteinase-9 from islets recruits the endothelial cells mostly from the recipient to form new blood vessels. Over-expression of these factors in islets or helper cells leads to accelerated revascularization of islets post-transplantation (119). According to a number of reports, a VEGF mimetic helical peptide (QK) can bind and activate VEGF receptors to enhance the revascularization process (120). Coverage of islets with an angiogenic growth factor through modification of the islet surface with an anchor molecule attracts endothelial cells and induces islet revascularization (121). Pretreatment of islets with stimulators of vascularization is another strategy (122).

Concomitant transplantation of islets with BM stem cells, vascular endothelial cells, endothelial progenitor cells (EPCs) and MSCs creates a suitable niche for promotion of revascularization and enhancement of grafted islet survival and function (123, 124, 125, 126).

ECM-based strategies can be used to enhance grafted islet vascularization. It has been shown that fibrin induces differentiation of human EPCs and provides a suitable

Review	M Khosravi-Maharlooei, E Hajizadeh-Saffar and others	Islet transplantation for type 1 diabetes	173:5	R173
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niche for islet vascularization (127). Collagen and collagen mimetics have been used to stimulate islet vascularization (128, 129). Another possible solution is to prepare a pre-vascularized site before islet transplantation. A related novel idea is to create a sandwich comprised of two layers of pre-vascularized collagen gels around a central islet containing-collagen gel (130).

Oxygen delivery to the islets

Under hypoxic conditions, β -cell mitochondrial oxidative pathways are compromised due to alterations in gene expression induced by activation of HIF-1 α . In addition, activation of HIF-1 α reduces glucose uptake and changes aerobic glucose metabolism to anaerobic glycolysis. During isolation and early post-transplantation, providing oxygen solely by gradient-driven passive diffusion results in decreasing oxygen pressure in islets radially from the periphery to the core (131). Different strategies suggested to overcome the hypoxia challenge include hyperbaric oxygen (HBO) therapy (132), design of gas permeable devices (133), oxygen carrier agents (134) and *in situ* oxygen generators (135).

Hyperbaric oxygen therapy has been shown to mitigate hypoxic conditions during early post-islet transplantation in recipient animals frequently exposed to high pressure oxygen. This therapy improves functionality of islets transplanted intraportally or under the kidney capsule, reduces apoptosis, HIF-1 α and VEGF expression, and enhances vessel maturation (132, 136).

Gas permeable devices are another strategy for oxygenation of islets during culture and transplantation. Due to hydrophobicity and oxygen permeability of silicone rubber membranes, culturing of islets on these membranes prevents hypoxia-induced death (133, 137).

Oxygen carrier agents such as hemoglobin and perfluorocarbons (PFCs) are alternative techniques to prevent hypoxia. The hemoglobin structure is susceptible to oxidization and converts to methemoglobin in the presence of hypoxia-induced free radicals and environmental radical stresses (138). Therefore, hemoglobin cross-linking and the use of antioxidant systems like ascorbate–glutathione have been employed (138). Hemoglobin conjugation with SOD and catalase (CAT), as antioxidant enzymes, can create an Hb-conjugate system (Hb–SOD–CAT) for oxygenation of islets (134). Perfluorocarbons are biologically inert and non-polar substances where all hydrogens are substituted by fluorine in the hydrocarbon chains without any reaction with proteins or enzymes in the biological environment (139). O₂, CO₂ and N₂ can be

physically dissolved in PFCs which lead to more rapid oxygen release from this structure compared to oxyhemoglobin (140, 141). Perfluorocarbons have been applied to oxygenate islets in culture, in addition to fibrin matrix as an oxygen diffusion enhancing medium to hinder hypoxia induced by islet encapsulation (142).

Hydration of solid peroxide can be an effective way for *in situ* generation of oxygen. Encapsulation of solid peroxide in polydimethylsiloxane (PDMS) as a hydrophobic polymer reduces the rate of hydration and provides sustained release of oxygen. Through this approach, metabolic function and glucose-dependent insulin secretion of the MIN6 cell line and islet cells under hypoxic *in vitro* conditions have been retained (135).

Alleviating hypoxia for protection of normal islet function results in reduced expression of pro-angiogenic factors and delayed revascularization (118). Therefore, hypoxia prevention methods are necessary to apply in combination with other methods to increase the islet revascularization process.

Immune rejection of transplanted islets

After allogeneic islet transplantation, both allogeneic immune reactions and previously existing autoimmunity against islets contribute to allograft rejection. The ideal immune-modulation or immune-isolation approach should target both types of immune reactions.

Central tolerance induction

Central tolerance is achieved when B and T cells are rendered non-reactive to self in primary lymphoid organs, BM and the thymus by presentation of donor alloantigens to these organs. BM transplantation and intra-thymic inoculation of recipient antigen presenting cells (APCs) pulsed with donor islet antigens (143) have been successfully tested to develop central tolerance. Hematopoietic chimerism induced by body irradiation followed by BM transplantation eliminates alloimmune reactions (144, 145). To reduce the toxic effects of irradiation, a sub-lethal dose can be combined with co-stimulatory blockade or neutralizing antibodies to induce mixed hematopoietic tolerance (146).

Suppressor cells: tolerogenic dendritic cells, regulatory T cells and MSCs

Different suppressor cells are candidates to induce peripheral immune tolerance. Although tolerogenic

Review	M Khosravi-Maharlooei, E Hajizadeh-Saffar and others	Islet transplantation for type 1 diabetes	173:5	R174
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dendritic cells (tol-DCs) are potent APCs that present antigens to T cells, they fail to present the adequate co-stimulatory signal or deliver net co-inhibitory signals. The major characteristics of tol-DCs include low production of interleukin-12p70 and high production of IL10 and indoleamine 2,3-dioxygenase (IDO), as well as the ability to generate alloantigen-specific regulatory T cells (T_{regs}) and promote apoptotic death of effector T cells (reviewed in (147)). These characteristics make tol-DCs good candidates for induction of immune tolerance in recipients of allogenic islets.

Application of donor tol-DCs mostly suppresses the direct allorecognition pathway while recipient tol-DCs pulsed with donor antigens prevent indirect allorecognition and chronic rejection of islets. These cells are not clinically favorable for transplantation from deceased donors because of the number of culture days needed to prepare donor derived DCs (147). Giannoukakis *et al.* (148) have conducted a phase I clinical trial on T1D patients and reported the safety and tolerability of autologous DCs in a native state or directed *ex vivo* toward a tolerogenic immunosuppressive state.

Blockade of NF- κ B has been employed to maintain DCs in an immature state for transplantation. Blockade of co-stimulatory molecules, CD80 (B7-1) and CD86 (B7-2) on DCs (149), genetic modification of DCs with genes encoding immunoregulatory molecules such as IL10 and TGF- β (150, 151), and treatment of DCs with vitamin D3 (152) are among approaches to induce tol-DCs. Uptake of apoptotic cells by DCs converts these cells to tol-DCs that are resistant to maturation and able to induce T_{regs} (153). Due to limitations in clinical application of *in vitro* induced tol-DCs, systemic administration of either donor cells undergoing early apoptosis (154) or DC-derived exosomes (155) are more feasible approaches to induce donor allopeptide specific tol-DCs *in situ*.

T_{regs} are a specialized subpopulation of $CD4^{+}$ T cells that participate in maintenance of immunological homeostasis and induction of tolerance to self-antigens. These cells hold promise as treatment of autoimmune diseases and prevention of transplantation rejection. Naturally occurring T_{regs} (n T_{regs}) are selected in the thymus and represent ~5–10% of total $CD4^{+}$ T cells in the periphery. Type 1 regulatory T (Tr1) cells are a subset of induced T_{regs} (iT T_{regs}) induced in the periphery after encountering an antigen in the presence of IL10. They regulate immune responses through secretion of immunosuppressive cytokines IL10 and TGF- β (156).

It has been shown that antigen-specific Tr1 cells are more potent in induction of tolerance in islet

transplantation compared to polyclonal Tr1 cells (157). Similarly, antigen-specificity of n T_{regs} is an important factor in controlling autoimmunity and prevention of graft rejection in islet transplantation (158). Co-transplantation of islets and recipient T_{regs} induced *in vitro* through incubation of recipient $CD4^{+}$ T cells with donor DCs in the presence of IL2 and TGF- β 1 (159) or donor DCs conditioned with rapamycin (160) are effective in prevention of islet allograft rejection. Donor specific Tr1 cells can be induced *in vivo* through administration of IL10 and rapamycin to islet transplant recipients (161). Coating human pancreatic islets with $CD4^{+}$ $CD25^{\text{high}}$ $CD127^{-}$ T_{reg} cells has been used as a novel approach for the local immunoprotection of islets (162). The chemokine CCL22 can be used to recruit the endogenous T_{regs} toward islets in order to prevent an immune attack against them (163). Regulatory B cells can induce T_{regs} and contribute to tolerance induction against pancreatic islets by secretion of TGF- β (164). Attenuation of donor reactive T cells increases the efficacy of T_{regs} therapy in prevention of islet allograft rejection (165).

Several studies have proven the immunomodulatory effects of MSCs and efficacy of these cells to preserve islets from immune attack when co-transplanted (166, 167, 168, 169, 170). Different immunosuppressive mechanisms proposed for MSCs include Th1 suppression (167), Th1 to Th2 shift (166), reduction of CD25 surface expression on responding T-cells through MMP-2 and 9 (169), marked reduction of memory T cells (166), enhancement of IL10 producing $CD4^{+}$ T cells (167), increase in peripheral blood T_{reg} numbers (168), suppression of DC maturation and endocytic activity of these cells (166), as well as reduction of pro-inflammatory cytokines such as IFN- γ (170). An ongoing phase 1/2 clinical trial in China has assessed the safety and efficacy of intra-portal co-transplantation of islets and MSCs (ClinicalTrials.gov, identifier: NCT00646724).

Signal modification: co-stimulatory and trafficking signals

In addition to the signal coded by interaction of the peptide-MHC complex on APCs with T cell receptors, secondary co-stimulatory signals such as the B7-CD28 and CD40-CD154 families are needed for complete activation of T cells.

While CTLA4 is expressed on T cells its interaction with B7 family molecules transmits a tolerogenic signal. Efficacy of CTLA4-Ig to prevent rejection of transplanted islets has been proven in both rodents and clinical studies

Review	M Khosravi-Maharlooei, E Hajizadeh-Saffar and others	Islet transplantation for type 1 diabetes	173:5	R175
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(171, 172). B7H4 is a co-inhibitory molecule of the B7 family expressed on APCs that interacts with CD28 on T cells. Over-expression of B7H4 in islets has been shown to increase their survival in a murine model of islet transplantation (173, 174).

Interaction of CD40 on APCs with CD40L (CD154) on T cells indirectly increases B7-CD28 signaling, enhances inflammatory cytokines, and activates T cell responses. Although blockade of B7-CD28 and CD40-CD154 pathways by CTLA4-Ig and anti-CD154 antibody can enhance the survival of islets in a mouse model of islet transplantation, rejection eventually occurs. This rejection may be due to the compensatory increase of another co-stimulatory signal through interaction of inducible co-stimulator (ICOS) on T cells with B7-related protein-1 (B7RP-1) on APCs. The combination of anti-ICOS mAb to the previous treatments increases islet survival (175).

Prevention of migration and recruitment of pro-inflammatory immune cells into the islets has emerged as an effective approach for inhibition of graft rejection. Expressions of chemokines such as RANTES (CCL5), IP-10 (CXCL10), I-TAC (CXCL11), MCP-1 (CCL2), and MIP-1 (CCL3) increase islet allograft rejection compared to isografts (176).

CXCL1 is highly released by mouse islets in culture and its serum concentration is increased within 24 h after intra-portal infusion of islets, as with CXCL8, the human homolog of CXCL1. Pharmacological blockade of CXCR1/2 (the chemokine receptor for CXCL1 and CXCL8) by reparixin has been shown to improve islet transplantation outcome both in a mouse model and in the clinical setting (177).

Encapsulation strategies

Encapsulated islets are surrounded by semi-permeable layers that allow diffusion of nutrients, oxygen, glucose and insulin while preventing entry of immune cells and large molecules such as antibodies. Three major devices developed for islet immune-isolation include intravascular macrocapsules, extravascular macrocapsules and microcapsules. Clinical application of intravascular macrocapsule devices is limited due to the risk of thrombosis, infection and need for major transplantation surgery (178, 179, 180). Extravascular devices are more promising as they can be implanted during minor surgery. These devices have a low surface-to-volume ratio; hence there is a limitation in seeding density of cells for sufficient diffusion of nutrients (181).

Microencapsulation surrounds a single islet or small groups of islets as a sheet or sphere. Due to the high surface to volume ratio, microcapsules have the advantage of high oxygen and nutrient transport rates. Although preliminary results in transplantation of encapsulated islets have shown promising results, further application in large animals is challenging due to the large implant size. Living Cell Technologies (LCT) uses the microencapsulation approach for immunoisolation of porcine pancreatic islet cells. The LCT clinical trial report in 1995–1996 has shown that porcine islets within alginate microcapsules remained viable after 9.5 years in one out of nine recipients. More recent clinical studies by this company have revealed that among seven patients who received encapsulated porcine islets, two became insulin independent. Currently, LCT is performing a phase IIb clinical trial with the intent to commercialize this product in 2016. Unlike microspheres, thin sheets have the advantages of high diffusion capacity of vital molecules and retrievability (182). Islet Sheet Medical is an islet-containing sheet made from alginate which has successfully passed the preclinical steps of development. A clinical trial will be started in the near future (161).

Recently, engineered macrodevices have attracted attention for islet immunoisolation. Viacyte Company has designed a net-like structure that encapsulates islet-like cells derived from hESCs. After promising results in an animal model, Viacyte began a clinical trial in 2014 (157). Another recent technology is Beta-O2, an islet-containing alginate macrocapsule surrounded by Teflon membrane that protects cells from the recipient immune system (158). Benefits of Beta-O2 include supplying oxygen with an oxygenated chamber around the islet-containing module. Its clinical application has shown that the device supports islet viability and function for at least 10 months after transplantation (183).

Immune suppression medication regimens

Induction of immunosuppression is an important factor that determines the durability of insulin independence. Daclizumab (IL2R antibody) has been widely used to induce immunosuppression in years after the Edmonton protocol. Although the primary results were promising, long-term insulin independence was a challenge to this regimen. Bellin *et al.* compared the long-term insulin independence in four groups of islet transplanted patients with different induction immunosuppressant therapies. Maintenance immunosuppressives were approximately the same in all groups and consisted of a calcineurin

Review	M Khosravi-Maharlooei, E Hajizadeh-Saffar and others	Islet transplantation for type 1 diabetes	173:5	R176
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inhibitor, tacrolimus or cyclosporine, plus mycophenolate mofetil or a mammalian target of rapamycin (mTOR) inhibitor (sirolimus). The 5-year insulin independence was 50% for the group of patients that received anti-CD3 antibody (teplizumab) alone or T-cell depleting antibody (TCDAb), ATG, plus TNF- α inhibitor (TNF- α -i), etanercept, as the induction immunosuppressant. The next two groups that received TCDAb (ATG or alemtuzumab) with or without TNF- α -i had 5-year insulin independence rates of 50 and 0% respectively. The last group that received daclizumab as the induction immunosuppressant had a 5-year insulin independence rate of 20% (15). This study showed that potent induction immunosuppression (PII) regimens could improve long-term results of islet transplantation. This might be due to stronger protection of islets during early post-transplant and engraftment of a higher proportion of transplanted islets. Constant overstimulation of an inadequately low islet mass could cause their apoptosis. This would explain the unfavorable long-term insulin independence rate for daclizumab as the induction immunosuppressant.

On the other hand, anti-CD3, ATG and alemtuzumab may help to restore immunological tolerance towards islet antigens by enhancing T_{reg} cells and shift the balance away from effector cells towards a tolerogenic phenotype (184, 185). Toso *et al.* have studied the frequency of different fractions of immune cells within peripheral blood of islet recipients compared after induction of immunosuppression using either a depleting agent (alemtuzumab or ATG) or a non-depleting antibody (daclizumab). Both alemtuzumab and ATG led to prolonged lymphocyte depletion, mostly in CD4⁺ cells. Unlike daclizumab, alemtuzumab induced a transient reversible increase in relative frequency of T_{reg} cells and a prolonged decrease in frequency of memory B cells (185). Positive effect of alemtuzumab on T_{reg} cells has been further proved by *in vitro* exposure of peripheral blood mononuclear cells to this immunosuppressant (186). An anti-CD3 mAb was also shown to induce regulatory CD8⁺CD25⁺ T cells both *in vitro* and in patients with T1D (184).

In the study of Bellin *et al.*, co-administration of TNF- α inhibitor at induction led to a higher insulin independence rate. This result could be attributed to the protective effect of the TNF- α inhibitor against detrimental action of TNF- α on transplanted islets at the time of infusion (187) in addition to its inducing impact on T_{reg} expansion (188).

For the maintenance of immunosuppression, the Edmonton group used sirolimus (a macrolide antibiotic

which inhibits mTOR) and tacrolimus (a calcineurin inhibitor). Tacrolimus has been shown to have toxicity on nephrons, neurons and β cells (189), and inhibit spontaneous proliferation of β cells (65). Froud *et al.* (189) showed that substitution of tacrolimus with mycophenolatemofetil (MMF) in an islet recipient with tacrolimus-induced-neurotoxicity resulted in resolution of symptoms, as well as an immediate improvement in glycemic control. Unlike MMF, tacrolimus has been shown to impair insulin exocytosis and disturb human islet graft function in diabetic NOD-scid mice (190). MMF is now more commonly used in islet transplantation clinical trials.

A relatively new generation of immunosuppressants relies on blockade of co-stimulation signaling of T cells. Abatacept (CTLA-4Ig) and belatacept (LEA29Y) – a high affinity mutant form of CTLA-4Ig, selectively block T-cell activation through linking to B7 family on APCs and prevent interaction of the B7 family with CD28 on T cells (191). Substitution of tacrolimus with belatacept in combination with sirolimus or MMF, as the maintenance therapy, and ATG, as the induction immunosuppressant, has been tested in clinical islet transplantation. All five patients treated with this protocol achieved insulin independence after a single transplant (171). In another study, successful substitution of tacrolimus with efalizumab, an anti-leukocyte function-associated antigen-1 (LFA-1) antibody, was reported for maintenance of an immunosuppressant regimen of islet transplant patients. However, as this medication was withdrawn from the market in 2009, long-term evaluation was not possible (192).

In the current clinical settings, islets are transplanted into the portal vein. Oral immunosuppressants first pass through the portal system after which their concentration increases dramatically in the portal vein where the islets reside (193). This phenomenon may impose adverse toxic effects on islets. Therefore, other routes of administration of immunosuppressants may be preferable for islet transplantation.

Conclusion

Even if all BDD pancreata can be successfully used for single donor allogeneic islet transplantation, abundant β cell sources are required to meet the needs to treat all diabetic patients. Therefore, investigating alternative sources of β cells obtained by either differentiation or transdifferentiation, as well as xenogenic islet sources is of great importance.

Review	M Khosravi-Maharlooei, E Hajizadeh-Saffar and others	Islet transplantation for type 1 diabetes	173:5	R177
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Low islet quality, anoikis, oxidative damage, apoptosis, effect of inflammatory cytokines, hypovascularization and hypoxia as well as activation of the coagulation and complement system contribute to limited engraftment of islets after transplantation. A combined approach applying the different aforementioned strategies to overcome these detrimental factors is probably necessary to optimize the engraftment rate of the transplanted islets. Recent advances in immunosuppressive medications have led to improved long-term outcome of islet transplantation. However, the final goal is to find a permanent treatment that induces/mediates tolerance of the immune system against the transplanted islet antigens.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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Author contribution statement

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Review	M Khosravi-Maharlooei, E Hajizadeh-Saffar and others	Islet transplantation for type 1 diabetes	173:5	R178
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