Mechanisms of Angiogenesis Process after Pancreatic Islet Cell Transplantation: Role of Intra-islet Endothelial Cells

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Abstract

Angiogenic sprouting is a complex, multi-step process involving highly integrated cell behaviours, initial interaction with the environment and signalling pathways. Endothelial cells (ECs) are central to the angiogenic process, with recent insights establishing how these cells communicate with each other and with their microenvironment to form branched vascular networks. Using pancreatic islets as a model for vascularized tissue, this review will present a general overview of EC behaviour dynamics in sprouting angiogenesis, particularly focusing on the interplay between VEGF and Notch pathways. A better understanding of molecular mechanisms associated with intra-islet EC cross-talk and its micro-environment may present exciting new perspectives on islet graft to host revascularization and in supporting islet graft survival.

Keywords: Transplantation; Endothelial cells; Angiogenesis; Revascularization; VEGF; Notch signaling

Introduction

Pancreatic islets are highly vascularized and receive 10% of the pancreatic blood flow despite comprising of only 1-2% of the overall tissue mass [1]. Islets represent endocrine “island” clusters, embedded and scattered within large amounts of exocrine acinar tissue [2]. Most islets are irregularly shaped spheroids with a size distribution ranging from 50–200 μm, composed of 800–3,000 cells. In the context of islet studies and transplantation, 1 islet equivalent (IEQ) is often considered as a size of 150 mm, consisting of an average 2,500 cells. The cellular components of the islet include β-cells with the remainder of the islet comprised of other endocrine cells (including glucagon-secreting α-cells, somatostatin secreting δ-cells, pancreatic polypeptide-secreting γ-cells, and ghrelin-producing ε-cells), as well as ECs and support cells such as pericytes [3-12]. Species heterogeneity exists with respect to cellular composition of islets. Rodent islets are primarily composed of β-cells located in the center with other cell types in the periphery, human islets exhibit interconnected α- and β-cells [3-13,14], β-cell, the central regulator of glucose homeostasis is the largest cellular component of islets in most species [12,13]. Vascular endothelial cells represent a major cell type present in islets and these cells are organized into a highly regulated and morphologically unique microcirculation. Studies using vascular corrosion casts have shown that 1-3 arterioles feed larger islets [15]. The capillary network within islets is about five times denser in comparison with exocrine tissue [16]. The capillary wall is composed of a permeable layer of ECs and contain ten times more fenestrae than ECs present in the exocrine pancreas [17,18]. Rapid and adequate revascularization is critical for survival and function of transplanted islets [19-21]. Unlike whole organ transplantation where revascularization occurs through surgical anastomosis of vessels, the revascularization of islets requires the formation of vessel patencies either through insolation of host and recipient microvessels or through neo-vessel penetration into the islet. The return of islet function depends on reestablishment of new vessels within islet grafts to derive blood flow from the host vascular system [22,23]. Transplanted islet grafts initially have a significant reduction in vascular supply and low oxygen tension in comparison to normal islets [24-26]. The human islet isolation technique completely severs the islet vasculature [20,27], the enzymatic digestion step contributing towards partially disrupting intra-islet ECs [22,28,29]. 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 insolation [30]. Studies involving cell and tissue engineering approaches have considered factors such as pancreatic islet size-dependency [31], use of stem cells [32-35], endothelial progenitor cell derived microvessicles [36], creating engineered vascular beds and hydrogels [37-39] and repurposed biological scaffolds [40] to improve islet revascularization potential. The angiogenic capacity of islet ECs has been previously determined [41]. These cells have been shown to support revascularization of fresh islets by participating in the early processes of vessel formation [30,42]. Unpublished data from our lab demonstrates that fresh islets, immediately after isolation, are capable of forming peri-islet vessels in a 3D-gel construct (Figure 1 & 2). The initial molecular events by which intra-islet ECs result in the formation of such vessels have not yet been explored. This review will focus on the VEGF-Notch signalling pathways and their associated molecular regulation which have been well characterized and shown to play key roles in endothelial crosstalk critical to proper vessel sprouting.

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Regulation of angiogenesis

VEGF family: critical regulators of angiogenesis

The family of VEGF (vascular endothelial growth factor) ligands and their receptors are major regulators of sprouting angiogenesis. VEGFs are critical, as they regulate vessel formation during embryonic development, play a major role in wound healing and in maintaining vessel homeostasis in adult organisms. In addition, impaired vessel function resulting from defects in VEGF ligands or receptors is the cause of many diseases. VEGF was originally described as a vascular permeability factor (VPF), an activity released by tumor cells that promotes vascular leakage [43,47-56]. VEGF secretion is stimulated by tumor, hypoxia, low pH and many other factors. The VEGF binds to its receptor (VEGFR) located on the blood vessel ECs. The ECs upon activation produce enzymes and other molecules for EC growth and proliferation. Other effects include mobilization of endothelial progenitor cells from bone marrow, increased vascular permeability and tissue factor induction. The VEGF family comprises seven secreted glycoproteins that are designated VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, placental growth factor (PlGF) and VEGF-F [57-59]. VEGF-A, the most well studied factor within the VEGF family, is expressed in the extra-embryonic endoderm and mesoderm as blood islands, and within the intra-embryonic endoderm at E8.5 [60] (Table 1).

### Table 1: Types of vascular endothelial growth factors (VEGFs) with evidence demonstrating their involvement in regulating endothelial cells.

| Type of VEGF | Role in regulating/modulating ECs                                                                 | References |
|--------------|--------------------------------------------------------------------------------------------------|------------|
| VEGF-A       | Most potent pro-angiogenic protein described to date, implicated in both vasculogenesis and angiogenesis. It induces proliferation, sprouting and tube formation of ECs. Also induces angiogenesis in endothelial cells. | [49,57]    |
|              | Causes vasodilation by inducing the endothelial nitric oxide synthase and so increasing nitric oxide production. VEGF-A binds many receptors on hematopoietic stem cells (HSCs), monocytes, osteoblasts and neurons; induces HSC mobilization from the bone marrow, monocyte chemo-attraction and osteoblast-mediated bone formation. | [61,62]    |
|              | Many cytokines including platelet-derived growth factor, basic fibroblast growth factor, the epidermal growth factor and transforming growth factors induce VEGF-A expression in cells. | [63]       |
| VEGF-B       | Several reports suggest that VEGF-B may modulate cell proliferation and vessel growth. Conditioned medium from transfected cells expressing VEGF-B stimulates DNA synthesis in endothelial cells. Shown to play a central role in cardiac development. | [64]       |
| VEGF-C       | The mature form of VEGF-C induces mitogenesis, migration and survival of ECs. VEGF-C mRNA transcription is induced in ECs in response to pro-inflammatory cytokines (IL-β). Promote lymphatic vessel development and may also contribute to angiogenesis. | [65]       |
| VEGF-D       | The mature human VEGF-D is mitogenic, angiogenic and lymphogenic in vivo. Stimulates growth of vascular and lymphatic ECs by signaling through the tyrosine kinase receptors (VEGFR-2, VEGFR-3). Promote lymphatic vessel development and may also contribute to angiogenesis. | [66]       |
| VEGF-E       | Highly specific isoform that acts only on the endocrine gland endothelial cells. VEGF-E is a potent angiogenic factor and data strongly indicates that the activation of VEGFR-2 alone can stimulate angiogenesis efficiently. | [67]       |
| PIGF         | Originally identified in the placenta; occurs at low levels in the embryo and adult and has primarily been studied in pathological conditions where it is thought to stimulate angiogenesis in coordination with VEGF-A. | [68]       |

**VEGF family members interact with three main receptors, VEGFR-1 (FLT-1), VEGFR-2 (KDR in humans and Flk-1 in mouse) and VEGFR-3 (Flt4), all tyrosine kinase receptors and members of the PDGF receptor family. VEGF receptors possess an extracellular domain consisting of immunoglobulin repeats responsible for VEGF binding and intracellular tyrosine kinase domains. VEGF binding to its receptor leads to receptor dimerization and activation of receptor tyrosine kinases by autophosphorylation. This leads to several biologic effects on endothelial cells. The VEGF receptor transmembrane tyrosine kinases, which upon binding of their ligands to the extracellular domain of the receptor, activate a cascade of downstream proteins after the dimerization and autophosphorylation of the intracellular receptor tyrosine kinases. VEGFR-2 appears to be the main receptor responsible for mediating the proangiogenic effects of VEGF-A [57,79,80]. VEGF-A and its receptors VEGFR-1 and VEGFR-2 are expressed early in embryonic development (Table 2).**
Type of VEGFR | Role in regulating/modulating endothelial cells (ECs) | References
--- | --- | ---
VEGFR-1 | Expressed in ECs as well as osteoblasts, monocytes/macrophages, placental trophoblasts, renal mesangial cells and also in some hematopoietic stem cells (HSCs). VEGFR-1 expression is upregulated by hypoxia (HIF1 dependent mechanism). Has an active functional role and participates in monocyte migration, recruits EC progenitors and increases adhesive properties of natural killer cells. | [81], [82], [83-86]
VEGFR-2 | Undergoes dimerization and strong ligand-dependent tyrosine phosphorylation in intact cells and results in a mitogenic, chemotactic, and pro-survival signal. Y1175 and Y1214 are the two major VEGF-A-dependent autophosphorylation sites in VEGFR-2. However, only autophosphorylation of Y1175 is imperative for VEGF dependent EC proliferation. In addition to the ECs, VEGFR-2 is also expressed on neuronal cells, osteoblasts, megakaryocytes and HSCs. It is down-regulated in the blood vascular ECs, and is again up-regulated in angiogenic blood vessels. Sequestration of VEGF-A results in down-regulation of VEGFR-2 and in apoptotic death of some capillary endothelial cells in vivo. It is an early marker of endothelial and hematopoietic precursor cells in blood islands. | [87], [88], [57,87], [89,90], [91,92]
VEGFR-3 | Recently shown to be strongly modulated by Notch upregulating angiogenesis in absence of VEGF-VEGFR2 signalling. VEGFR-3 is up-regulated on blood vascular ECs in pathologic conditions such as in vascular tumors and in the periphery of solid tumors. Widely distributed in vascular tumors and can be considered as a marker of endothelial cell differentiation of vascular neoplasms. is down-regulated in vivo at sites of endothelial cell–pericyte/smooth muscle cell contacts; suggesting that VEGFR-3 signaling is important in nascent blood vessels, and it becomes redundant as the vessels mature. In humans, VEGFR-3 expression was upregulated in blood vessel endothelium in chronic inflammatory wounds. | [93], [89], [94], [95]

Table 2: An overview of vascular endothelial growth factor receptors and their roles in regulating endothelial cells.

**Notch signaling**

In addition to the VEGF receptor tyrosine kinases and their ligands, several recent studies demonstrate the importance of Notch signaling components such as ligands Dll4 (Delta-like ligand 4), Jagged-1 and Notch1 in EC specification during formation of a functional vascular network [96-99]. In mammals there are 5 DSL (Delta Serrate Lag-2) ligands: Delta-like 1 (Dll1), Delta-like 3 (Dll3), Delta-like 4 (Dll4), Jagged-1 (Jag1) and Jagged-2 (Jag2). These ligands are type I cell-surface proteins with multiple tandem epidermal growth factor (EGF) repeats in their extracellular domains (ECDs). DSL ligands bind to Notch receptors, which are large, single pass, type 1 transmembrane receptors. There are 4 known Notch receptors, Notch1 to Notch4. Binding of a DSL ligand to the ECD of the Notch receptor (NECD) triggers a series of proteolytic cleavages of Notch, first by a member of the disintegrin and metalloproteases (ADAM) family within the juxta-membrane region, followed by γ-secretase within the transmembrane domain (Table 3). The Notch receptors, ligands, and several signaling pathway components have been identified in endothelial cells in vitro and in vivo, during development and tumor angiogenesis [100-102].

Functional studies using gene targeting in mice, mutagenesis and knockdown in zebrafish, and biochemical analysis in cultured endothelial cells have demonstrated that Notch signaling plays a fundamental role in many aspects of endothelial cell biology during angiogenesis [113] (Table 4).

| Endothelial function | Notch component(s) involved | References |
| --- | --- | --- |
| Tip/stalk specification cell | Dll4 | [97-99,114,115] |
| | Notch1 | [97] |
| | Rbpj (zebrafish) | [98] |
| Proliferation | Dll4 | [99,110,115-117] |
| | Notch1 | [110] |
| | Notch4 | [118] |
| | Rbpj/Rbpja (zebrafish) | [98,106] |
| | Mam1 | [110] |
| | Hes1 | [110] |
| Vessel stability | Nrarp | [112] |
| Motility | Dll4 | [114,117] |
| | rbpj (zebrafish) | [98] |
| Filopodia protrusion | Dll4 | [97,99,114,115] |
| | Notch1b (zebrafish) | [114] |

Table 3: Notch pathway components expressed in endothelial cells.
Notch appears to act as a negative feedback mechanism to regulate VEGF signaling. This regulation may explain the observation that decreased VEGFR-2 allows for local differentiation of endothelial tip cells prior to sprout initiation with VEGF action on tip cells leading to increased DI4 expression and activation of Notch signaling, which in turn downregulates VEGFR-2 in neighboring stalk cells [46]. Tip cells with higher VEGFR-2 expression will, therefore, readily respond to VEGF while stalk cells with fewer receptors will be less responsive. Interestingly, tip cells do not proliferate in response to VEGF, but rather form filopodia and migrate in the direction of the VEGF gradient. It is the stalk endothelial cells of the growing capillary branch that proliferate [127].

In mouse and zebrafish angiogenesis, VEGF-R3 is strongly expressed in the leading tip cell and is downregulated by Notch signalling in the stalk cell [98,133]. Notch1 and Notch4 and the three Notch ligands JAG-1, DII and DI4 are expressed in ECs for the induction of arterial cell fate and for the selection of endothelial tip and stalk cells during sprouting angiogenesis [134]. Activation of Notch signalling reduces while its loss induces sprouting. Notch-1 deficient ECs adopt tip cell characteristics [97,98,129] whereas in stalk cells, activation of Notch by DI4 leads to downregulation of VEGFR-2 and -3 [101,135]. Cells dynamically compete for tip position utilizing differential VEGF levels, as cells with higher VEGF signalling produces more DI4 and therefore inhibit their neighbouring cells. VEGF has been shown to induce the expression of DI4 and Notch signalling [136]. Elevated DI4 and VEGF-R2 expression was detected in tip cells compared to neighboring stalk cells [96]. Blockage of VEGF in animal models, caused a decrease of DI4 in vessels and inhibited Sprouting [99] whereas administration of VEGF induced DI4 expression [115].

Notch signaling also influences VEGF receptor expression, leading to the downregulation of VEGFR-2, as evidenced by decreased VEGFR-2 levels after Notch activation in ECs and in DI4-deficient mice [99,109]. Endothelial Notch activation regulates the expression of different VEGFRs (VEGFR1, 2, and 3) as well as the co-receptor Nrp1 [46,93,97,98,101,114-116]. VEGF receptor expression, leading to the downregulation of VEGFR-2, as evidenced by decreased VEGFR-2 levels after Notch activation in ECs and in DI4-deficient mice [99,109]. Endothelial Notch activation regulates the expression of different VEGFRs (VEGFR1, 2, and 3) as well as the co-receptor Nrp1 [46,93,97,98,101,114-116]. VEGF receptor expression, leading to the downregulation of VEGFR-2, as evidenced by decreased VEGFR-2 levels after Notch activation in ECs and in DI4-deficient mice [99,109]. Endothelial Notch activation regulates the expression of different VEGFRs (VEGFR1, 2, and 3) as well as the co-receptor Nrp1 [46,93,97,98,101,114-116]. VEGF receptor expression, leading to the downregulation of VEGFR-2, as evidenced by decreased VEGFR-2 levels after Notch activation in ECs and in DI4-deficient mice [99,109]. Endothelial Notch activation regulates the expression of different VEGFRs (VEGFR1, 2, and 3) as well as the co-receptor Nrp1 [46,93,97,98,101,114-116]. VEGF receptor expression, leading to the downregulation of VEGFR-2, as evidenced by decreased VEGFR-2 levels after Notch activation in ECs and in DI4-deficient mice [99,109]. Endothelial Notch activation regulates the expression of different VEGFRs (VEGFR1, 2, and 3) as well as the co-receptor Nrp1 [46,93,97,98,101,114-116]. VEGF receptor expression, leading to the downregulation of VEGFR-2, as evidenced by decreased VEGFR-2 levels after Notch activation in ECs and in DI4-deficient mice [99,109]. Endothelial Notch activation regulates the expression of different VEGFRs (VEGFR1, 2, and 3) as well as the co-receptor Nrp1 [46,93,97,98,101,114-116]. VEGF receptor expression, leading to the downregulation of VEGFR-2, as evidenced by decreased VEGFR-2 levels after Notch activation in ECs and in DI4-deficient mice [99,109]. Endothelial Notch activation regulates the expression of different VEGFRs (VEGFR1, 2, and 3) as well as the co-receptor Nrp1 [46,93,97,98,101,114-116].

Table 4: Evidence for the role of Notch components involved in endothelial cell function.

**Table 4: Evidence for the role of Notch components involved in endothelial cell function.**

| Matrix assembly and cell adhesion | DI4 | [116,117,119,120] |
|----------------------------------|-----|------------------|
| Notch1                           | [119]|
| Notch4                           | [121]|
The vasculature within the pancreas is an important determinant in the yield and function because of its critical involvement in debilitating diseases such as Type-1 diabetes and chronic pancreatitis. The dense vasculature within the islet is an important determinant in the study of ECs with other islet cells, such as the β-cells has been evaluated particularly in increasing β-cell mass and thereby insulin production.

In the last two decades, focus has been paramount on the study of human pancreatic islets, its isolation techniques and in improving islet yield and function because of its critical involvement in debilitating diseases such as Type-1 diabetes and chronic pancreatitis. The dense vasculature within the islet is an important determinant in the study of ECs with other islet cells, such as the β-cells has been evaluated particularly in increasing β-cell mass and thereby insulin production. Moreover, a number of factors which may potentially improve islet transplantation involve ECs. Vascular ECs of the embryonic aorta have been shown to learn more about microvasculature and in this context the study of ECs within islets has potential benefits. The islet EC model represents an excellent platform to better understand molecular mechanisms associated with vessel sprouts, an important but greatly understudied area within islet research. Crosstalk of ECs with other islet cells, such as the β-cells has been evaluated [171-175] particularly in increasing β-cell mass and thereby insulin production. Moreover, a number of factors which may potentially improve islet transplantation involve ECs. Vascular ECs of the embryonic aorta have been shown to induce the development of endocrine cells from pancreatic epithelium in mouse [176,177] and overexpression of VEGF-A in transplanted mouse islets was shown to improve insulin secretion and blood glucose regulation in recipient mice [165,178]. Utilizing intra-islet ECs as a model to better understand mechanisms associated with sprouting angiogenesis is likely to generate exciting new hypotheses and offer new insights of how transplanted islets can reestablish vasculature more efficiently and successfully.

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**Table 5**: Novel regulators recently identified to play a role in angiogenesis (ECs/VEGF/Notch pathways).

| Novel regulators/components | Recently identified for sprouting angiogenesis (VEGF/Notch pathways) | References |
|----------------------------|-------------------------------------------------|------------|
| Deubiquilinases            | Notch                                           | [145]      |
| Cholesterol                | VEGF                                            | [146-148]  |
| MEF2 transcription factors | VEGF-Notch                                      | [149]      |
| Podosomes                  | VEGF-Notch                                      | [150]      |
| Adipogenic proteins        | VEGF-Notch                                      | [151,152]  |
| Glucose regulators         | VEGF-Notch                                      | [152,153]  |
| Foxo1 transcription factor | EC metabolism                                   | [154]      |
| Lactate                    | Angiogenesis                                    | [155]      |
| ROS and redox events       | VEGF                                            | [156-158]  |
| Cilia                      | Angiogenesis                                    | [159,160]  |
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