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The pancreatic beta-cell in human Type 2 diabetes

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Abstract *Aim:* There is growing evidence that the beta-cell is central to the development of Type 2 diabetes. In this brief review we discuss the factors predisposing to beta-cell dysfunction and some characteristics of islet cells in Type 2 diabetes.
Data synthesis: Several genes have been associated with islet cell dysfunction in Type 2 diabetes, including those encoding for transcription factors, glucose metabolism proteins, molecules of the insulin signaling pathways, and several others. On the other hand, many environmental factors can directly or indirectly affect pancreatic islet cells, and possibly contribute to the development and/or progression of Type 2 diabetes. In this regard, the role of prolonged exposure to high glucose (glucotoxicity) and high fatty acid (lipotoxicity) concentrations seems to be of particular relevance. More recently, it has been possible to directly evaluate some properties of pancreatic islets prepared from Type 2 diabetic donors. Consistently, a marked decrease in insulin secretion during glucose stimulation has been found, although the secretory response to amino acids or sulphonylurea is usually less severely affected. In addition, increased beta-cell apoptosis in Type 2 diabetes islets has been reported. Interestingly, experimental data show that in vitro manipulation of human Type 2 diabetes islets by agents that are able to reduce oxidative stress can improve beta-cell function and survival.
Conclusion: Available data are consistent with the concept that the defect of the beta-cell is of primary importance in Type 2 diabetes; the evidence that some alterations in Type 2 diabetes beta-cells can be reverted, at least in vitro, may open new perspectives in the treatment of this disease.

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Introduction

Type 2 diabetes results from a combination of genetic and acquired factors that impair beta-cell function on one side, and tissue insulin sensitivity on the other [1]. Although the discussion on the relative importance of these two alterations is still ongoing, growing evidence is swinging the pendulum over to the concept that there is no hyperglycemia without beta-cell dysfunction [1,2]. We also know that in the natural history of polygenic Type 2 diabetes, a progressive loss of beta-cell functional mass can be demonstrated, leading from normal glucose homeostasis to mild degrees of glucose intolerance first, and then to overt diabetes [1,2]. In this brief overview we will discuss the factors predisposing to beta-cell dysfunction and some characteristics of islet cells in Type 2 diabetes.

The role of genetic and acquired factors

Several genes have been associated with islet cell dysfunction in Type 2 diabetes (Table 1), including some encoding for transcription factors, glucose metabolism proteins, molecules of the insulin signaling pathways, and several others, such as calpain10 [3]. We investigated on how the Arg972 polymorphism of the insulin receptor substrate-1 (IRS-1) affects human beta-cells, and found that, compared to wild type islets, the islets carrying the polymorphism have increased serum deprivation induced beta-cell apoptosis and reduced insulin secretion [4]. In addition, we showed that beta-cells with the polymorphism have an increased number of immature insulin granules, suggesting some defects in the mechanisms of the formation of the granules [4].

On the other hand, many environmental factors can directly or indirectly affect pancreatic islet cells, and possibly contribute to the development and/or progression of Type 2 diabetes [1,2]. In this regard, the role of prolonged exposure to high glucose (glucotoxicity) and high fatty acid (lipotoxicity) concentrations has been particularly investigated. The discussion on glucotoxicity began approximately 15 years ago [5], and since then many groups have addressed this issue (recently reviewed [6,7]). It is now clear that glucotoxicity leads to increased beta-cell apoptosis and altered insulin secretion by several mechanisms, with enhanced oxidative stress playing a major role [8,9]. The effects of lipotoxicity have been investigated, in particular, by Unger [10], followed by a few additional researchers [11]. In our experience, we found that exposure of isolated human islets (Fig. 1) to increased free fatty acid concentration can indeed cause apoptosis of beta-cells and a marked decrease in insulin secretion [12]. These effects were associated with decreased Bcl2 expression and partially dependent on ceramide pathway [12].

Table 1 Some candidate genes associated with beta-cell dysfunction in polygenic Type 2 diabetes

Transcription factors (HNF_{alpha}, $PPAR_{gamma}$, PDX-1, IB1, and NeuroD1)
Glucose metabolism (glucotransporters, glucokinase, FABP2, and UCP-2)
Insulin signaling pathways (IRS-1 and IRS-2)
Others (calpain10)

The beta-cell in overt diabetes

According to recent evidence, it may be possible to directly evaluate some properties of pancreatic islets prepared from Type 2 diabetic donors [13–18] (Table 2). Consistently, a marked decrease in insulin secretion during glucose stimulation has been found, although the secretory response to amino acids or sulphonylurea is usually less severely affected. In addition, it has been observed that the islets from Type 2 diabetic donors release insulin in pulses with reduced amplitude [14] and that they have reduced efficacy in curing immunodeficient diabetic mice by transplantation [15]. We have focused on some primary alterations in insulin secretion and islet cell survival in Type 2 diabetes isolated islets [16–18]. We found that the functional defects of such islets were accompanied by reduced mRNA expression of glucose transporter-1, glucose transporter-2 and glucokinase, and diminished glucose oxidation. In addition, AMP-activated protein kinase activation was reduced, the expression of insulin was decreased, and that of PDX-1 and Foxo-1 were increased [18]. Furthermore, diabetic islets were characterized by increased apoptosis with enhanced caspase-3 and -8 activity [16]. All these alterations were associated with increased oxidative stress, as shown by higher concentrations of oxidative stress markers (nitrotyrosine and 8-hydroxy-2′-deoxyguanosine concentrations), increased expression of PKC beta 2 and NADPH-oxidase, changes in mRNA expression of Mn-SOD, Cu/Zn-SOD, catalase and GSH