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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 inosculation 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 inosculation [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 microvesicles [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.

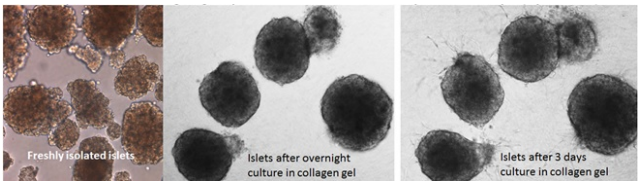

Figure 1: Islet sprout monitoring in group of human islets in time lapse microscope (Cytation™ 5 with Augmented Microscopy™) [BioTek Instruments, Inc.,].

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 [43-46]. 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 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).

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.	[49,57]
	Is a potent survival factor for ECs and has been shown to induce the expression of anti-apoptotic proteins in these cells.	[61,62]
	Causes vasodilation by inducing the endothelial nitric oxide synthase and so increasing nitric oxide production.	[63]
	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	[57,64]
	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.	[65]
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.	[66]
	Shown to play a central role in cardiac development.	[67,68]
VEGF-C	The mature form of VEGF-C induces mitogenesis, migration and survival of ECs	[69]
	VEGF-C mRNA transcription is induced in ECs in response to pro-inflammatory cytokines (IL-β).	[70]
	Promote lymphatic vessel development and may also contribute to angiogenesis.	[71-73]
VEGF-D	The mature human VEGF-D is mitogenic, angiogenic and lymphogenic *in vivo*	[69]
	Stimulates growth of vascular and lymphatic ECs by signaling through the tyrosine kinase receptors (VEGFR-2, VEGFR-3)	[74]
	Promote lymphatic vessel development and may also contribute to angiogenesis.	[71-73]
VEGF-E	Highly specific isoform that acts only on the endocrine gland endothelial cells.	[75]
	VEGF-E is a potent angiogenic factor and data strongly indicates that the activation of VEGFR-2 alone can stimulate angiogenesis efficiently.	[76]
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.	[77,78]

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

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 PGDF 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).	[81]
	VEGFR-1 expression is upregulated by hypoxia (HIF1 dependent mechanism).	[82]
	Has an active functional role and participates in monocyte migration, recruits EC progenitors and increases adhesive properties of natural killer cells.	[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.	[87]
	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.	[88]
	In addition to the ECs, VEGFR-2 is also expressed on neuronal cells, osteoblasts, megakaryocytes and HSCs.	[57,87]
	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*.	[89,90]
	It is an early marker of endothelial and hematopoietic precursor cells in blood islands.	[91,92]
VEGFR-3	Recently shown to be strongly modulated by Notch upregulating angiogenesis in absence of VEGF-VEGFR2 signalling.	[93]
	VEGFR-3 is up-regulated on blood vascular ECs in pathologic conditions such as in vascular tumors and in the periphery of solid tumors.	[89]
	Widely distributed in vascular tumors and can be considered as a marker of endothelial cell differentiation of vascular neoplasms.	[94]
	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.	[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 signalling 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 type1 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, type1 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].

Notch pathway	Pathway component expressed by ECs	References
Receptors	Notch1 and Notch4	[101,103-105]
Ligands	DSL ligands Dll1, Dll4, Jag1 and Jag2	[101,103-105]
Key Notch signaling components	Rbpj, Hey1, Hey2, Maml1, Numb and Nrarp	[104,106-112]

Table 3: Notch pathway components expressed in endothelial cells.

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 cell specification	Dll4	[97-99,114,115]
	Notch1	[97]
	Rbpja (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]
	rbpja (zebrafish)	[98]
Filopodia protrusion	Dll4	[97,99,114,115]
	Notch1b (zebrafish)	[114]

Matrix production/ assembly and cell adhesion	Dll4	[116,117,119,120]
	Notch1	[119]
	Notch4	[121]

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

EC phenotypes: Interplay between VEGF and Notch signaling in regulating EC sprouting

An exciting breakthrough within angiogenic research in the past decade has been the identification of different EC phenotypes with different cellular fate specifications that are key in forming a vessel branch [122]. Leading the trail are 'tip cells' which sense and respond to guidance cues. 'Stalk cells' follow behind the tip cells and elongate the stalk of the sprout by proliferating, forming junctions, modulating the extracellular matrix and forming a lumen. 'Phalynx cells', the most quiescent of the ECs, line vessels once new vessel branches have formed. These cells form a monolayer, are covered by pericytes, attached via tight junctions, and strongly held by a robust basement membrane. Phalynx cells are engaged in optimizing blood flow, tissue perfusion and oxygenation [123-125].

Specification of ECs into tip and stalk cells bearing different morphologies and functional properties is central to sprouting initiation [113,126]. Vessel networks, while expanding, require ECs to undergo frequent cycles of sprouting and branching. This results in dynamic transitions between the two cell phenotypes [113,126]. Tip cells express high levels of Dll4, platelet derived growth factor-b (PDGF-b), unc-5 homolog b (UNC5b), VEGFR 2/3 and has low levels of Notch signalling activity [98,99,103,127, 128]. Stalk cells produce fewer filopodia, are more proliferative, form tubes, branches and a vascular lumen, establish junctions with neighbouring cells and synthesise basement membrane components [113,129]. Tip cell migration depends on a VEGF gradient migrating outward from parent vessel whereas stalk cell proliferation is regulated by VEGF concentration [127,130]. VEGF stimulates tip cell induction and filopodia formation via VEGFR2 (abundant on filopodia), whereas VEGFR2 blockade is associated with sprouting defects [113]. VEGFR1 expression is induced by Notch signalling to reduce VEGF ligand availability preventing tip cell outward migration. VEGFR1 is predominantly expressed in stalk cells and is involved in guidance and limiting tip cell formation. Loss of VEGFR1 results in increased sprouting and vascularization [131,132].

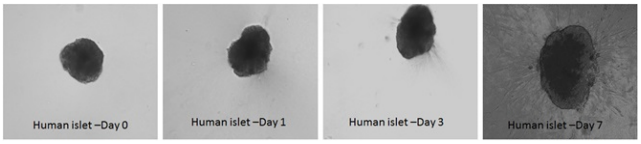

Figure 2: Islet sprout monitoring in single human islets in time lapse microscope (Cytation™ 5 with Augmented Microscopy™)[BioTek Instruments, Inc.,]

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 Dll4 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, VEGFR3 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, Dll1 and Dll4 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 Dll4 leads to downregulation of VEGFR-2 and -3 [101,135]. Cells dynamically compete for tip position utilizing differential VEGFR levels, as cells with higher VEGFR signalling produces more Dll4 and therefore inhibit their neighbouring cells. VEGF has been shown to induce the expression of Dll4 and Notch signaling [136]. Elevated Dll4 and VEGFR-2 expression was detected in tip cells compared to neighboring stalk cells [96]. Blockage of VEGF, in animal models, caused a decrease of Dll4 in vessels and inhibited sprouting [99] whereas administration of VEGF induced Dll4 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 Dll4-deficient mice [99,109]. Endothelial Notch activation regulates the expression of different VEGFRs (VEGFR1, 2, and 3) as well as the co-receptor Nrp1 [46,93,97,98,103,114,115,137]. Dll4 activates Notch in adjacent cells, which suppresses the expression of VEGF receptors and thereby restrains endothelial sprouting and proliferation [98,99,113,138]. Notch activation in HUVECS leads to VEGFR1 mRNA induction [120,139]. In contrast, VEGFR2 and Nrp1 mRNA is markedly reduced by Notch activation in HUVECs [137,140,141], indicating that Notch signaling is able to regulate how the ECs respond to VEGF. The Notch and VEGF signaling appear to be intimately associated in angiogenesis. It has been shown that Notch signalling acts downstream of the VEGF pathway during physiological and pathological angiogenesis [115,140,142-144], suggesting that VEGF pathway controls expression of different Notch components (Table 5).

Conclusions and Future Perspectives

Significant progress has been made in our understanding of importance of angiogenesis in health and disease but our knowledge of coordinated events that result in vessel branching and inosculation remains incomplete. We are just beginning to appreciate the interplay of other signalling pathways such as Wnt and BMP in regulating vessel sprouting. Angiogenesis is a complex, multi-step process. Key to this process are ECs, which are pivotal to sprouting angiogenesis and have been implicated in many diseases [60,161-163].

Novel regulators/components	Recently identified for sprouting angiogenesis (VEGF/Notch pathways)	References
Deubiquitinases	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]

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

It has been shown that EC proliferative capacities can be stimulated by various inducers [41,42,164,165]. A variety of *in vivo* and *in vitro* models for understanding EC behaviour during angiogenesis at the cellular level have been derived from systems such as rabbit cornea [166], developing mouse retina [167], intersegmental vessel growth in zebrafish [168] and using ECs embedded in collagen or fibrin gels [169,170].

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 pancreas is an important determinant in the physiology and disease of islets. The pancreatic islets is an ideal model 'tissue' 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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References

1. Chandra R, Liddle RA (2009) Neural and hormonal regulation of pancreatic secretion. Curr Opin Gastroenterol 25: 441-446.
2. Stendahl JC, Kaufman DB, Stupp SI (2009) Extracellular matrix in pancreatic islets: relevance to scaffold design and transplantation. Cell Transplant 18: 1-12.
3. Brissova M, Fowler MJ, Nicholson WE, Chu A, Hirshberg B, et al. (2005) Assessment of human pancreatic islet architecture and composition by laser scanning confocal microscopy. J Histochem Cytochem 53: 1087-1097.
4. Khandekar N, Berning BA, Sainsbury A, Lin S (2015) The role of pancreatic polypeptide in the regulation of energy homeostasis. Mol Cell Endocrinol 4181: 33-41.
5. Katsuura G, Asakawa A, Inui A (2002) Roles of pancreatic polypeptide in regulation of food intake. Peptides 23: 323-329.
6. Yada T, Damdindorj B, Rita RS, Kurashina T, Ando A, et al. (2014) Ghrelin signalling in beta-cells regulates insulin secretion and blood glucose. Diabetes Obes Metab 1: 111-117.
7. DiGruccio MR, Mawla AM, Donaldson CJ, Noguchi GM, Vaughan J, et al. (2016) Comprehensive alpha, beta and delta cell transcriptomes reveal that ghrelin selectively activates delta cells and promotes somatostatin release from pancreatic islets. Mol Metab 5: 449-458.
8. Wierup N, Svensson H, Mulder H, Sundler F (2002) The ghrelin cell: A novel developmentally regulated islet cell in the human pancreas. Regul Pept 107: 63-69.
9. Wierup N, Sundler F (2004) Circulating levels of ghrelin in human fetuses. Eur J Endocrinol 150: 405.
10. Kailey B, van de Bunt M, Cheley S, Johnson PR, MacDonald PE, et al. (2012) SSTR2 is the functionally dominant somatostatin receptor in human pancreatic beta- and alpha-cells. Am J Physiol Endocrinol Metab 303: 1107-1116.
11. Braun M (2014) The somatostatin receptor in human pancreatic beta-cells. Vitam Horm 95: 165-193.
12. Brereton MF, Vergari E, Zhang Q, Clark A (2015) Alpha, Delta and PP-cells: Are they the architectural cornerstones of islet structure and co-ordination? J Histochem Cytochem 63: 575-591.
13. Cabrera O, Berman DM, Kenyon NS, Ricordi C, Berggren PO, et al. (2006) The unique cytoarchitecture of human pancreatic islets has implications for islet cell function. Proc Natl Acad Sci U S A 103: 2334-2339.

14. Roder PV, Wu B, Liu Y, Han W (2016) Pancreatic regulation of glucose homeostasis. Exp Mol Med 48: e219.
15. Bonner-Weir S, Orci L (1982) New perspectives on the microvasculature of the islets of Langerhans in the rat. Diabetes 31: 883-889.
16. Henderson JR, Moss MC (1985) A morphometric study of the endocrine and exocrine capillaries of the pancreas. Q J Exp Physiol 70: 347-356.
17. Olsson R, Carlsson PO (2006) The pancreatic islet endothelial cell: emerging roles in islet function and disease. Int J Biochem Cell Biol 38: 710-714.
18. Cao Z, Wang X (2014) The endocrine role between beta cells and intra-islet endothelial cells. Endocr J 61: 647-654.
19. Zeng W, Gouw AS, van den Heuvel MC, Zwiers PJ, Zondervan PE, et al. (2008) The angiogenic makeup of human hepatocellular carcinoma does not favor vascular endothelial growth factor/angiopoietin-driven sprouting neovascularization. Hepatology 48: 1517-1527.
20. Bellacen K, Kalay N, Ozeri E, Shahaf G, Lewis EC, et al. (2013) Revascularization of pancreatic islet allografts is enhanced by alpha-1-antitrypsin under anti-inflammatory conditions. Cell Transplant 22: 2119-2133.
21. Jiang X, Abiatari I, Kong B, Erkan M, De Oliveira T, et al. (2009) Pancreatic islet and stellate cells are the main sources of endocrine gland-derived vascular endothelial growth factor/prokineticin-1 in pancreatic cancer. Pancreatology 9: 165-172.
22. Jansson L, Carlsson PO (2002) Graft vascular function after transplantation of pancreatic islets. Diabetologia 45: 749-763.
23. Menger MD, Yamauchi J, Vollmar B (2001) Revascularization and microcirculation of freely grafted islets of Langerhans. World J Surg 25: 509-515.
24. Mattsson G, Jansson L, Carlsson PO (2002) Decreased vascular density in mouse pancreatic islets after transplantation. Diabetes 51: 1362-1366.
25. Carlsson PO, Palm F, Andersson A, Liss P (2001) Markedly decreased oxygen tension in transplanted rat pancreatic islets irrespective of the implantation site. Diabetes 50: 489-495.
26. Lau J, Carlsson PO (2009) Low revascularization of human islets when experimentally transplanted into the liver. Transplantation 87: 322-325.
27. Zhao M, Choudhary P, Srinivasan P, Tang H, Heaton N, et al. (2015) Modification of human islet preparation: an effective approach to improve graft outcome after islet transplantation? Horm Metab Res 47: 72-77.
28. Konstantinova I, Lammert E (2004) Microvascular development: learning from pancreatic islets. Bioessays 26: 1069-1075.
29. Lukinius A, Jansson L, Korsgren O (1995) Ultrastructural evidence for blood microvessels devoid of an endothelial cell lining in transplanted pancreatic islets. Am J Pathol 146: 429-435.
30. Nyqvist D, Speier S, Rodriguez-Diaz R, Molano RD, Lipovsek S, et al. (2011) Donor islet endothelial cells in pancreatic islet revascularization. Diabetes 60: 2571-2577.
31. Kampf C, Mattsson G, Carlsson PO (2006) Size-dependent revascularization of transplanted pancreatic islets. Cell Transplant 15: 205-209.
32. Johansson U, Rasmusson I, Niclou SP, Forslund N, Gustavsson L, et al. (2008) Formation of composite endothelial cell-mesenchymal stem cell islets: a novel approach to promote islet revascularization. Diabetes 57: 2393-2401.
33. Ilgun H, Kim JW, Luo L (2015) Adult stem cells and diabetes therapy. J Stem Cell Res Transplant.
34. Rackham CL, Dhadda PK, Le Lay AM, King AJ, Jones PM, et al. (2014) Preculturing islets with adipose-derived mesenchymal stromal cells is an effective strategy for improving transplantation efficiency at the clinically preferred intraportal site. Cell Med 7: 37-47.
35. Fransson M, Brannstrom J, Duprez I, Essand M, Le Blanc K, et al. (2015) Mesenchymal stromal cells support endothelial cell interactions in an intramuscular islet transplantation model. Regen Med Res 3: 1.
36. Cantaluppi V, Biancone L, Figliolini F, Beltramo S, Medica D, et al. (2012) Microvesicles derived from endothelial progenitor cells enhance neoangiogenesis of human pancreatic islets. Cell Transplant 21: 1305-1320.
37. Kaufman-Francis K, Koffler J, Weinberg N, Dor Y, Levenberg S, et al. (2012) Engineered vascular beds provide key signals to pancreatic hormone-producing cells. PLoS One 7: e40741.
38. Phelps EA, Templeman KL, Thule PM, Garcia AJ (2015) Engineered VEGF-releasing PEG-MAL hydrogel for pancreatic islet vascularization. Drug Deliv Transl Res 5: 125-136.
39. Amer LD, Mahoney MJ, Bryant SJ (2014) Tissue engineering approaches to cell-based type 1 diabetes therapy. Tissue Eng Part B Rev 20: 455-467.
40. Willenberg BJ, Oca-Cossio J, Cai Y, Brown AR, Clapp WL, et al. (2015) Repurposed biological scaffolds: kidney to pancreas. Organogenesis 11: 47-57.
41. Linn T, Schneider K, Hammes HP, Preissner KT, Brandhorst H, et al. (2003) Angiogenic capacity of endothelial cells in islets of Langerhans. FASEB J 17: 881-883.
42. Nyqvist D, Kohler M, Wahlstedt H, Berggren PO (2005) Donor islet endothelial cells participate in formation of functional vessels within pancreatic islet grafts. Diabetes 54: 2287-2293.
43. Ferrara N (2002) VEGF and the quest for tumour angiogenesis factors. Nat Rev Cancer 2: 795-803.
44. Olsson AK, Dimberg A, Kreuger J, Claesson-Welsh L (2006) VEGF receptor signalling - in control of vascular function. Nat Rev Mol Cell Biol 7: 359-371.
45. Fong GH, Rossant J, Gertsenstein M, Breitman ML (1995) Role of the Flt-1 receptor tyrosine kinase in regulating the assembly of vascular endothelium. Nature 376: 66-70.
46. Patel-Hett S, D'Amore PA (2011) Signal transduction in vasculogenesis and developmental angiogenesis. Int J Dev Biol 55: 353-363.
47. Senger DR, Galli SJ, Dvorak AM, Perruzzi CA, Harvey VS, et al. (1983) Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. Science 219: 983-985.
48. Senger DR, Perruzzi CA, Feder J, Dvorak HF (1986) A highly conserved vascular permeability factor secreted by a variety of human and rodent tumor cell lines. Cancer Res 46: 5629-5632.
49. Senger DR, Connolly DT, Van de Water L, Feder J, Dvorak HF (1990) Purification and NH2-terminal amino acid sequence of guinea pig tumor-secreted vascular permeability factor. Cancer Res 50: 1774-1778.
50. Keck PJ, Hauser SD, Krivi G, Sanzo K, Warren T, et al. (1989) Vascular permeability factor, an endothelial cell mitogen related to PDGF. Science 246: 1309-1312.
51. Lobb RR, Key ME, Alderman EM, Fett JW (1985) Partial purification and characterization of a vascular permeability factor secreted by a human colon adenocarcinoma cell line. Int J Cancer 36: 473-478.
52. Bruce JN, Criscuolo GR, Merrill MJ, Moquin RR, Blacklock JB, et al. (1987) Vascular permeability induced by protein product of malignant brain tumors: inhibition by dexamethasone. J Neurosurg 67: 880-884.
53. Criscuolo GR, Merrill MJ, Oldfield EH (1988) Further characterization of malignant glioma-derived vascular permeability factor. Journal of neurosurgery 69: 254-262.
54. Connolly DT, Heuvelman DM, Nelson R, Olander JV, Eppley BL, et al. (1989) Tumor vascular permeability factor stimulates endothelial cell growth and angiogenesis. J Clin Invest 84: 1470-1478.
55. Rosenthal RA, Megyesi JF, Henzel WJ, Ferrara N, Folkman J (1990) Conditioned medium from mouse sarcoma 180 cells contains vascular endothelial growth factor. Growth Factors 4: 53-59.
56. Clauss M, Gerlach M, Gerlach H, Brett J, Wang F, et al. (1990) Vascular permeability factor: a tumor-derived polypeptide that induces endothelial cell and monocyte procoagulant activity and promotes monocyte migration. J Exp Med 172: 1535-1545.
57. Ferrara N, Gerber HP, LeCouter J (2003) The biology of VEGF and its receptors. Nat Med 9: 669-676.
58. Houck KA, Ferrara N, Winer J, Cachianes G, Li B, et al. (1991) The vascular endothelial growth factor family: identification of a fourth

molecular species and characterization of alternative splicing of RNA. Mol Endocrinol 5: 1806-1814.

59. Suto K, Yamazaki Y, Morita T, Mizuno H (2005) Crystal structures of novel vascular endothelial growth factors (VEGF) from snake venoms: insight into selective VEGF binding to kinase insert domain-containing receptor but not to fms-like tyrosine kinase-1. J Biol Chem 280: 2126-2131.
60. Patan S (2000) Vasculogenesis and angiogenesis as mechanisms of vascular network formation growth and remodeling. J Neurooncol 50: 1-15.
61. Benjamin LE, Keshet E (1997) Conditional switching of vascular endothelial growth factor (VEGF) expression in tumors: induction of endothelial cell shedding and regression of hemangioblastoma-like vessels by VEGF withdrawal. Proc Natl Acad Sci USA 94: 8761-8766.
62. Gerber HP, Dixit V, Ferrara N (1998) Vascular endothelial growth factor induces expression of the antiapoptotic proteins Bcl-2 and A1 in vascular endothelial cells. J Biol Chem 273: 13313-13316.
63. Hood JD, Meininger CJ, Ziche M, Granger HJ (1998) VEGF upregulates ecNOS message protein and NO production in human endothelial cells. Am J Physiol 274: H1054-1058.
64. Storkebaum E, Lambrechts D, Carmeliet P (2004) VEGF: once regarded as a specific angiogenic factor, now implicated in neuroprotection. Bioessays 26: 943-954.
65. Ferrara N (2004) Vascular endothelial growth factor: basic science and clinical progress. Endocr Rev 25: 581-611.
66. Olofsson B, Pajusola K, von Euler G, Chilov D, Alitalo K, et al. (1996) Genomic organization of the mouse and human genes for vascular endothelial growth factor B (VEGF-B) and characterization of a second splice isoform. J Biol Chem 271: 19310-19317.
67. Aase K, von Euler G, Li X, Ponten A, Thoren P, et al. (2001)Vascular endothelial growth factor-B-deficient mice display an atrial conduction defect. Circulation 104: 358-364.
68. Bellomo D, Headrick JP, Silins GU, Paterson CA, Thomas PS, et al. (2000) Mice lacking the vascular endothelial growth factor-B gene (Vegfb) have smaller hearts, dysfunctional coronary vasculature, and impaired recovery from cardiac ischemia. Circ Res 86: E29-35.
69. Saharinen P, Tammela T, Karkkainen MJ, Alitalo K (2004) Lymphatic vasculature: development, molecular regulation and role in tumor metastasis and inflammation. Trends Immunol 25: 387-395.
70. Ristimaki A, Narko K, Enholm B, Joukov V, Alitalo K, et al. (1998) Proinflammatory cytokines regulate expression of the lymphatic endothelial mitogen vascular endothelial growth factor-C. J Biol Chem 273: 8413-8418.
71. Karkkainen MJ, Haiko P, Sainio K, Partanen J, Taipale J, et al. (2004) Vascular endothelial growth factor C is required for sprouting of the first lymphatic vessels from embryonic veins. Nat Immunol 5: 74-80.
72. Tammela T, Alitalo K (2010) Lymphangiogenesis: Molecular mechanisms and future promise. Cell 140: 460-476.
73. Cao Y, Linden P, Farnebo J, Cao R, Eriksson A, et al. (1998) Vascular endothelial growth factor C induces angiogenesis in vivo. Proc Natl Acad Sci USA 95: 14389-14394.
74. Akahane M, Akahane T, Matheny SL, Shah A, Okajima E, et al. (2006) Vascular endothelial growth factor-D is a survival factor for human breast carcinoma cells. Int J Cancer 118: 841-849.
75. LeCouter J, Kowalski J, Foster J, Hass P, Zhang Z, et al. (2001) Identification of an angiogenic mitogen selective for endocrine gland endothelium. Nature 412: 877-874.
76. Meyer M, Clauss M, Lepple-Wienhues A, Waltenberger J, Augustin HG, et al. (1999) A novel vascular endothelial growth factor encoded by Orf virus, VEGF-E, mediates angiogenesis via signalling through VEGFR-2 (KDR) but not VEGFR-1 (Flt-1) receptor tyrosine kinases. EMBO J 18: 363-374.
77. Maglione D, Guerriero V, Viglietto G, Delli-Bovi P, Persico MG (1991) Isolation of a human placenta cDNA coding for a protein related to the vascular permeability factor. Proc Natl Acad Sci USA 88: 9267-9271.
78. Carmeliet P, Moons L, Luttun A, Vincenti V, Compernolle V, et al. (2001) Synergism between vascular endothelial growth factor and placental growth factor contributes to angiogenesis and plasma extravasation in pathological conditions. Nat Med 7: 575-583.
79. Dvorak HF (2002) Vascular permeability factor/vascular endothelial growth factor: a critical cytokine in tumor angiogenesis and a potential target for diagnosis and therapy. J Clin Oncol 20: 4368-4380.
80. Cross MJ, Dixelius J, Matsumoto T, Claesson-Welsh L (2003) VEGF-receptor signal transduction. Trends Biochem Sci 28: 488-494.
81. Zachary I, Gliki G (2001) Signaling transduction mechanisms mediating biological actions of the vascular endothelial growth factor family. Cardiovasc Res 49: 568-581.
82. Gerber HP, Condorelli F, Park J, Ferrara N (1997) Differential transcriptional regulation of the two vascular endothelial growth factor receptor genes Flt-1 but not Flk-1/KDR is up-regulated by hypoxia. J Biol Chem 272: 23659-23667.
83. Barleon B, Sozzani S, Zhou D, Weich HA, Mantovani A, et al. (1996) Migration of human monocytes in response to vascular endothelial growth factor (VEGF) is mediated via the VEGF receptor flt-1. Blood 87: 3336-3343.
84. Clauss M, Weich H, Breier G, Knies U, Rockl W, et al. (1996) The vascular endothelial growth factor receptor Flt-1 mediates biological activities. Implications for a functional role of placenta growth factor in monocyte activation and chemotaxis. J Biol Chem 271: 17629-17634.
85. Lyden D, Hattori K, Dias S, Costa C, Blaikie P, et al. (2001) Impaired recruitment of bone-marrow-derived endothelial and hematopoietic precursor cells blocks tumor angiogenesis and growth. Nat Med 7: 1194-1201.
86. Chen WS, Kitson RP, Goldfarb RH (2002) Modulation of human NK cell lines by vascular endothelial growth factor and receptor VEGFR-1 (FLT-1) In Vivo 16: 439-445.
87. Matsumoto T, Claesson-Welsh L (2001) VEGF receptor signal transduction. Sci STKE 2001: re21.
88. Takahashi T, Yamaguchi S, Chida K, Shibuya M (2001) A single autophosphorylation site on KDR/Flk-1 is essential for VEGF-A-dependent activation of PLC-gamma and DNA synthesis in vascular endothelial cells. EMBO J 20: 2768-2778.
89. Partanen TA, Alitalo K, Miettinen M (1999) Lack of lymphatic vascular specificity of vascular endothelial growth factor receptor 3 in 185 vascular tumors. Cancer 86: 2406-2412.
90. Baffert F, Thurston G, Rochon-Duck M, Le T, Brekken R, et al. (2004) Age-related changes in vascular endothelial growth factor dependency and angiopoietin-1-induced plasticity of adult blood vessels. Circ Res 94: 984-992.
91. Choi K, Kennedy M, Kazarov A, Papadimitriou JC, Keller G, et al. (1998) A common precursor for hematopoietic and endothelial cells. Development 125: 725-732.
92. Yamaguchi TP, Dumont DJ, Conlon RA, Breitman ML, Rossant J, et al. (1993) Flk-1 an flt-related receptor tyrosine kinase is an early marker for endothelial cell precursors. Development 118: 489-498.
93. Benedito R, Rocha SF, Woeste M, Zamykal M, Radtke F, et al. (2012) Notch-dependent VEGFR3 upregulation allows angiogenesis without VEGF-VEGFR2 signalling. Nature 484: 110-114.
94. Veikkola T, Lohela M, Ikenberg K, Makinen T, Korff T, et al. (2003) Intrinsic versus microenvironmental regulation of lymphatic endothelial cell phenotype and function. FASEB J 17: 2006-2013.
95. Paavonen K, Puolakkainen P, Jussila L, Jahkola T, Alitalo K, et al. (2000) Vascular endothelial growth factor receptor-3 in lymphangiogenesis in wound healing. Am J Pathol 156: 1499-1504.
96. Benedito R, Roca C, Sorensen I, Adams S, Gossler A, et al. (2009) The notch ligands Dll4 and Jagged1 have opposing effects on angiogenesis. Cell 137: 1124-1135.
97. Hellstrom M, Phng LK, Hofmann JJ, Wallgard E, Coultas L, et al. (2007) Dll4 signalling through Notch1 regulates formation of tip cells during angiogenesis. Nature 445: 776-780.

98. Siekmann AF, Lawson ND (2007) Notch signalling limits angiogenic cell behaviour in developing zebrafish arteries. Nature 445: 781-784.
99. Suchting S, Freitas C, le Noble F, Benedito R, Breant C, et al. (2007) The Notch ligand Delta-like 4 negatively regulates endothelial tip cell formation and vessel branching. Proc Natl Acad Sci USA 104: 3225-3230.
100. Gridley T (2007) Vascular biology: vessel guidance. Nature 445: 722-723.
101. Hofmann JJ, Iruela-Arispe ML (2007) Notch signaling in blood vessels: who is talking to whom about what? Circ Res 100: 1556-1568.
102. Roca C, Adams RH (2007) Regulation of vascular morphogenesis by notch signaling. Genes Dev 21: 2511-2524.
103. Claxton S, Fruttiger M (2004) Periodic Delta-like 4 expression in developing retinal arteries. Gene Expr Patterns 5: 123-127.
104. Favre CJ, Mancuso M, Maas K, McLean JW, Baluk P, et al. (2003) Expression of genes involved in vascular development and angiogenesis in endothelial cells of adult lung. Am J Physiol Heart Circ Physiol 285: H1917-1938.
105. Villa N, Walker L, Lindsell CE, Gasson J, Iruela-Arispe ML, et al. (2001) Vascular expression of Notch pathway receptors and ligands is restricted to arterial vessels. Mech Dev 108: 161-164.
106. Dou GR, Wang YC, Hu XB, Hou LH, Wang CM, et al. (2008) RBP-J the transcription factor downstream of Notch receptors is essential for the maintenance of vascular homeostasis in adult mice. FASEB J 22: 1606-1617.
107. Fischer A, Schumacher N, Maier M, Sendtner M, Gessler M, et al. (2004) The Notch target genes Hey1 and Hey2 are required for embryonic vascular development. Genes Dev 18: 901-911.
108. Iso T, Chung G, Hamamori Y, Kedes L (2002) HERP1 is a cell type-specific primary target of Notch. J Biol Chem 277: 6598-6607.
109. Taylor KL, Henderson AM, Hughes CC (2002) Notch activation during endothelial cell network formation in vitro targets the basic HLH transcription factor HESR-1 and downregulates VEGFR-2/KDR expression. Microvasc Res 64: 372-383.
110. Liu ZJ, Xiao M, Balint K, Soma A, Pinnix CC, et al. (2006) Inhibition of endothelial cell proliferation by Notch1 signaling is mediated by repressing MAPK and PI3K/Akt pathways and requires MAML1. FASEB J 20: 1009-1011.
111. Krebs LT, Deftos ML, Bevan MJ, Gridley T (2001) The Nrarp gene encodes an ankyrin-repeat protein that is transcriptionally regulated by the notch signaling pathway. Dev Biol 238: 110-119.
112. Phng LK, Potente M, Leslie JD, Babbage J, Nyqvist D, et al. (2009) Nrarp coordinates endothelial Notch and Wnt signaling to control vessel density in angiogenesis. Dev Cell 16: 70-82.
113. Phng LK, Gerhardt H (2009) Angiogenesis: A team effort coordinated by notch. Dev Cell 16: 196-208.
114. Leslie JD, Ariza-McNaughton L, Bermange AL, McAdow R, Johnson SL, et al. (2007) Endothelial signalling by the Notch ligand Delta-like 4 restricts angiogenesis. Development 134: 839-844.
115. Lobov IB, Renard RA, Papadopoulos N, Gale NW, Thurston G, et al. (2007) Delta-like ligand 4 (Dll4) is induced by VEGF as a negative regulator of angiogenic sprouting. Proc Natl Acad Sci USA 104: 3219-3224.
116. Benedito R, Trindade A, Hirashima M, Henrique D, da Costa LL, et al. (2008) Loss of Notch signalling induced by Dll4 causes arterial calibre reduction by increasing endothelial cell response to angiogenic stimuli. BMC Dev Biol 8: 117.
117. Trindade A, Kumar SR, Scehnet JS, Lopes-da-Costa L, Becker J, et al. (2008) Overexpression of delta-like 4 induces arterialization and attenuates vessel formation in developing mouse embryos. Blood 112: 1720-1729.
118. Noseda M, Chang L, McLean G, Grim JE, Clurman BE, et al. (2004) Notch activation induces endothelial cell cycle arrest and participates in contact inhibition: role of p21Cip1 repression. Mol Cell Biol 24: 8813-8822.
119. Hodkinson PS, Elliott PA, Lad Y, McHugh BJ, MacKinnon AC, et al. (2007) Mammalian NOTCH-1 activates beta1 integrins via the small GTPase R-Ras. J Biol Chem 282: 28991-29001.
120. Harrington LS, Sainson RC, Williams CK, Taylor JM, Shi W, et al. (2008) Regulation of multiple angiogenic pathways by dll4 and notch in human umbilical vein endothelial cells. Microvasc Res 75: 144-154.
121. Leong KG, Hu X, Li L, Noseda M, Larrivee B, et al. (2002) Activated Notch4 inhibits angiogenesis: role of beta 1-integrin activation. Mol Cell Biol 22: 2830-2841.
122. Horowitz A, Simons M (2009) Branching morphogenesis. Circ Res 103: 784-795.
123. Blancas AA, Wong LE, Glaser DE, McCloskey KE (2013) Specialized tip/stalk-like and phalanx-like endothelial cells from embryonic stem cells. Stem Cells Dev 22: 1398-1407.
124. De Smet F, Segura I, De Bock K, Hohensinner PJ, Carmeliet P, et al. (2009) Mechanisms of vessel branching: filopodia on endothelial tip cells lead the way. Arterioscler Thromb Vasc Biol 29: 639-649.
125. Mazzone M, Dettori D, Leite de Oliveira R, Loges S, Schmidt T, et al. (2009) Heterozygous deficiency of PHD2 restores tumor oxygenation and inhibits metastasis via endothelial normalization. Cell 136: 839-851.
126. Eilken HM, Adams RH (2010) Dynamics of endothelial cell behavior in sprouting angiogenesis. Curr Opin Cell Biol 22: 617-625.
127. Gerhardt H, Golding M, Fruttiger M, Ruhrberg C, Lundkvist A, et al. (2003) VEGF guides angiogenic sprouting utilizing endothelial tip cell filopodia. J Cell Biol 161: 1163-1177.
128. Lu X, Le Noble F, Yuan L, Jiang Q, De Lafarge B, et al. (2004) The netrin receptor UNC5B mediates guidance events controlling morphogenesis of the vascular system. Nature 432: 179-186.
129. Thurston G, Kitajewski J (2008) VEGF and Delta-Notch: interacting signalling pathways in tumour angiogenesis. Br J Cancer 99: 1204-1209.
130. Ruhrberg C, Gerhardt H, Golding M, Watson R, Ioannidou S, et al. (2002) Spatially restricted patterning cues provided by heparin-binding VEGF-A control blood vessel branching morphogenesis. Genes Dev 16: 2684-2698.
131. Chappell JC, Bautch VL (2010) Vascular development: genetic mechanisms and links to vascular disease. Curr Top Dev Biol 90: 43-72.
132. Chappell JC, Taylor SM, Ferrara N, Bautch VL (2009) Local guidance of emerging vessel sprouts requires soluble Flt-1. Dev Cell 17: 377-386.
133. Shawber CJ, Funahashi Y, Francisco E, Vorontchikhina M, Kitamura Y, et al. (2007) Notch alters VEGF responsiveness in human and murine endothelial cells by direct regulation of VEGFR-3 expression. J Clin Invest 117: 3369-3382.
134. Kume T (2009) Novel insights into the differential functions of Notch ligands in vascular formation. J Angiogenes Res 1: 8.
135. Zhang P, Yan X, Chen Y, Yang Z, Han H, et al. (2014) Notch signaling in blood vessels: from morphogenesis to homeostasis. Sci China Life Sci 57: 774-780.
136. Liu ZJ, Shirakawa T, Li Y, Soma A, Oka M, et al. (2003) Regulation of Notch1 and Dll4 by vascular endothelial growth factor in arterial endothelial cells: implications for modulating arteriogenesis and angiogenesis. Mol Cell Biol 23: 14-25.
137. Soker S, Takashima S, Miao HQ, Neufeld G, Klagsbrun M (1998) Neuropilin-1 is expressed by endothelial and tumor cells as an isoform-specific receptor for vascular endothelial growth factor. Cell 92: 735-745.
138. Tammela T, Zarkada G, Wallgard E, Murtomaki A, Suchting S, et al. (2008) Blocking VEGFR-3 suppresses angiogenic sprouting and vascular network formation. Nature 454: 656-60.
139. Funahashi Y, Hernandez SL, Das I, Ahn A, Huang J, et al. (2008) A notch1 ectodomain construct inhibits endothelial notch signaling, tumor growth, and angiogenesis. Cancer Res 68: 4727-4735.
140. Ridgway J, Zhang G, Wu Y, Stawicki S, Liang WC, et al. (2006) Inhibition of Dll4 signalling inhibits tumour growth by deregulating angiogenesis. Nature 444: 1083-1087.

141. Williams CK, Li JL, Murga M, Harris AL, Tosato G, et al. (2006) Up-regulation of the Notch ligand Delta-like 4 inhibits VEGF-induced endothelial cell function. Blood 107: 931-939.

142. Stone J, Itin A, Alon T, Pe'Er J, Gnessin H, et al. (1995) Development of retinal vasculature is mediated by hypoxia-induced vascular endothelial growth factor (VEGF) expression by neuroglia. The Journal of neuroscience 15: 4738-4747.

143. Lawson ND, Vogel AM, Weinstein BM (2002) Sonic hedgehog and vascular endothelial growth factor act upstream of the Notch pathway during arterial endothelial differentiation. Dev Cell 3: 127-136.

144. Patel NS, Li JL, Generali D, Poulsom R, Cranston DW, et al. (2005) Up-regulation of delta-like 4 ligand in human tumor vasculature and the role of basal expression in endothelial cell function. Cancer Res 65: 8690-8697.

145. Zhang J, Liu M, Su Y, Du J, Zhu AJ, et al. (2012) A targeted in vivo RNAI screen reveals deubiquitinases as new regulators of Notch signaling. G3 (Bethesda) 2: 1563-1575.

146. Fang L, Choi SH, Baek JS, Liu C, Almazan F, et al. (2013) Control of angiogenesis by AIBP-mediated cholesterol efflux. Nature 498: 118-122.

147. Avraham-Davidi I, Ely Y, Pham VN, Castranova D, Grunspan M, et al. (2012) ApoB-containing lipoproteins regulate angiogenesis by modulating expression of VEGF receptor 1. Nat Med 18: 967-973.

148. Angius F, Uda S, Piras E, Spolitu S, Ingianni A, et al. (2012) Neutral lipid alterations in human herpesvirus 8-infected HUVEC cells and their possible involvement in neo-angiogenesis. BMC Microbiol 15: 74.

149. Sacilotto N, Chouliaras KM, Nikitenko LL, Lu YW, Fritzsche M, et al. (2016) MEF2 transcription factors are key regulators of sprouting angiogenesis. Genes Dev 30: 2297-2309.

150. Spuul P, Daubon T, Pitter B, Alonso F, Fremaux I, et al. (2016) VEGF-A/Notch-Induced Podosomes Proteolyse Basement Membrane Collagen-IV during Retinal Sprouting Angiogenesis. Cell Rep 17: 484-500.

151. Harjes U, Bridges E, McIntyre A, Fielding BA, Harris AL, et al. (2014) Fatty acid-binding protein 4 a point of convergence for angiogenic and metabolic signaling pathways in endothelial cells. J Biol Chem 289: 23168-23176.

152. Schoors S, De Bock K, Cantelmo AR, Georgiadou M, Ghesquiere B, et al. (2014) Partial and transient reduction of glycolysis by PFKFB3 blockade reduces pathological angiogenesis. Cell Metab 19: 37-48.

153. De Bock K, Georgiadou M, Schoors S, Kuchnio A, Wong BW, et al. (2013) Role of PFKFB3-driven glycolysis in vessel sprouting. Cell 154: 651-663.

154. Wilhelm K, Happel K, Eelen G, Schoors S, Oellerich MF, et al. (2016) FOXO1 couples metabolic activity and growth state in the vascular endothelium. Nature 529: 216-220.

155. Lee DC, Sohn HA, Park ZY, Oh S, Kang YK, et al. (2015) A lactate-induced response to hypoxia. Cell 161: 595-609.

156. Kang DH, Lee DJ, Lee KW, Park YS, Lee JY, et al. (2011) Peroxiredoxin II is an essential antioxidant enzyme that prevents the oxidative inactivation of VEGF receptor-2 in vascular endothelial cells. Mol Cell 44: 545-558.

157. Panieri E, Santoro MM (2015) ROS signaling and redox biology in endothelial cells. Cell Mol Life Sci 72: 3281-3303.

158. Warren CM, Ziyad S, Briot A, Der A, Iruela-Arispe ML, et al. (2014) A ligand-independent VEGFR2 signaling pathway limits angiogenic responses in diabetes. Sci Signal 7: 1.

159. Goetz JG, Steed E, Ferreira RR, Roth S, Ramspacher C, et al. (2014) Endothelial cilia mediate low flow sensing during zebrafish vascular development. Cell Rep 6: 799-808.

160. Dinsmore C, Reiter JF (2016) Endothelial primary cilia inhibit atherosclerosis. EMBO Rep 17: 156-166.

161. Risau W (1997) Mechanisms of angiogenesis. Nature 386: 671-674.

162. Patan S (2004) Vasculogenesis and angiogenesis. Cancer Treat Res 117: 3-32.

163. Karamysheva AF (2008) Mechanisms of angiogenesis. Biochemistry (Mosc) 73: 751-762.

164. Brissova M, Fowler M, Wiebe P, Shostak A, Shiota M, et al. (2004) Intraislet endothelial cells contribute to revascularization of transplanted pancreatic islets. Diabetes 53: 1318-1325.

165. Brissova M, Shostak A, Shiota M, Wiebe PO, Poffenberger G, et al. (2006) Pancreatic islet production of vascular endothelial growth factor--a is essential for islet vascularization, revascularization and function. Diabetes 55: 2974-2985.

166. Ausprunk DH, Folkman J (1977) Migration and proliferation of endothelial cells in preformed and newly formed blood vessels during tumor angiogenesis. Microvasc Res 14: 53-65.

167. Fruttiger M (2007) Development of the retinal vasculature. Angiogenesis 10: 77-88.

168. Lawson ND, Weinstein BM (2002) In vivo imaging of embryonic vascular development using transgenic zebrafish. Dev Biol 248: 307-318.

169. Bayless KJ, Davis GE (2002) The Cdc42 and Rac1 GTPases are required for capillary lumen formation in three-dimensional extracellular matrices. J Cell Sci 115: 1123-1136.

170. Nakatsu MN, Sainson RC, Aoto JN, Taylor KL, Aitkenhead M, et al. (2003) Angiogenic sprouting and capillary lumen formation modeled by human umbilical vein endothelial cells (HUVEC) in fibrin gels: the role of fibroblasts and Angiopoietin-1. Microvasc Res 66: 102-112.

171. Reinert RB, Brissova M, Shostak A, Pan FC, Poffenberger G, et al. (2013) Vascular endothelial growth factor-a and islet vascularization are necessary in developing but not adult pancreatic islets. Diabetes 62: 4154-4164.

172. Virtanen I, Banerjee M, Palgi J, Korsgren O, Lukinius A, et al. (2008) Blood vessels of human islets of Langerhans are surrounded by a double basement membrane. Diabetologia 51: 1181-1191.

173. Brissova M, Shostak A, Fligner CL, Revetta FL, Washington MK, et al. (2015) Human islets have fewer blood vessels than mouse islets and the density of islet vascular structures is increased in type 2 diabetes. J Histochem Cytochem 63: 637-645.

174. Cai Q, Brissova M, Reinert RB, Pan FC, Brahmachary P, et al. (2012) Enhanced expression of VEGF-A in beta cells increases endothelial cell number but impairs islet morphogenesis and beta cell proliferation. Dev Biol 367: 40-54.

175. Watada H (2010) Role of VEGF-A in pancreatic beta cells. Endocr J 57: 185-191.

176. Lammert E, Cleaver O, Melton D (2001) Induction of pancreatic differentiation by signals from blood vessels. Science 294: 564-567.

177. Yoshitomi H, Zaret KS (2004) Endothelial cell interactions initiate dorsal pancreas development by selectively inducing the transcription factor Ptf1a. Development 131: 807-817.

178. Zhang N, Richter A, Suriawinata J, Harbaran S, Altomonte J, et al. (2004) Elevated vascular endothelial growth factor production in islets improves islet graft vascularization. Diabetes 53: 963-970.