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COMMENTARY

Disruption of Insulin Receptor Signaling in Endothelial Cells Shows the Central Role of an Intact Islet Blood Flow for In Vivo β-Cell Function

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Worldwide there is massive increase in the prevalence of type 2 diabetes and the International Diabetes Federation predicts that in 20 years some 600 million people worldwide will be afflicted. In the U.S. alone, the annual cost for diabetes care is an astonishing $245 billion, of which 97% is targeted to type 2 diabetes. Hence, it is immediately apparent that there is an urgent need to find new strategies capable of preventing and treating this disease.

Loss of pancreatic islet function is a central hallmark in the progression of type 2 diabetes, and β-cell failure and dysfunction may even precede the advent of hyperglycemia. Most efforts to date have been put toward understanding the changes that occur in pancreatic islets in type 2 diabetes by in vitro studies of the endocrine cells, mainly the β-cells and the α-cells. However, what is often forgotten is that in the much more complex situation of in vivo these endocrine cells intercommunicate with the rest of the body by endocrine, neural, and paracrine signals. Endothelial cells in different organs substantially vary in their gene expression and thereby in their phenotype depending on signals from the surrounding parenchyma. In the islets of Langerhans, the endothelial cell phenotype differs from the rest of the pancreas by being exposed to vascular endothelial growth factor-A from the β-cells (1,2). However, the endothelial cells also provide important factors to support β-cell function and differentiation, such as laminins and thrombospondin-1 (3,4). Another aspect of the islet vascularity is the importance of this system for transport of oxygen and nutrients into the islets and transport of secreted hormones into the systemic vascular system. Islet blood perfusion is normally meticulously regulated at the arteriolar level to meet the various demands for insulin secretion. Hyperglycemia causes increased islet blood perfusion by combined vagal and metabolic mediators (5), and lipids increase the blood perfusion of islets through β_3-adrenoceptors (6). In animal models of type 2 diabetes, an early hyperperfusion of islets is consistently seen, followed by a decrease as overt diabetes ensues (7,8). A loss of islet capillaries has been described in overt diabetes that may contribute to this decrease (9).

In this issue, Hashimoto et al. (10) investigate the importance of insulin receptor substrate-2 (Irs2) in islet endothelial cells for the β-cell function. By combined in vitro and in vivo studies they elegantly show that disruption of endothelial cell–specific Irs2 causes a decreased islet blood perfusion, which leads to an impaired insulin response to a glucose load and thereby impaired glucose tolerance. The β-cells per se were obviously not changed in their phenotype by endothelial cell–specific knockout of Irs2, as disturbances in insulin release were only seen when glucose was administered via the vascular system in whole animals or via afferent vessels in a whole-pancreas perfusion system and not in vitro with isolated islets. No decrease in β-cell mass or in islet vascular density was observed. Low oxygenation of the β-cells may perturb the capacity for (pro)insulin biosynthesis and secretion (11), but hypoxia in the islets was not observed in the present model. Instead, the observed findings seemed to relate mainly to inadequate dispersal of insulin from the islets into the systemic circulation, which was reversible by increasing the islet blood perfusion by the ACE inhibitor enalapril maleate.

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Although the mechanism for the impaired insulin secretion was related to the blood perfusion of islets in a logic set of experiments, the reason as to why the lack of Irs2 in endothelial cells caused decreased blood perfusion was not elucidated. Skeletal muscle endothelium deficiency of Irs2 has previously been shown to reduce Akt and endothelial nitric oxide synthase phosphorylation influencing nitric oxide production (12). One possible mechanism therefore may be decreased nitric oxide generation in islet blood vessels (Fig. 1). This gas has previously been described as essential for the high normal islet blood flow and as a mediator of further increasing of islet blood flow during hyperglycemia following vagal stimulation (13,14). An interesting part of the present study by Hashimoto et al. (10) is that ACE inhibition was used to improve islet blood flow in the endothelial cell–specific Irs2 knockout mice and to reverse their defect insulin secretion. Besides the direct effects of angiotensin II on blood vessels, both angiotensin II and high glucose levels have previously been shown to inhibit tyrosine phosphorylation of Irs2 by protein kinase C activation and thereby decrease the phosphorylation of Akt and endothelial nitric oxide synthase (15). The existence of an islet renin angiotensin system and an upregulation of its components during experimental type 2 diabetes have been described (16–18), and this system and chronic hyperglycemia could induce insulin resistance in islet endothelial cells. It is noteworthy that the inhibition of the renin angiotensin system seems to exert effects to improve insulin secretion not only by acting directly on β-cells (18) but also by preventing changes in islet morphology (17) as well as by increasing the islet blood perfusion (14,19). All of these mechanisms could help to explain the clinical beneficial effect of this treatment in patients susceptible for type 2 diabetes development (20).

Based on the study by Hashimoto et al. (10), it would be of great interest to investigate if changes in Irs2 and its phosphorylation occur during the development of or in manifest type 2 diabetes and, if so, the implications of this for islet blood perfusion and β-cell function. Such studies could add to the proposed mechanism of how islet function is affected during type 2 diabetes development. Important parts of such work would be to combine in vivo or ex vivo studies of islet blood perfusion with mechanistic studies on isolated islet endothelial cells and Irs2 expression and phosphorylation during different conditions. An approach to consider all islet components has, in this case, proven necessary to understand islet pathophysiology in type 2 diabetes.

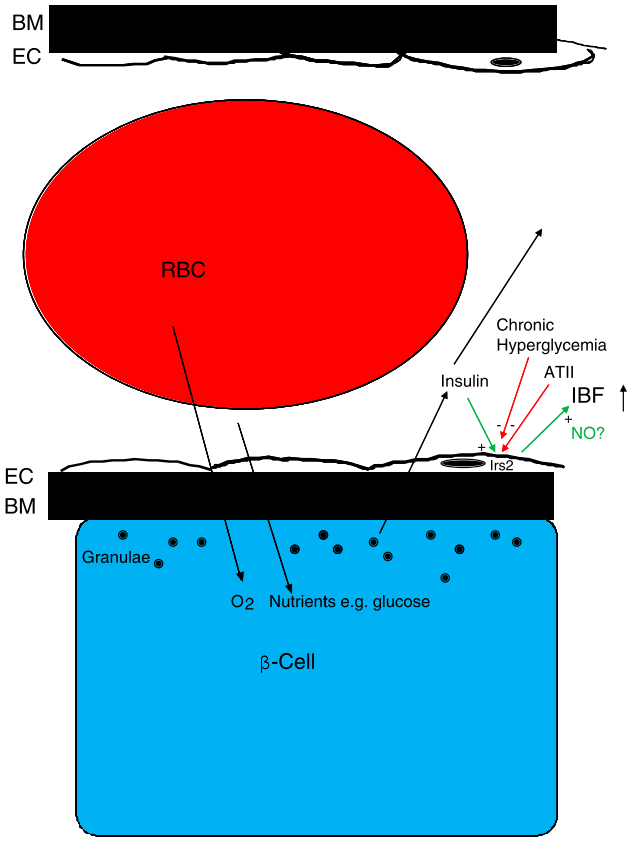

Figure 1—Hashimoto et al. (10) provide the data that insulin produced by β-cells is important for the maintenance of islet blood perfusion, and thereby islet function, by phosphorylation of endothelial cell–specific Irs2. The mechanism for how Irs2 increases islet blood flow remains to be determined, but nitric oxide is one of the candidates. In type 2 diabetes, both chronic hyperglycemia and increased local angiotensin II (ATII) concentrations may inhibit Irs2 phosphorylation in islet endothelium, causing islet blood flow disturbances and islet dysfunction. BM, basement membrane; EC, endothelial cells; IBF, islet blood flow; RBC, red blood cell.

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