Role of Plasmacytoid Dendritic Cells in Type 1 Diabetes: Friend or Foe?

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Type 1 diabetes is characterized by T-cell–mediated destruction of insulin-producing β-cells. Progression of β-cell autoimmunity is simplistically viewed as a functional imbalance favoring the development of β-cell–specific pathogenic type 1 versus immunoregulatory T-cells (Tregs) (1,2). The latter consist of a number of distinct subsets with varying functions that can prevent differentiation or function of type 1 T-cells (3). It is unclear how this functional balance between pathogenic T-cells and Tregs goes awry, leading to massive β-cell destruction, or is maintained in at-risk individuals who remain diabetes free. In this issue of *Diabetes*, Peakman and colleagues (4) investigate dendritic cells in diabetic patients and provide suggestive evidence for a new player in regulating β-cell–specific T-cell reactivity.

Dendritic cells are a heterogeneous group of innate effectors that serve two general functions in controlling T-cell immunity. The first is to process and present antigens to T-cells, which is essential for T-cell activation and expansion. Second, dendritic cells secrete cytokines that condition the extracellular milieu and determine the nature of the T-cell response. Although much attention has been focused on the capacity of dendritic cells to initiate proinflammatory responses to microbial pathogens, it is clear that dendritic cells serve an important role in establishing and maintaining tolerance to self-antigens (5). These opposing functions are governed by the maturation status and types of cytokines secreted by dendritic cells (6). For instance, infectious microbes in contact with immature dendritic cells promote maturation, which is characterized by the following: *1*) an increased capacity to present antigens and stimulate T-cells and *2*) secretion of proinflammatory cytokines, which promote differentiation of type 1 T-cells that efficiently clear the infectious agent (6). Depending on the type of dendritic cell, different cytokines are secreted to establish a proinflammatory milieu. Mature myeloid dendritic cells (mDCs) secrete interleukin (IL)-12, which directly induces differentiation of type 1 T-cells (6). Plasmacytoid dendritic cells (pDCs), the focus of the Peakman group's study, secrete interferon (IFN)-α, which is well known for its potent antiviral properties (7).

Self-tolerance is mediated by the dendritic cell via passive and active processes. Under noninflammatory or homeostatic conditions, the majority of dendritic cells are found in an immature state. Immature dendritic cells presenting self-antigens fail to both stimulate T-cells and secrete cytokines (8). Under certain conditions, immature dendritic cells presenting self-antigens can be tolergenic by inducing either a state of unresponsiveness or apoptosis in the autoreactive T-cells (9). In addition, immature dendritic cells stimulated by apoptotic bodies or cytokines such as transforming growth factor-β and IL-10 develop a tolergenic phenotype upon subsequent maturation, characterized by the secretion of anti-inflammatory cytokines or a capacity to preferentially expand Treg (9).

In view of their pivotal role regulating T-cell immunity, dendritic cells would be expected to impact the functional balance between pathogenic T-cells and Tregs in type 1 diabetes. Indeed, studies in the nonobese diabetic (NOD) mouse, a spontaneous model of type 1 diabetes, have shown that mDCs exhibit a hyperinflammatory phenotype. Namely, NOD dendritic cells have an elevated capacity to stimulate T-cells and secrete proinflammatory cytokines such as IL-12 (10,11). This dendritic cell phenotype would be expected to directly drive differentiation of pathogenic type 1 T-cells and promote β-cell destruction. Studies in diabetic patients, however, suggest a different scenario. Monocyte-derived dendritic cells from peripheral blood of diabetic patients exhibit a limited T-cell stimulatory capacity relative to at-risk or healthy individuals (12,13). Accordingly, it has been proposed that these "immature-like" dendritic cells are less effective at stimulating Tregs, which in turn would be predicted to indirectly favor differentiation and expansion of pathogenic type 1 T-cells (12,13).

Whereas most studies to date have investigated mDCs in diabetic individuals, the report by Peakman and colleagues focuses on pDCs. pDCs are of particular interest in view of studies linking this dendritic cell subset with other types of autoimmunity, most notably systemic lupus erythematosus (SLE). Patients with SLE exhibit elevated levels of serum IFN-α, which activates several pathways that promote inflammation (e.g., autoimmunity) (14). Interestingly, pDC activation and IFN-α secretion are attributed to binding of immune complexes consisting of autoantibodies and nucleic acids (15). These immune complexes are bound and internalized by the FcγRIIA receptor expressed by pDC. The nucleic acid moieties are then recognized by Toll-like receptors residing in the cytoplasm of pDCs, which initiate a cascade of signaling events that lead to the production of copious amounts of IFN-α (16). The role of pDCs in antigen presentation to autoreactive T-cells, however, is ill defined in SLE.

Peakman and colleagues compared the frequency of pDCs and subsets of mDCs in peripheral blood of patients with recent-onset diabetes, patients with long-standing diabetes, and matching healthy control subjects. A modest

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DOI: 10.2337/db08-1341

See accompanying original article, p. 138.

but significant increase in the frequency of pDCs and a concomitant decrease in mDCs in patients with recent-onset diabetes versus control subjects was found. Importantly, the indirect effects of hyperglycemia on dendritic cells were ruled out by demonstration that the frequency of pDCs and mDCs in type 2 diabetic patients was unchanged compared with that in healthy control subjects. Interestingly, long-standing diabetic patients exhibited a normal frequency of pDCs (and mDCs), and a similar trend was detected in a small number of patients monitored over a 2-year period, beginning at the time of diabetes onset. Therefore, the increase in pDCs appears to be selective for the onset of diabetes. Furthermore, pDCs in patients with recent-onset diabetes exhibited an immature or resting phenotype, consistent with the observation that serum levels of IFN-α were normal in these patients. Therefore, unlike SLE, in which activated pDCs are believed to drive autoimmunity via IFN-α secretion, pDCs may serve a distinct role in type 1 diabetes independent of cytokine secretion.

A clue to the role pDC may have in the diabetogenic response came from experiments assessing the T-cell stimulatory capacity of pDCs. The latter was tested employing a clever in vitro assay system that exploited the use of a recombinant insulinoma-associated protein 2 (IA2) molecule, containing an influenza hemagglutinin peptide, and sera from diabetic patients, containing anti-IA2–specific autoantibodies. pDCs were found to stimulate a hemagglutinin-specific T-cell clone after incubation with immune complexes of the IA2-hemagglutinin fusion molecule and serum anti-IA2 autoantibodies. Importantly, efficacy of T-cell stimulation by pDCs, but not mDCs, was dependent on the concentration of serum anti-IA2 autoantibody. These results suggest that at least one role for the pDC in type 1 diabetes is to present β-cell–autoantigen–autoantibody complexes to the corresponding autoreactive T-cells.

This study raises a number of interesting questions for future work. First and foremost, what is the outcome of autoantigen presentation by pDCs to T-cells? For instance, do pDCs preferentially induce type 1 versus Treg responses? The latter possibility is suggested by the fact that, in diabetic individuals, pDCs exhibit an immature status consistent with a tolergenic phenotype. However, whether pDCs residing in the draining pancreatic lymph nodes or infiltrating the islets have a similar phenotype is obviously not known. It is noteworthy that a recent study by Katz and colleagues (16) demonstrated that pDCs have a protective function in NOD mice. A related question deals with the relevance of the elevated frequency of pDCs in peripheral blood at the onset of diabetes. Accordingly, it will be important to determine whether the increase in pDCs parallels the appearance of islet-specific autoantibodies in at-risk individuals and whether pDCs are bound by immune complexes. In conclusion, the study by Peakman and colleagues provides a key starting point to study pDCs and their potential role in regulating β-cell–specific T-cell responses.

ACKNOWLEDGMENTS

R.T. is supported by grants from the National Institutes of Health and the Juvenile Diabetes Research Foundation. B.W. is supported by a Career Development Award from the American Diabetes Association.

No potential conflicts of interest relevant to this article were reported.

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