β-Cells, Autoimmunity, and the Innate Immune System: "un Ménage á Trois"?

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Type 1 diabetes is generally believed to result from an autoimmune attack selectively destroying β-cells in the pancreatic islets of Langerhans. Indeed, with the recent discovery of cytotoxic T cells specifically recognizing β-cells infiltrating insulitic lesions in the pancreas, the ultimate proof of an autoimmune nature in human type 1 diabetes seems to be framed (1). This could imply that one of the last pieces of the puzzle of the pathogenesis of type 1 diabetes has been laid. But is this all there is to it?

In this issue of *Diabetes*, Valle et al. (2) present their perhaps surprising observation that slightly reduced circulating neutrophil counts associate with type 1 diabetes. The authors demonstrate that this phenomenon is not necessarily a consequence of impaired glycemic control because similarly reduced frequencies of neutrophils could also be found in nondiabetic first-degree relatives of type 1 diabetic patients with increased risk to disease but with normoglycemia, whereas type 2 diabetic patients showed neutrophils in the blood at normal counts. In contrast, the authors could demonstrate mild neutrophil infiltrates in exocrine pancreas tissue in some type 1 diabetic organ donors but not in pancreata of type 2 diabetic patients.

The consequences of this observation, as well as any mechanistic implications in relation with β-cell destruction and type 1 diabetes, remain elusive and could represent an epiphenomenon. Yet, neutrophils play a crucial role in several autoimmune diseases including systemic lupus erythematosus and rheumatoid arthritis. Neutrophils are among the first immune cells to respond to inflammation. They can aggravate chronic inflammation by recruitment of macrophages and interaction with antigen-presenting cells. Perhaps preclinical animal models of diabetes can prove to be of some guidance after all (3,4). Indeed, in a coinciding report elsewhere, Lehuen and colleagues report a role for neutrophils in the earliest stages of autoimmune diabetes in NOD mice. Here, death of β-cells leads to activation of B lymphocytes producing antibodies against double-stranded DNA that in turn activate neutrophils to produce peptides binding to self-DNA (5). Collectively, DNA antibodies and DNA-binding peptide activate plasmacytoid dendritic cells to produce interferon-α, a cytokine that is indeed mysteriously expressed in pancreatic islets of mice and humans even before leukocyte infiltration and insulitis (6). Although these observations in mice do not explain why neutrophil numbers are reduced in type 1 diabetes and are in discord with a lack of anti-DNA antibodies in the majority of type 1 diabetic patients, the new insight substantiates that the innate immunity is an important component in the pathogeneses of both type 1 and type 2 diabetes (7,8). In the context of animal models of type 2 diabetes, neutrophils mediated insulin resistance in mice fed a high-fat diet through secreted elastase (9), pointing to the possibility that neutrophils may add to β-cell stress, with potential consequence for loss of immune tolerance.

In the case of type 1 diabetes, a picture is emerging in which β-cells and innate and adaptive immune systems are engaged in intrinsic conversations ultimately determining the fate of the β-cells (Fig. 1).

Do these novel findings challenge the current paradigms of islet autoimmunity being the cause of type 1 diabetes? Not quite. They do open another can of worms, but they leave an overwhelming body of evidence supporting an autoimmune nature of type 1 diabetes untouched. Indeed, type 1 diabetes serves as the prototype of tissue-specific autoimmune disease: no type 1 diabetes without islet autoimmunity (10). Only autoreactive T cells responsive to β-cells are detectable in human insulitis (1). Autoimmunity in type 1 diabetes is largely β-cell specific or associated,

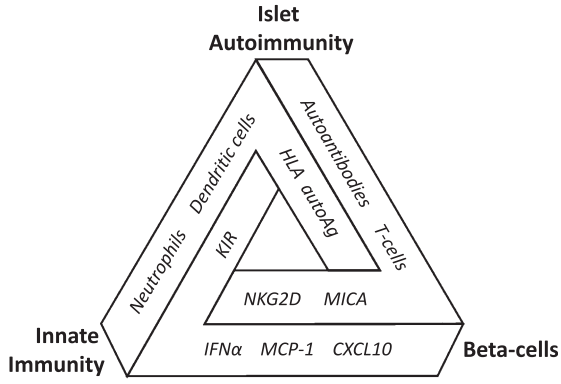

FIG. 1. Interactions between β-cells, the innate immune system, and the adaptive immune system. Autoreactive T cells and islet autoantibodies can recognize β-cell proteins (autoantigens) directly on the surface of β-cells or via cells of the innate immune system (dendritic cells, macrophages). Distressed β-cells produce chemokines (CXC chemokine ligand 10 [CXCL10], monocyte chemoattractant protein-1 [MCP-1], interferon-α [IFNα]) that can attract both adaptive and innate immune cells to pancreatic islets causing inflammation. Neutrophils can directly affect β-cells, or activate dendritic cells, perhaps via autoantibodies, that in turn can activate the adaptive immune system. The innate and adaptive immune system keep each other in check, for instance by natural killer receptors (KIR) and production of cytokines (interferon-α, interleukin-10), while the innate immune system can also communicate with β-cells through ligation of natural killer receptors (KIR, NKG2D) on innate cells and expression of MHC class I-like molecules (MICA) on β-cells.

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and β-cells are the driving force of insulitis (1). Nonspecific pancreas inflammation (pancreatitis) and β-cell death does not cause autoimmunity or type 1 diabetes, even in cases with HLA-associated risk (11). Adoptive transfer of T cells from type 1 diabetic donors causes disease, matching Koch's postulates modified for autoimmune disease (12,13).

The discovery by Valle et al. does not infringe the notion that type 1 diabetes is an autoimmune disease by nature. Yet, it is an important reminder to keep thinking out of the box and to concede that we haven't yet seen everything to fully understand the sequences of events causing type 1 diabetes.

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