

Cells in focus

The pancreatic islet endothelial cell: Emerging roles in islet function and disease[☆]

Richard Olsson^a, Per-Ola Carlsson^{a,b,*}

^a Department of Medical Cell Biology, Biomedical Center, Husargatan 3, Box 571, SE-75123 Uppsala, Sweden

^b Department of Medical Sciences, Uppsala University, SE-75123 Uppsala, Sweden

Received 21 April 2005; received in revised form 2 June 2005; accepted 24 June 2005

Abstract

The pancreatic islets are one of the most vascularized organs of the body. This likely reflects the requirements of the organ for a rich supply of nutrients and oxygen to the tissue, as well as the need for rapid disposal of metabolites and secreted hormones. The islet endothelium is richly fenestrated to facilitate trans-endothelial transport of secreted hormones, has a unique expression of surface markers, and produces a number of vasoactive substances and growth factors.

The islet endothelial cells play a critical role in the early phase of type 1 diabetes mellitus by increasing the expression of surface leucocyte-homing receptors, thereby enabling immune cells to enter the endocrine tissue and cause β -cell destruction. Following transplantation, pancreatic islets lack a functional capillary system and need to be properly revascularized. Insufficient revascularization may severely affect the transport properties of the islet endothelial system, resulting in a dysfunctional islet graft. © 2006 Elsevier Ltd. All rights reserved.

Keywords: Endothelial cell; Islet; Fenestrations; Diabetes mellitus

Cell facts

1. The islet endothelial cells are due to secretion of vascular endothelial growth factor from the neighbouring β -cells highly permeable with ten times more fenestrae than endothelial cells in the exocrine pancreas.
2. The islet endothelial cells function not only as a cellular barrier, but also produce a number of vasoactive substances, angiogenic substances and growth factors.
3. The islet endothelial cells play a critical role in the development of type 1 diabetes, and in the regain of islet function following transplantation.

1. Introduction

Pancreatic islets have a dense network of sinusoidal capillaries (Fig. 1) with a morphological resemblance to the renal glomerulus. Large islets receive blood from one to three afferent arterioles, whereas the capillaries of smaller islets seem to be integrated with the exocrine capillary system (Bonner-Weir, 1993). The islet capil-

[☆] This article was originally published in issue 38/4, doi: 10.1016/j.biocecl.2005.06.021.

* Corresponding author. Tel.: +46 18 471 4425; fax: +46 18 471 4059.

E-mail address: Per-Ola.Carlsson@medcellbiol.uu.se (P.-O. Carlsson).

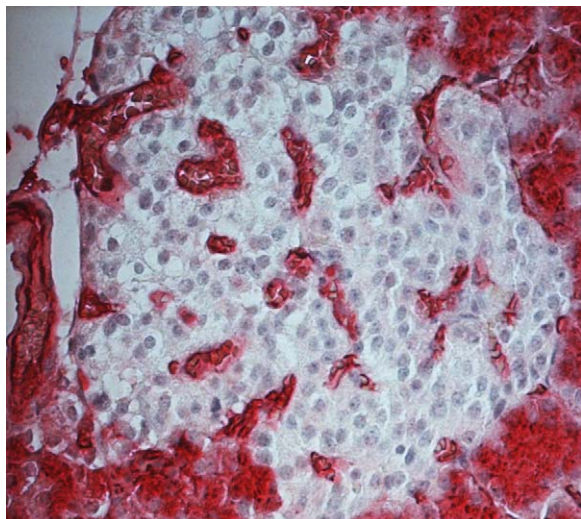


Fig. 1. Micrograph showing the rich vascularity of a human pancreatic islet. The microvascular endothelium is visualized by staining with the lectin *Bandeiraea simplicifolia* (red).

laries empty into either efferent small venules connected with exocrine capillary plexa, thereby forming an insulo-acinar portal system, or collecting venules that empty directly into larger veins. Within the islets, the insulin-producing β -cells are arranged in a polarized manner with 8–10 cells oriented with their apices towards a capillary. This arrangement means that all β -cells are not more than one cell away from arterial blood. The islet capillaries are highly permeable, and the endothelial cells have about 10 times more fenestrations than those of the exocrine tissue (Henderson & Moss, 1985). The diameter of the capillary lumen is about 5 μm , and the endothelial cell body extremely thin, about 100 nm in width. The pattern of blood flow within the islet has been a matter of debate (Brunnicardi et al., 1996). According to the perhaps most acknowledged theory, β -cells are perfused before non- β -cells, although some studies suggest the opposite direction of microcirculation. A third theory is that blood enters an arterial pole of the islet and then is transported in a regulated fashion through the islet capillaries to a venous pole. The order of blood perfusion is most likely of importance for the communication and interactions between different cell types within the islets.

2. Cell origin and plasticity

Endothelial cells and hematopoietic cells seem to derive from the same precursor cell, the hemangioblast. Precursor cell development is thought to arise from the ventral floor of the dorsal aorta within the aorto-gonadomesonephros region (Marshall et al., 1999). Develop-

ment of the pancreatic endocrine tissue has been shown to crucially depend on signals from neighbouring blood vessel endothelium in the dorsal aorta (Konstantinova & Lammert, 2004). The β -cells signal back to adjacent endothelial cells through the secretion of vascular endothelial growth factor (VEGF-A). This induces the formation of a dense capillary network within the islet (Konstantinova & Lammert, 2004). VEGF-A does not seem to be required for the development of all islet capillaries, but when VEGF-A was deleted in knock-out experiments, the number of endothelial cells in the islets become similar to that of the surrounding exocrine tissue. Expansion of the islet endothelial cell mass mainly occurs in the postnatal period (Chilvers & Thomas, 1983).

3. Functions

The endothelium has previously been considered merely a form of nucleated cellophane, being important, besides its anti-thrombotic function, mainly as a barrier for the maintenance of the vessel wall. However, at the same time as it functions as a cellular barrier, the capillaries need to be highly permeable in order to permit the transport of oxygen and nutrients to the islet endocrine cells, as well as allow rapid passage of proteins such as the endocrine hormones into the blood stream (Fig. 2). The islet endothelial fenestrae are sites through which proteins can quickly permeate. The islet endothelial fenestrations crucially depend on VEGF-A secreted from the neighbouring β -cells (Konstantinova & Lammert, 2004). However, since mice lacking islet VEGF-A are capable of responding to a glucose load, other modes of insulin transport also likely contribute.

The blood perfusion of the pancreatic islets is very high, and constitutes 7–10% of the whole pancreatic blood flow, despite the islets contributing only $\sim 1\%$ to the pancreatic volume (Jansson & Carlsson, 2002). The blood perfusion is meticulously regulated, predominantly at the precapillary level (Carlsson, Jansson, Östenson, & Källskog, 1997), by an interplay of locally produced factors, gastrointestinal hormones and the nervous system, to meet the different needs for hormone secretion imposed on the tissue (Jansson & Carlsson, 2002). This allows an adequate nutrient supply and glucose sensing of the islet tissue, and at the same time facilitates an adequate and rapid disposal of islet hormones secreted to the blood stream. It also means that the islet tissue oxygen tension is kept in close equilibrium with that of venous blood. Several of the most important vasoactive substances are produced or pro-

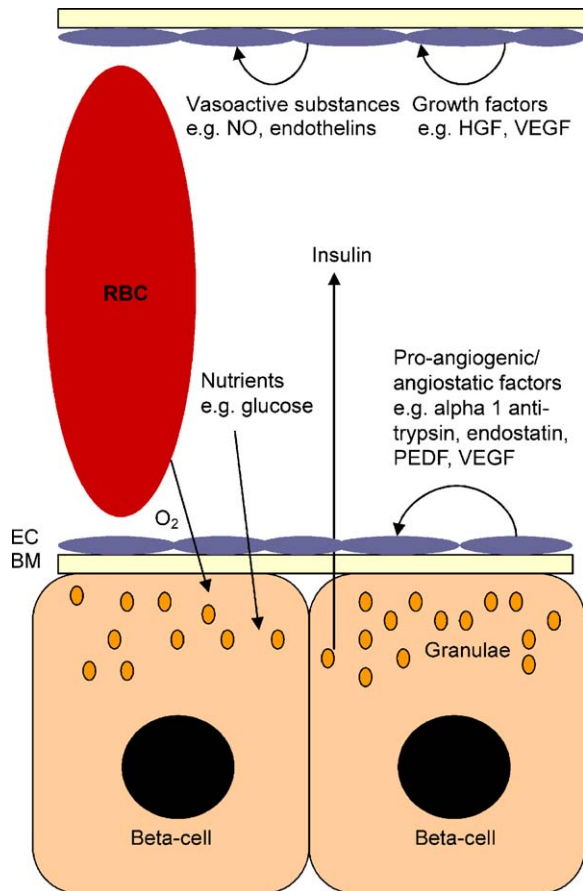


Fig. 2. Schematic picture outlining some major functions of the islet endothelial cell. RBC, red blood cell; NO, nitric oxide; HGF, hepatocyte growth factor; VEGF, vascular endothelial growth factor; PEDF, pigment endothelial derived growth factor; EC, endothelial cell; BM, basal membrane.

cessed by the islet endothelial cells themselves, e.g. nitric oxide (NO), angiotensin II and endothelin (Jansson & Carlsson, 2002). Moreover, the activities of both the constitutive and the cytokine-inducible endothelial NO synthases, which form the key islet vasodilator NO, seem to be specifically regulated by glucose concentration in islets in contrast to other endothelium (Suschek, Fehsel, Kröncke, Sommer, & Kolb-Bachofen, 1994).

Islet endothelial cells display common endothelial markers such as von Willebrand factor, CD31, induction of endothelial cell leucocyte adhesion molecule-1 and uptake of acetylated low density lipoprotein (Lou et al., 1999). However, ~84% of vascular receptors on the islet endothelial cells are unique to the islet vasculature, and cannot be found on endothelial cells in the surrounding exocrine tissue (Yao et al., 2005). This underlines the heterogeneity of the microvasculature not

Table 1

Summary of unique features of islet endothelial cells

Highly permeable with 10 times more fenestrae than endothelial cells in exocrine pancreas
Glucose-dependent regulation of both constitutive and inducible endothelial nitric oxide synthase
More than 80% of surface receptors differ from those of endothelial cells in exocrine pancreas
Produce a number of both pro-angiogenic and angiostatic factors (e.g. vascular endothelial growth factor, basic fibroblast growth factor, α 1-antitrypsin, endostatin and pigment epithelial-derived factor)

only between different organs, but also between functionally distinct regions of organs (Table 1). A specific feature of the islet endothelial cells is their unique expression of the proteinase inhibitor and angiostatic factor α ₁-antitrypsin (Lou et al., 1999). Recent studies also show that the islet endothelial cells may produce a number of other factors involved in the regulation of angiogenesis, including both potent pro-angiogenic factors such as VEGF and angiostatic factors such as endostatin and pigment epithelial-derived factor (Mattsson, Danielsson, Kriz, Carlsson, & Jansson, in press). In adulthood, however, the islet endothelial cell mass is in most cases stable, and the islet endothelial cell turnover rate low, suggesting that the amount of pro-angiogenic and angiostatic factors produced is kept in close equilibrium.

Endothelial signals play a crucial role for the development of an endocrine pancreas in the early embryo (Konstantinova & Lammert, 2004). The close proximity of endothelial cells and endocrine cells to each other in adults suggests that paracrine signals between these cell types may be exchanged. It is, for example, known that VEGF-A produced by the β -cells may induce vascular proliferation (Konstantinova & Lammert, 2004). To what extent islet endothelial-derived substances may affect islet endocrine function and growth in adults is largely unknown. A recent report, however, shows that collagen IV, secreted by islet endothelial cells, potentiates insulin secretion via interaction with integrin α ₁ β ₁ on β -cells (Kaido, Yebra, Cirulli, & Montgomery, 2004). Recent work in our group also indicates that during certain conditions the islet endothelial cells may produce growth factors, such as hepatocyte growth factor (HGF), promoting β -cell growth (Johansson M., et al., unpublished observation). NO produced by the islet endothelial cells has potential to influence β -cell insulin release, but whether the effects of NO are stimulatory or inhibitory is highly controversial (Henningsson, Salehi, & Lundquist, 2002).

4. Associated pathologies

Accumulating evidence suggests that the vascular endothelium is of crucial importance for the development of inflammatory reactions. Adherence of lymphocytes and other inflammatory cells to the islet vascular endothelium, followed by transendothelial migration into the endocrine tissue, is essential for tissue damage and development of type 1 diabetes. Studies in an animal model of autoimmune diabetes, the non-obese diabetic (NOD) mouse, have revealed that a number of leucocyte homing receptors become expressed or upregulated at the islet endothelial surface early in the insulinitis process. By blocking some of these homing receptors, e.g. for l-selectin, very late antigen 4, mucosal addressin cell adhesion molecule-1, or β -7 integrin, the development of diabetes may be prevented (Yang et al., 1996). The insulinitis process in the NOD mouse, as well as in another animal model for type 1 diabetes, the multiple low-dose streptozotocin-treated mouse, also seems associated with a NO-dependent hyperperfusion of the islet (Carlsson, Flodstrom, & Sandler, 2000). Such vasodilation may decrease shear stress and cause margination of leucocytes, which may enhance the accumulation of inflammatory cells. Increased vascular permeability, as observed in a third animal model of autoimmune diabetes, the BioBreeding (BB) rat (De Paepe, Corriveau, Tannous, Seemayer, & Colle, 1992), may also contribute. Moreover, it is interesting to note that there seems to be a regulatory defect in the endothelial constitutive NO synthase, which correlates with probability of disease manifestation in the BB rat (Suschek, Bonmann, & Kolb-Bachofen, 1999), and that the islet endothelial cells contain a cytokine-inducible NO synthase that may generate NO in concentrations that lyse β -cells (Steiner, Kröncke, Fehsel, & Kolb-Bachofen, 1997).

An augmented islet blood flow has been reported after short-term modest hyperglycemia, as well as in several animal models of type 2 diabetes, including the Goto-Kakizaki (GK) rat (Carlsson et al., 1997) and the obese-hyperglycemic mouse (Carlsson, Andersson, & Jansson, 1998). At least in the GK rat, the islet blood hyperperfusion is accompanied by an islet capillary hypertension. Such shear stress changes are known to change the gene expression of surrounding cells, but the influence on islet function remains to be determined. With age, persistent hyperglycemia causes an islet hypoperfusion in both GK rats and obese-hyperglycemic mice. It is possible that an initial hyperperfusion followed by a late hypoperfusion of the islets is a general property of hyperglycemic subjects.

Isolation of pancreatic islets for transplantation disrupts the arterial and venous connections. The transplanted islets thus depend on a rapid and adequate revascularization for their survival and optimal function. Although the angiogenic process is rapidly initiated, transplanted islets acquire a decreased blood perfusion, capillary hypertension in the newly formed microvessels, and decreased partial pressure of oxygen compared with endogenous islets (Jansson & Carlsson, 2002). This likely reflects that the vascular density becomes persistently lower than in endogenous islets. The islet graft metabolism tends to be much more anaerobic than that of endogenous islets, which may indicate that the oxygen transport to the islet tissue does not fully meet the demands. Increased islet vascular density attained either through stimulated vasculogenesis or angiogenesis also seems to correlate to improvements in graft function. Most interventions to improve angiogenesis so far have focused to enhance pro-angiogenic factors, e.g. VEGF, HGF and basic fibroblast growth factor, in the islets. It is possible that blockage of one or several of the angiostatic factors produced by the islets or the islet endothelial cells themselves (cf. above) may prove an alternative, and perhaps even more potent strategy in the clinical situation.

Accumulating data indicate an important role for islet endothelial cells in normal islet function. At the same time, during disease or following transplantation of islets, several alterations occur in the islet vascular system, which may contribute to a progressive islet dysfunction. Continued studies of islet endothelial cells are clearly warranted.

Acknowledgements

Due to the limitation of the references allowed for this review, a sincere apology is given for all the omitted references that have contributed to the understanding of the function of the islet endothelial cells.

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