Big Mac Attack: Does It Play a Direct Role for Monocytes/Macrophages in Type 1 Diabetes?

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Type 1 diabetes is conventionally thought to result from T-cell–mediated autoimmune destruction of pancreatic β-cells (1–3). Experimental and clinical evidence accumulated over the past two decades indicates that T-cells play a critical role in the pathogenesis of type 1 diabetes in both humans and the nonobese diabetic (NOD) mouse model of this disease (4). Indeed, the important contribution of T-cells toward the pathogenesis of type 1 diabetes has been supported not only by a variety of physiologic and histological studies but, in addition, through a number of immunotherapeutic-based studies involving selective targeting of T-cells (4,5). More recently, it has been shown that B-cells also play an important role in type 1 diabetes development (6), since NOD mice deficient in these cells do not develop insulitis or overt diabetes (7), and that the depletion of B-cells with anti-CD20 antibody prevents disease (8).

Apart from diabetogenic T- and B-cells, emerging evidence suggests that macrophages are involved in the final stage of autoimmune-mediated β-cell destruction (9,10). For example, after monocyte depletion, passively transferred diabetogenic T-cells fail to induce diabetes, and activated macrophages can directly kill β-cells in vitro (10). However, direct evidence that activated monocytes/macrophages kill β-cells is minimal or lacking, depending on one's perspective. In the current issue of *Diabetes*, Martin et al. (11), using multiple transgenic mouse models, provide convincing evidence that monocytes can be recruited to pancreatic islets when the chemokine CCL2 is expressed transgenically in β-cells and that these immune system cells are capable of destroying β-cells, resulting in diabetes in the absence of mature T- and B-cells. Therefore, this observation adds monocytes/macrophages to the growing list of immune cells involved in islet cell destruction in type 1 diabetes.

There are two distinct phases for autoimmune-mediated diabetes: insulitis and diabetes. In the early stages of insulitis, mixed leukocytes including activated macrophages, B-cells, T-cells, and NK cells are attracted to the islets by chemokines. Chemokines are chemoattractant proteins (12,13) produced by cells in response to infection or cell damage (13). Leukocytes, such as lymphocytes, monocytes, and NK cells, expressing the appropriate receptors, migrate toward the source of chemokine production. Chemokines are subdivided into four subfamilies (C, CC, CXC, and CX3C) based on the location of the first conserved NH_2-terminal cysteine residues (13). The largest group is the CC family, where two cysteine residues are immediately adjacent to each other.

CCL2, also known as monocyte chemoattractant protein-1 (MCP-1), is a CC chemokine produced by lymphocytes, monocytes, endothelial cells, and other cells in response to inflammatory stimuli (14). Through its receptor CCR2, MCP-1/CCL2 potently attracts monocytes, T-cells, and NK cells. Although MCP-1 is expressed in normal human and rodent islets (15), transgenic mice overexpressing MCP-1 under control of the insulin promoter develop an intense insulitis, but overt diabetes was not seen in early studies (16). The temporal pattern of MCP-1 and other chemokine expression correlates with the progression of insulitis and β-cell destruction in NOD mice (17).

Despite substantial indirect evidence that CCL2 is involved in the pathogenesis of type 1 diabetes, its precise role in the development of insulitis and islet cell destruction is incompletely understood. Martin et al. (11) add to the accumulating evidence that CCL2 production and numbers of circulating monocytes play a more important role in the onset of diabetes than was previously suspected.

The investigators demonstrate that monocytes/macrophages are recruited in a concentration-dependent manner to the islets by transgenic expression of CCL2 in β-cells under the control of the insulin promoter. The CCL2-mediated monocyte recruitment requires the CCL2 receptor (CCR2), since deletion of CCR2 in RIPCCL2 mice abolishes homing to the islets. Strikingly, and in contrast to previous studies (16,18), transgenic mice displaying high MCP-1 expression and serum MCP-1 levels not only develop insulitis but also go on to islet cell destruction and clinical diabetes. The explanation for this apparent discrepancy may lie both in the relatively high level of MCP-1 expressed (up to 1.4 ng/ml in the serum) and in the fact that MCP-1 production in the Martin et al. (11) study was restricted to islets, whereas expression was more widespread in the study of Rutledge et al. (18). Importantly, to assess the influence of T- and B-cells, Martin et al. bred the RIPCCL2 transgene onto a Rag-$1^{-/-}$ background to generate mice expressing CCL2 in β-cells in the absence of mature T- and B-cells. Remarkably, the hybrid mice developed diabetes with a similar time course to that of immunocompetent Rag$1^{+/-}$ controls.

Thus, although diabetogenic T- and B-cells may be central to the pathogenesis of type 1 diabetes under "physiological" conditions (2,19), the Martin et al. study extends data from several other laboratories (9,10,16,20), suggesting that monocytes/macrophages also may play a critical role. Most current therapies, such as the induction

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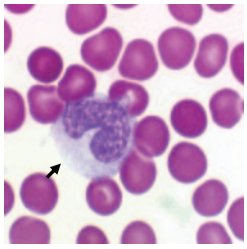

Circulating Monocyte

FIG. 1. Arrow indicates a circulating monocyte on peripheral blood smear.

of immunoregulatory T-cells, costimulatory blockade, and T- or B-cell depletion with anti-CD3 or -CD20 antibodies (5,8,19,21), target the lymphocyte arm of the autoimmune response to islets. One implication of the current study is that therapy directed at the antigen-presenting cells also may be effective. Indeed, a variety of MCP-1/CCL2 inhibitors are under development, and it has been shown that anti-CCL2 therapy can reverse other autoimmune disorders in animal models, such as murine demyelinating disease (22) and lupus nephritis (23). The Martin et al. study may provide a conceptual framework for the design of monocyte therapy aimed at interrupting insulitis and the destruction of pancreatic β-cells. This study may also provide a rationale for monitoring CCL2 levels and circulating monocyte numbers in the blood as parameters to predict the disease onset and monitor the disease progression (Fig. 1).

However, caution should be exercised in evaluating and interpreting this study. Transgenic overexpression of CCL2 in β-cells does not necessarily reproduce the defect in human type 1 diabetes, although pancreatic islet tissue from patients with recent-onset type 1 diabetes exhibits macrophages and dendritic cells infiltrating the islets and the production of inflammatory cytokines (tumor necrosis factor-α and interleukin-1β) (24). Moreover, in view of the redundancy of chemokine pathways, the efficacy of disrupting a single chemokine pathway remains to be determined. Nevertheless, further investigation of the potential for monocyte therapy of type 1 diabetes seems warranted.

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