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Editorial Board Member of *World Journal of Transplantation*, Frieder Keller, MD, Doctor, Nephrology Division, Medical Department Innere 1, University Hospital, D-89070 Ulm, Germany

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REVIEW

# Intra-islet endothelial cell and β-cell crosstalk: Implication for islet cell transplantation

Siddharth Narayanan, Gopalakrishnan Loganathan, Maheswaran Dhanasekaran, William Tucker, Ankit Patel, Venugopal Subhashree, SriPrakash Mokshagundam, Michael G Hughes, Stuart K Williams, Appakalai N Balamurugan

Siddharth Narayanan, Gopalakrishnan Loganathan, Maheswaran Dhanasekaran, William Tucker, Ankit Patel, SriPrakash Mokshagundam, Michael G Hughes, Stuart K Williams, Appakalai N Balamurugan, Clinical Islet Cell Laboratory, Center for Cellular Transplantation, Cardiovascular Innovation Institute, Department of Surgery, University of Louisville, Louisville, KY 40202, United States

Venugopal Subhashree, School of Biosciences and Technology, VIT University, Vellore 632014, India

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Correspondence to: Appakalai N Balamurugan, PhD, Clinical Islet Cell Laboratory, Center for Cellular Transplantation, Cardiovascular Innovation Institute, Department of Surgery, University of Louisville, 302 E Muhammad Ali Blvd., Louisville, KY 40202, United States. bala.appakalai@louisville.edu
Telephone: +1-502-7947070
Fax: +1-502-8540558

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## Abstract

The intra-islet microvasculature is a critical interface between the blood and islet endocrine cells governing a number of cellular and pathophysiological processes associated with the pancreatic tissue. A growing body of evidence indicates a strong functional and physical interdependency of β-cells with endothelial cells (ECs), the building blocks of islet microvasculature. Intra-islet ECs, actively regulate vascular permeability and appear to play a role in fine-tuning blood glucose sensing and regulation. These cells also tend to behave as "guardians", controlling the expression and movement of a number of important immune mediators, thereby strongly contributing to the physiology of islets. This review will focus on the molecular signalling and crosstalk between the intra-islet ECs and β-cells and how their relationship can be a potential target for intervention strategies in islet pathology and islet transplantation.

**Key words:** Islets; Endothelial cells; Islet cell transplantation; Beta-cells; Microvasculature; Paracrine signalling



**Core tip:** This review article summarizes recent developments in the cross-talk relationship between intra-islet endothelial cells and beta cells. The molecules involved in the signalling pathways can be potential targets for therapeutic strategies and islet transplantation.

Narayanan S, Loganathan G, Dhanasekaran M, Tucker W, Patel A, Subhashree V, Mokshagundam S, Hughes MG, Williams SK, Balamurugan AN. Intra-islet endothelial cell and β-cell crosstalk: Implication for islet cell transplantation. *World J Transplant* 2017; 7(2): 117-128 Available from: URL: http://www.wjgnet.com/2220-3230/full/v7/i2/117.htm DOI: http://dx.doi.org/10.5500/wjt.v7.i2.117

## INTRODUCTION

Pancreatic islets represent endocrine "island" cell clusters, embedded and scattered throughout the pancreas within large amounts of exocrine acinar tissue[1]. Islets are perfused by a dense, specialized microcirculation and receive 10% of the pancreatic blood flow despite comprising only 1%-2% of the overall tissue mass[2]. Most islets are irregularly shaped spheroids with a size distribution ranging from 50-500 μm, each composed of 800-3000 individual cells. The islet microcirculation is characterized by pre islet arterioles that rapidly arcade to a dense population of capillaries[3].

The cellular components of the islet include β-cells, other endocrine cells, as well as endothelium, perivascular, and support cells such as pericytes[4-9]. The cellular composition of islets is not uniform across species. Rodent and rabbit islets are primarily composed of a β-cell core with other cell types in the periphery whereas human and primate islets exhibit endocrine cell types intermingled with each other[4,10,11]. Beta cells, the central regulator of glucose homeostasis, are the largest cellular component of islets in most species[9,10].

Studies using vascular corrosion casts have demonstrated that 1-3 arterioles feed larger islets[12]. The capillary network within islets is about five times denser in comparison with exocrine tissue[3]. The capillary wall is composed of a permeable layer of ECs and contains ten times more fenestrae than ECs present in the exocrine pancreas[13,14]. The islet endothelial fenestra are highly specialized and contain a diaphragm that regulates solute transport[15,16]. Typically, a microvessel consists of ECs arranged into a tube formation wrapped by one or more layers of perivascular cells. Vascular ECs represent a major cell type present in islets and these cells are organized into a highly regulated and morphologically unique microcirculation. In culture, islet ECs express the classic endothelial markers such as von Willebrand factor, CD31, CD105, CD146, uptake of acetylated LDL, expression of leucocyte adhesion molecules, contain Weibel-Palade bodies in the cytoplasm, and form tight junctions[17,18]. Other markers expressed within islet ECs include α-1 antitrypsin, a major proteinase inhibitor[17,19,20]; nephrin, a highly specific barrier protein[16]; platelet-activating factor receptor[21], and genes expressing angiogenic (vascular endothelial growth factor, VEGF) and angiostatic (endostatin, pigment epithelial-derived factor) molecules[22].

Islet ECs have a significant relationship with islet function. For example, islets grafts, when co-transplanted[23] with ECs in diabetes induced rats or coated[24] with ECs in diabetes induced mice, have better engraftment capacity and improved islet function. Donor islet ECs, immediately after transplantation, participate in neovascularization by increasing β-cell survival[25] and promote both pancreatic stem cell proliferation and islet regeneration after β-cell injury[26]. Research performed over the last two decades has evaluated the link between islets and the ECs, demonstrating how the molecular interplay between these two cell types can regulate many critical physiological processes associated with the islet.

## THE SIGNALS FROM β-CELL TO ECS

*In vitro* studies demonstrate that conditioned medium derived from cultured rat islets induces liver and islet-derived EC proliferation and migration[27], suggesting presence and secretion of paracrine pro-angiogenic factors (Figure 1) which promote islet vascularization[28]. As a major soluble β-cell secreted product, insulin promotes β-cell survival. In addition, insulin causes the upregulation of endothelial nitric oxide synthase in ECs promoting intra-islet blood flow[29]. Post-natal beta mass is dynamic and can increase in function and mass to compensate for additional physiological requirements[30].

### *VEGFs*

The family of VEGF ligands and their receptors are critical as they regulate a number of developmental processes and play major roles in wound healing and vessel homeostasis in adult organisms[31,32]. VEGF secretion is stimulated by tumor, hypoxia, low pH and many other factors. Beta-cells secrete large amounts of VEGF-A early in development and throughout adult life[33]. The VEGF binds to its receptor (VEGFR) located on the blood vessel ECs, which activates multiple signalling cascades eventually resulting in the production of enzymes and other specific molecules required for EC growth and proliferation. Other activation effects include mobilization of endothelial progenitor cells from bone marrow, increased vascular permeability and tissue factor induction[34]. The VEGF family comprises seven secreted glycoproteins that are designated VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, placental growth factor and VEGF-F[35-37]. VEGF family members interact with three main receptors, VEGFR-1 (FLt-1), VEGFR-2 (KDR in humans and Flk-1 in mice) and VEGFR-3 (Flt4), all tyrosine kinase receptors and members of the PGDF receptor family. VEGFR-2 appears to be the main receptor responsible for mediating the proangiogenic effects of VEGF-A[35,38,39]. The consequence of this specific ligand-receptor interaction facilitates EC proliferation *via* the PKC-Ras pathway (by inducing MAPK/ERK pathways)[40,41]; promotes cytoskeletal reorganization and cell migration *via* p38 and focal adhesion kinase

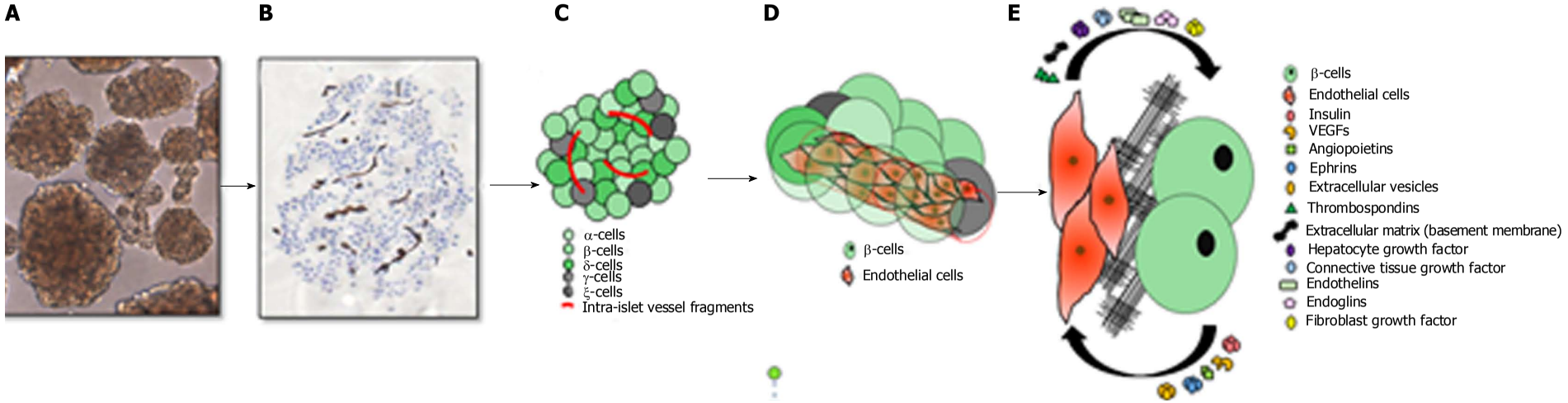


**Figure 1 A model demonstrating the intra-islet endothelial cell and β-cell crosstalk.** A: An image of freshly isolated human islets; B: Immunohistochemical staining of an islet demonstrating intra-islet vessels stained with CD31 (brown); C: Schematic representation of different cells within an islet along with intra-islet vessel fragments; D: A three dimensional (3D) depiction of islet cells and how these surround the intra-islet vessels, which are a group of endothelial cells arranged into a tube like structure; E: A model demonstrating a cross-talk relationship between endothelial cells and β-cells mediated by various endocrine factors/molecules. VEGFs, angiopoietins, insulin, cell surface molecules including ephrins mainly produced by the β-cell, are important factors for endothelial cell proliferation. Endothelium-derived factors such as hepatocyte growth factor, thrombospondins, basement membrane components (laminins, collagens) improve β-cell survival and promote insulin transcription and secretion. Other EC-derived factors include fibroblast growth factor and the vasoconstrictive endothelin-1. VEGF: Vascular endothelial growth factor; EC: Endothelial cell.

activation[42]; and supports EC cell survival and migration by activating the PI3K/Akt/PKB pathway[43,44].

VEGF-A is known to utilize the VEGFR-2 receptor on ECs[45], with the receptor highly expressed in intra-islet capillaries[46]. VEGF likely stimulates EC growth in neonatal pancreas; increased levels of VEGF-A correspond with islet growth in pregnant rats[47]. VEGF-A signaling is also essential in maintaining vascular beds in adult islets, this was validated using VEGF receptor antagonists[48]. VEGF-A expression is further upregulated in islets by hypoxia and glucose[49,50] and is important for the establishment of native intra-islet vasculature[51], maintenance of β-cell mass[52], and the revascularization of islets following transplantation[53].

### *Angiopoietins*

Apart from VEGF-A, other known factors such as those within Ang/Tie family are known to contribute towards the survival and integrity of blood vessels[33,54,55]. These angiogenic factors consist of ligands Ang-1, Ang-2 and Ang-4 (its mouse orthologue, Ang-3) and the tyrosine kinase receptors Tie-1 and Tie-2. Ang-1 is expressed mainly by the perivascular cells and β-cells in mouse and human islets[33], and its agonist Tie-2 is expressed by the ECs. Ang-1 activates the pI3k/Akt pathway and prevents cytokine mediated apoptosis in ECs[56]. Moreover, β-cell specific overexpression of Ang-1 or Ang-2 only slightly impairs insulin secretion and glucose tolerance together with marginal altered vascularization, islet mass and morphology[57]. Reports also suggest that Ang-1/Tie-2 signaling promotes cell-cell contacts and contact to extracellular matrix (ECM)[58,59]. Ang-2 however, expressed by ECs, classically antagonizes Tie-2 signaling[60] and plays key roles in angiogenesis and inflammation.

### *Ephrins*

Ephrin ligands and their tyrosine kinase receptors are involved in various aspects of cell communication[61,62]. Each ephrin ligand together with its specific receptor (Eph) is categorised either into the A or B subclass. Most EphA receptors bind to ephrin-A ligand, while most EphB receptors bind to ephrin-B ligands[63]. Transcriptome analyses

suggest that Eph-ephrin interaction between exocrine and endocrine cells contributes to pancreatic function[64]. Ephrin-A and its receptor EphA play a role in β-cell to β-cell communication; specifically, ephrin subtype A5 is required for glucose stimulated insulin secretion and the EphA-ephrin-A mediated interaction between β-cells is bidirectional[65]. The blood vessel ECs within pancreatic islets express Eph subtype A4 receptors[66] but how these ligands and receptors play a role between EC and β-cell crosstalk is subject to investigation.

### *Extracellular vesicles*

Recent reports establish extracellular vesicles (EVs) as a novel player in cell-to-cell communication[67,68] and have been characterized both in human islets[69] and in experimental models of human islet xenotransplantation in SCID mice[70]. Studies exploring the functional contribution of β-cell EVs on islet ECs demonstrate that islet-derived EVs have the capacity to affect the surrounding ECs, which are then able to internalize the islet EVs in a dose dependent manner[69]. Furthermore, internalization of islet EVs results in transfer of multiple RNAs, including insulin mRNA and various microRNAs. Uptake of islet EVs conferred endothelial cell resistance to apoptosis and up-regulated expression of numerous proangiogenic factors[69]. In a different study, endothelial progenitor cell EVs, when internalized by islet α-, β- and ECs resulted in improved glucose-stimulated proliferation and angiogenesis[70].

## THE ENDOCRINE EFFECT OF ISLET ECS ON β-CELLS

Islet ECs, apart from their pivotal role in angiogenesis, also possess endocrine function. They produce multiple factors (Figure 1) that govern proliferation, survival, and gene expression, which contribute to the physiology and function of the β-cell[71-75].

### *Basement membrane*

ECM proteins provide biochemical cues interpreted by cell surface receptors and initiate signalling cascades controlling morphogenesis, cell survival, proliferation, differentiation, and stem cell state[76-78]. Islets are surrounded by a peri-islet basement membrane (BM) and an associated interstitial matrix containing multiple components such as collagen, laminin, fibronectin, perlecans, nidogens, and heparin sulphate[79,80]. Beta-cells depend on intra-islet ECs to synthesize their ECM components[75]. It has been reported that collagen IV, secreted by islet endothelium, can potentiate insulin secretion *via* interaction with its receptor integrin $\alpha_1\beta_1$ on β-cells[81] similar to other BM components such as laminins and fibronectin which have been reported to act as endothelial signals promoting insulin gene expression and proliferation in β-cells[75,82]. Interaction of collagen IV with its receptors also contributes to β-cell differentiation, maturation, and survival[83-85]. Other BM components such as fibronectin and heparin sulfate also play roles in β-cell migration, growth, differentiation and survival[1,86-88].

### *Connective tissue growth factor*

The β-cell proliferative factor, connective tissue growth factor (CTGF/CCN2), is a member of the CCN family of secreted ECM-associated proteins[89,90] and is expressed in ECs during development[90,91]. It induces expression of platelet derived growth factor B (PDGF-B) in ECs, required for pericyte recruitment and retention[91]. CTGF promotes β-cell regeneration[92], proliferation[93], and modulates the response to high glucose[94]. Its inactivation results in defects in islet cell lineage allocation and β-cell proliferation during embryogenesis[95].

### *Hepatocyte growth factor*

Islet ECs release the hepatocyte growth factor (HGF)[13] which induces β-cell proliferation and differentiation in embryonic and postnatal pancreas[47,75,95-98]. HGF plays a positive role in β-cell mitogenesis, differentiation, glucose sensing, and transplant survival[99,100]. *In vitro*, VEGF-A and insulin are islet-derived factors that induce the HGF secretion within purified islet ECs. *In vivo*, utilizing of pregnant rat pancreas, where a high physiological proliferation of β cells occur, resulted in a prominent expression of HGF, coinciding with the peak of β-cell proliferation[74].

### *Thrombospondins*

Thrombospondins are matricellular glycoproteins that participate in a regulating cell proliferation, migration, and apoptosis, and have been implicated in angiogenesis, tumour invasion, and metastasis[101,102]. Thrombospondin-1 (TSP-1) is almost exclusively expressed by the intra-islet endothelium[71,103,104] and is not downregulated by hypoxia[105]. TSP-1 is mainly known for its antiangiogenic properties[106] but also may alter the morphology of pancreatic islets and function as a major activator of transforming growth factor TGFβ-1[107]. Animals deficient of this glycoprotein are characterized by hypervascular islets[107] and the EC-derived TSP-1 is important to maintain β-cell function postnatally[71].

### *Endothelins*

Endothelin is a vasoconstrictive protein. Endothelin-1 (ET-1) predominantly is found to have strong effects on native islet blood vessels[108] while ET-1 and ET-3 may directly stimulate β-cell insulin secretion and release[73,109]. The gene expression of ET-1 in both ECs and islet endocrine cells is regulated by hypoxia[110,111]. Insulin can also stimulate the expression and secretion of ET-1 from bovine ECs[112] and endogenous insulin can regulate circulating ET-1 concentrations in humans[113]. ET-1 also upregulates the expression of the *FOXO1* gene

(encoding a transcription factor) on ECs contributing to its survival[114].

### *Endoglin*

Endoglin (Eng) is a homodimeric transmembrane glycol protein within the TGF-β superfamily and is expressed by vascular ECs[115-118]. Studies have identified two distinct Eng positive cell types within human and mouse islets: The ECs and the mesenchymal stromal cells[119]. EC-specific endoglin expression in islets is sensitive to VEGF playing partial roles in driving islet vascular development[120].

## IMPLICATIONS OF β-CELL AND ENDOTHELIAL CROSSTALK ON ISLET TRANSPLANTATION

### *Islet transplantation and revascularization*

The human islet isolation technique completely severs the islet vasculature[121,122]. During the enzymatic digestion step, islets undergo a number of cellular assaults such as ischemia, mechanical stress, loss of basement proteins, and partial disruption of intra-islet ECs[123-125] resulting in a substantial loss of viability before transplantation. Other than being devoid of ECs to support rapid revascularization, cytotoxic damage and cell death account for a loss of up to 80% of transplanted islets[126,127]. Rapid and adequate revascularization is critical for survival and function of transplanted islets[121,128,129]. Transplanted islet grafts initially have a significant reduction in vascular supply and low oxygen tension in comparison to normal islets[130-132]. The return of islet function depends on re-establishment of new vessels within islet grafts to derive blood flow from the host vascular system[123,133]. Islet engraftment is a slow process, while the islet blood flow re-establishment requires about two weeks, vessel maturation is likely to take a much longer period. Using immunosuppressive drugs such as rapamycin further affect this process by exerting antiangiogenic activities on mouse and human islet endothelium[134].

Though transplanted islets are considered avascular, freshly isolated islets retain angiogenic capacity as they contain intra-islet ECs. These cells can be triggered by various inducers such as VEGF to form vessels *via* angiogenic sprouting[33,135,136]. Revascularization is an important process for adequate engraftment of islets. Prevascularizing islets prior to transplantation could potentially improve islet survivability and function by aiding islet-to-host inosculation[25]. The intra-islet vasculature can also act as a barrier against infiltrating insults of autoreactive cells in type 1 diabetes (T1D) thereby implicating ECs as an important target in type 2 diabetes (T2D)[137-139].

Studies involving cell and tissue engineering approaches have considered factors such as pancreatic islet size-dependency[140], use of stem cells[141-144], creating engineered vascular beds and hydrogels[145-147], endothelial progenitor cell derived microvesicles[70], and repurposed biological scaffolds[148] to improve islet revascularization potential. The angiogenic capacity of islet ECs has been previously determined[136]. A number of factors which may potentially improve islet transplantation involve ECs. For example, vascular ECs of the embryonic aorta induce the development of endocrine cells from pancreatic epithelium in mice[149,150] and the overexpression of VEGF-A in transplanted mouse islets improves insulin secretion and blood glucose regulation in recipient mice[33,53]. Identifying novel factors and understanding nature of mechanisms that underlie bidirectional communication between β-cells and ECs should be of immense relevance for improved human islet transplantation or preventing pancreas associated diseases such as pancreatitis and diabetes.

### *ECs and β-cell crosstalk: Islet pathophysiology, current perspectives and future directions*

Evaluation of factors contributing to mechanisms responsible for regulating the interaction between β-cells and intra-islet ECs would broaden our understanding of pancreatic tissue function, growth, and disease. In this context, VEGF-A has been the most well studied molecule[51,53]; however, reports have suggested the detrimental effects of VEGF on islets. Continued β-cell overexpression of VEGF-A impairs islet morphology and function by eliciting an inflammatory response[57,151]. Elevated levels of serum VEGF, Ang-2, and soluble Tie-2 have also been associated with T2D and vascular dysfunction[152-154]. Achieving an optimal VEGF-A dose to potentiate islet vascularization is subject to further investigation. The HGF production is increased during pregnancy in adult rats[74] and helps balance high glucose levels in diabetes induced mice[155]. *HGF* gene therapy has been suggested as a potential approach for improving islet transplantation rates and treatment of diabetes[156,157].

The dense pancreatic vasculature along with its associated ECM plays a key role in the physiology and disease associated with pancreatic islets. The islet is an ideal "tissue" model because of its heterogeneous cell population embedded within the ECM. Understanding the nature of how these cells communicate with each other and with their underlying BM is crucial for normal islet physiology and pathology. The β-cells rely on intra-islet ECs to synthesise their ECM components[75]. This dependency may potentially be compromised in chronic inflammatory pancreatic diseases such as chronic pancreatitis which is characterized by a number of alterations within ECM formation and composition resulting in destruction of acinar and islet cells, and subsequent replacement by connective tissue[158,159]. This connective tissue appears to result from an increased deposition and disorganization of the ECM proteins including collagens, fibronectins, and laminins[160-163]. Moreover, reports also suggest that one of the most

enriched groups of over-expressed proteins in pancreatitis (mild and severe) and pancreatic ductal adenocarcinoma include those involved in the ECM structure and organization[164,165]. In addition, glycoproteins, especially those with N-linked glycosylation sites, are significantly enriched among the over-expressed proteins in mild and chronic pancreatitis[164]. Collagen, proteoglycans, and other ECM specialized glycoproteins such as fibrillin, fibronectin, and laminin, all part of the peri-islet BM, contain various degrees of glycosylation[166].

The connection between ECs and β-cells has been previously evaluated[28,51,57,167,168], particularly where different approaches have been utilized to increase β-cell mass and thereby insulin production. New factors have also been identified which may potentially contribute in further understanding islet cell communication and function. For example, R-spondins-1, an intestinal growth factor containing a thrombospondin domain, has been identified as a novel β-cell growth factor and insulin secretagogue[169]. It has potential to enhance β-cell growth and function in patients with T2D, and enhance of β-cell mass[170]. Connexins, ephrins, and cadherins, members of the transmembrane family of proteins are expressed in pancreatic islets. The major β-cell connexin is Cx36[171], Cx43, and Cx45 are specifically expressed on intra-islet ECs[172] whereas Cx30.2, recently identified, is expressed at cell-cell junctions in both cell types[173].

A number of studies have demonstrated that ECs play a very critical role within the islet microenvironment. A dysfunctional intra-islet vascular endothelium may contribute to the severity or progression of pancreatic disease etiologies. A deeper knowledge of islet endothelial phenotype and function will help identify specific targets and strategies for T1D prevention and successful outcomes for islet transplantation. Identifying and validating the potential therapeutic benefits of novel factors which either maintain the integrity of EC and β-cell communication or reinstate and balance the disrupted crosstalk is likely to benefit patients with diabetes and other pancreatic disorders.

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