5. Mechanisms of Beta-Cell Death in Diabetes

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Summary. A decrease in both mass and secretory function of insulin-producing beta cells contribute to the pathophysiology of type 1 and type 2 diabetes. In this chapter, we review the evidence that glucose, inflammation, dyslipidemia, leptin, autoimmunity, amyloid and some sulfonylureas may contribute to the maladaptation of beta cells. With respect to these causal factors, we focus on IL-1beta, Fas, IRS-2, oxidative stress, NF-kappaB, ER stress, mitochondrial dysfunction, and the KATP-channel as potential mechanisms of action. Interestingly, most of these factors are involved in inflammatory processes in addition to playing a role in both the regulation of beta-cell secretory function and cell turnover. To this end, we believe the mechanisms regulating beta-cell proliferation, apoptosis and function are inseparable processes.

Introduction

For many years the contribution of a reduction in beta-cell mass to the development of type 2 diabetes was heavily debated. Recently, several studies have convincingly confirmed this hypothesis [1–3], leading to a rapid over-emphasis of this etiological factor. Indeed, other mechanisms contributing to the failure of the beta cell to produce enough insulin appear more and more neglected. While we strongly believe that beta-cell destruction is an important etiological factor in the development and progression of type 2 diabetes, in this chapter we will highlight evidence that this is not dissociable from an intrinsic secretory defect. To this end, we will show that pathways regulating beta-cell turnover are also implicated in beta-cell insulin secretory function. It follows that adaptive mechanisms of function and mass share common regulatory pathways and will therefore act in concert. Depending on the

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prevailing concentration and the intracellular pathways activated, some factors may be deleterious to beta-cell mass while enhancing beta-cell function, protective to beta-cell mass while inhibiting function, or even protective to beta-cell mass while enhancing function.

The failure of the beta cell in type 2 diabetes is akin to a multi-factorial equation, with an overall negative result. Thus, although we will discuss the factors and mechanisms regulating beta-cell mass individually, only in a minority of diabetic patients does one single etiological factor underlie the failure of the beta-cell. In addition to MODYs (maturity onset diabetes in the young), another common example of this is autoimmune-mediated destruction of beta cells in young, lean individuals. However, given that the incidence of type 1 diabetes increases with obesity [4], that insulin resistance is a risk factor for the progression of type 1 diabetes [5], and that approximately 50% of the general population carry the same genetic predisposition [6], this example already implicates multiple etiological factors. Recognition of beta-cell destruction not only in type 1 but also 2 diabetes led us to recently propose a unifying classification of diabetes [7,8].

**Glucose and the Interleukin-1beta-FAS–FLIP Pathway: From Adaptation to Failure**

Glucose is the key physiological regulator of insulin secretion. Therefore, it appears logical that it also regulates the long-term adaptation of insulin production by regulating beta-cell turnover. Indeed, in all species, short-term exposure of beta cells to increasing glucose concentrations induces proliferation in a concentration-dependent manner [9–11]. However, in *Psammomys obesus* and humans, the proliferative capacity of these cells is suppressed following a prolonged exposure to increased glucose concentrations. With respect to the role of glucose in beta-cell apoptosis, the importance of the genetic background also appears crucial. In rodent islets, increasing glucose from a physiological concentration of 5.5 to 11 mM decreases apoptosis [12]. Further increases above 11 mM will be either pro- or anti-apoptotic depending on the age of the rodent, the culture conditions, e.g. purified beta cells versus whole islets, or culture on matrix versus in suspension [10,12,13]. The fact that rodent islets survive best at 11 mM glucose is empirically reflected by the standard use of medium containing this concentration of glucose for optimal culture conditions. In contrast, in human and *Psammomys obesus* islets, an increase in glucose from 5.5 to 33 mM induces a linear and much stronger increase in beta-cell apoptosis [10,11,14] (Fig. 1). This difference in glucose sensitivity may explain why in animals genetically predisposed to diabetes, hyperglycemia increases rates of apoptosis, whereas in rats