

# Islet Inflammation in Type 2 Diabetes

## From metabolic stress to therapy

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Decreases in both mass and secretory function of insulin-producing  $\beta$ -cells contribute to the pathophysiology of type 2 diabetes. The histology of islets from patients with type 2 diabetes displays an inflammatory process characterized by the presence of cytokines, apoptotic cells, immune cell infiltration, amyloid deposits, and eventually fibrosis. This inflammatory process is probably the combined consequence of dyslipidemia, hyperglycemia, and increased circulating adipokines. Therefore, modulation of intra-islet inflammatory mediators, in particular interleukin-1 $\beta$ , appears as a promising therapeutic approach.

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Inflammation is defined as the local response to tissue injury. It is characterized by immune cell invasion and local release of cytokines and chemokines and is sometimes accompanied by functional or structural damage of the invaded tissue. It is not in itself a disease, but a manifestation of disease. Inflammation has beneficial effects such as preventing spread of infections or promoting regeneration. Equally, it may exacerbate disease by tissue destruction due to inflammatory mediators, reactive oxygen species, and complement components. In this review, we propose to revisit the pathology of islet failure in type 2 diabetes and highlight evidence that this includes an inflammatory process in response to metabolic stress.

### GLUCOSE-INDUCED $\beta$ -CELL PRODUCTION OF INTERLEUKIN-1 $\beta$ : FROM ADAPTATION TO FAILURE

Glucose is the main physiological regulator of insulin secretion. In addition to this acute ef-

fect, glucose also regulates the long-term adaptation of insulin production by affecting  $\beta$ -cell turnover. Indeed, short-term exposure of  $\beta$ -cells to increasing glucose concentrations induces proliferation (1–3). However, in *Psammomys obesus*, an animal model of type 2 diabetes, and in humans, the proliferative capacity of the  $\beta$ -cell is suppressed after a prolonged exposure to increased glucose concentrations (2,3). Moreover, elevated glucose concentrations induce  $\beta$ -cell apoptosis in cultured islets from diabetes-prone *Psammomys obesus* (2) and from humans (3,4).

Interleukin (IL)-1 $\beta$  is a pro-inflammatory cytokine acting during the autoimmune process of type 1 diabetes (5). IL-1 $\beta$  inhibits  $\beta$ -cell function and promotes Fas-triggered apoptosis in part by activating the transcription factor nuclear factor (NF)- $\kappa$ B. We tested the hypothesis that IL-1 $\beta$  may mediate the deleterious effects of high glucose on human  $\beta$ -cells (6). In vitro exposure of islets from nondiabetic organ donors to high

glucose levels resulted in increased production and release of IL-1 $\beta$ , followed by NF- $\kappa$ B activation, Fas upregulation, DNA fragmentation, and impaired  $\beta$ -cell secretory function. The IL-1 receptor antagonist (IL-1Ra) protected cultured human islets from these deleterious effects.  $\beta$ -Cells themselves were identified as the islet cellular source of glucose-induced IL-1 $\beta$ . In vivo, IL-1 $\beta$ -producing  $\beta$ -cells were observed in pancreatic sections of type 2 diabetic patients but not in nondiabetic control subjects. These findings implicate an inflammatory process in the pathogenesis of glucotoxicity in type 2 diabetes and identify the IL-1 $\beta$  pathway as a target to preserve  $\beta$ -cell mass and function in this condition.

Recently, the role of IL-1 $\beta$  in type 2 diabetes has been challenged based on findings in islets isolated from patients with this condition (7). Unfortunately, these islets were placed in medium containing 5.5 mmol/l glucose for 3–4 days before experimentation. The reversibility of glucotoxicity is well documented (8) as well as the reversibility of glucose-induced IL-1 $\beta$  expression (6). It is therefore not surprising that increased levels of IL-1 $\beta$  were not detectable in these islets. Furthermore, there are numerous methodological differences, including the lack of use of extracellular matrix and the low number of organ donor samples that may account for some reported differences. Finally, a recent gene array analysis of near-pure populations of  $\beta$ -cells obtained by laser capture dissection displayed increased IL-1 $\beta$  mRNA expression in samples obtained from patients with type 2 diabetes (9).

Based on these findings, we conducted a clinical trial of IL-1 receptor antagonism in type 2 diabetes (10). The primary end-point, glycated hemoglobin, was significantly lower in IL-1Ra-treated versus placebo-treated patients, associated with enhanced insulin secretion. This study is proof of principle that antagonism of IL-1 has therapeutic potential in the treatment of diabetes, and supports the concept that islet inflammation is present and detrimental to islet function in type 2 diabetes.

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M.Y.D. is listed as the inventor on a patent (WO6709) filed in 2003 for the use of an interleukin-1 receptor antagonist for the treatment of or prophylaxis against type 2 diabetes. The patent is owned by the University of Zurich, and M.Y.D. has no financial interest in the patent. No other potential conflict of interest relevant to this article was reported.

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**Abbreviations:** IL, interleukin;  $K_{ATP}$  channel, ATP-sensitive  $K^+$  channel.

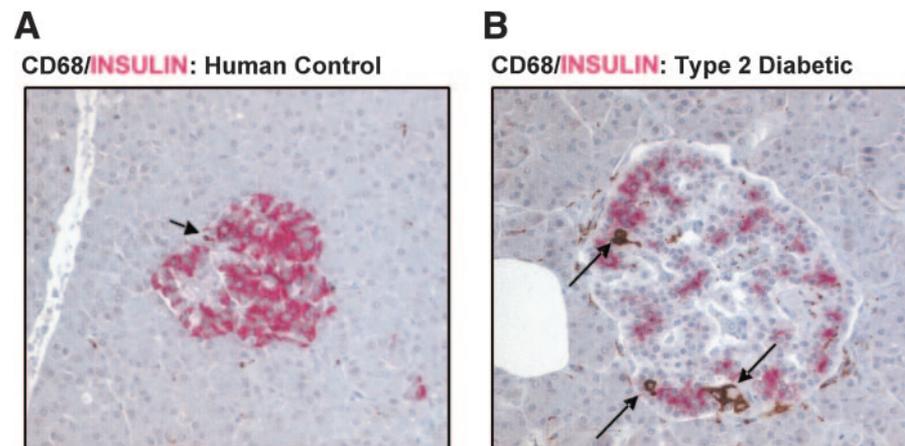
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## DYSLIPIDEMIA, LEPTIN, AND CIRCULATING CYTOKINES: LINKING OBESITY TO $\beta$ -CELL FAILURE

Obesity is the main risk factor for the development of diabetes. It is often part of the metabolic syndrome and is accompanied by dyslipidemia and increased circulating leptin and cytokine levels. All of these factors have been shown to modulate  $\beta$ -cell function and survival. The influence of dyslipidemia on the  $\beta$ -cells of an individual will depend on his or her specific lipid profile. Whereas some free fatty acids and lipoproteins have been shown to be pro-apoptotic for the  $\beta$ -cell, others are protective. For example, long-term exposure of  $\beta$ -cells to saturated fatty acids such as palmitate appears highly toxic, whereas monounsaturated fatty acids such as oleate protect against both palmitate- and glucose-induced  $\beta$ -cell apoptosis (11,12). It is of interest to note that similar toxic effects are also observed in non- $\beta$ -cells such as cardiac cells (13). These effects are paralleled by effects on  $\beta$ -cell function (i.e., saturated fatty acids are detrimental, whereas monounsaturated fatty acids are protective). Lipoproteins may also affect  $\beta$ -cell survival and function in a similar way, whereby VLDL and LDL are pro-apoptotic, while HDL is protective (14–16). These lipotoxic effects may also be influenced by the prevailing glycemia (17,18).

Leptin was initially identified as an adipocyte-derived satiety factor. Recently, leptin has also been considered as a proinflammatory cytokine because of its structural similarity with other cytokines and its receptor-induced signaling pathways (19). Interestingly, leptin accelerates autoimmune diabetes in NOD mice (20), providing an additional link between type 1 and type 2 diabetes (21). Of note, leptin also promotes other autoimmune diseases, including inflammatory bowel disease (22), multiple sclerosis (23), and rheumatoid arthritis (19). We have found that leptin, in addition to its established negative effect on insulin secretion (24,25), induces  $\beta$ -cell apoptosis via increasing release of IL-1 $\beta$  and decreasing release of IL-1Ra in human islets (26). Other cytokines released by adipocytes, including tumor necrosis factor- $\alpha$  and IL-6, may also modulate  $\beta$ -cell survival, although it is unclear if the amount released into the circulation is sufficient to affect  $\beta$ -cells (27,28). Furthermore, it may well be that these cytokines are only



**Figure 1**—Increased number of islet macrophages in type 2 diabetic islets. Pancreatic section from a nondiabetic patient (A) and a patient with type 2 diabetes (B) displaying increased numbers of islet-associated macrophages detected by double immunostaining for CD68 in brown (arrows) and insulin in red. For detailed methods and quantification, see Ehses et al. (38).

effective in the presence of other cytokines. Details regarding how all the above-mentioned factors affect  $\beta$ -cell secretory function have been reviewed elsewhere (27).

## IMMUNE CELL INFILTRATION IN ISLETS FROM TYPE 2 DIABETIC PATIENTS

Pancreatic islets from type 2 diabetic patients are known to present with amyloid deposits, fibrosis, and increased cell death (29–31). All of these hallmarks are associated with an inflammatory response. Indeed, given that pancreatic  $\beta$ -cell mass is now known to decrease in type 2 diabetes (31–33), the immune system is most likely associated with the removal of these apoptotic or necrotic endocrine cells. However, before massive cell death and immune infiltration, pancreatic islets may respond to metabolic stress by producing inflammatory factors. As mentioned above, the human pancreatic  $\beta$ -cell produces increased IL-1 $\beta$  in response to glucotoxicity (6). Various other inflammatory factors and nutrients have also been shown to induce an islet inflammatory response in vitro (34–36). In support of this hypothesis, there is now evidence that islet macrophage infiltration occurs in the GK rat (37), the high-energy diet-fed mouse, the *db/db* mouse, and human type 2 diabetes before the onset or independently of significant islet cell death (Fig. 1) (38). Given that type 2 diabetes is characterized by hyperglycemia, dyslipidemia, and increased circulating inflammatory factors (so-called low-grade inflammation), in-

creased cellular stress may be critical in precipitating islet inflammation in vivo.

## ISLET INFLAMMATION: FROM PHYSIOLOGY TO FAILURE

The impact of islet-derived inflammatory factors and islet inflammation on  $\beta$ -cell function and mass may be both beneficial and/or deleterious. Low concentrations of IL-1 $\beta$  promote  $\beta$ -cell function and survival (39). Other chronically elevated cytokines and chemokines in obesity and type 2 diabetes, such as IL-6, IL-8, and monocyte chemoattractant protein (MCP)-1, may also play a role in pancreatic islet adaptation (28,40,41). Indeed, the immune system is classically involved in both adaptation and repair; however, if this response becomes prolonged, it may become deleterious to organ function. All this emerging evidence reinforces the paradigm that islet inflammation is involved in the regulation of  $\beta$ -cell function and survival in type 2 diabetes.

## ANTI-DIABETIC DRUGS AND ISLET INFLAMMATION

Understanding that islet inflammation is an important factor in the pathogenesis of type 2 diabetes raises a concern regarding the application of drugs potentially harmful to the remaining  $\beta$ -cells. Conversely, protection of  $\beta$ -cells from death presents itself as a new therapeutic target. In this context, modulation of the  $\beta$ -cell ATP-sensitive K<sup>+</sup> (K<sub>ATP</sub>) channels (octamers composed of four inwardly rectifying K<sup>+</sup>-channels [Kir 6.2] and four sulfonylurea receptors [SUR1]) appears particularly in-

teresting. Indeed, closure of the  $K_{ATP}$  channels by the sulfonylureas tolbutamide and glibenclamide may induce  $Ca^{2+}$ -dependent  $\beta$ -cell apoptosis in rodent and human islets (42–44). This effect was observed only in vitro and not consistently (45). However, in an important recent clinical study comparing insulin and sulfonylurea treatment of type 2 diabetes, it was shown that treatment with insulin preserved  $\beta$ -cell function more effectively than glibenclamide (46). It remains to be established whether it is the beneficial effects of insulin per se or the possible  $\beta$ -cell toxicity of glibenclamide that accounts for this observation. Whereas a deterioration of insulin secretion was seen in patients treated with sulfonylureas in the U.K. Prospective Diabetes Study, those treated with insulin were not evaluated in this regard (47). Given the possible deleterious effect of some sulfonylureas, alternatives to these as well as alternative insulin secretagogues may have to be considered. When applied at the concentration of their respective circulating half-lives in vitro, repaglinide and nateglinide do not appear to have an apoptotic effect on human islets (44). In contrast to sulfonylureas,  $K_{ATP}$  channel openers may exert protective effects on  $\beta$ -cells (48,49). In 1976, Greenwood et al. (50) were the first to report an improvement in insulin secretion after administration of diazoxide for 7 days to diabetic subjects. Similar protective effects were observed more recently in patients classified with type 1 and type 2 diabetes (51,52). Finally, other antidiabetic drugs that have emerged as putative protectors of  $\beta$ -cells include thiazolidinediones, GLP-1 analogs, insulin (44,53–55), and last but not least, IL-1Ra (10).

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