B lymphocytes (B cells) play a key role in type 1A diabetes (T1D) via antigen presentation to T cells, but our understanding of their mechanism of action is still evolving (1–6). Pathogenic B cells recognize autoantigens, indicated by T1D-predictive autoantibodies against insulin, GAD65, transmembrane tyrosine phosphatase (IA-2), and zinc transporter 8 (ZnT8) (7). These autoantibodies are not thought to cause T1D but, rather, provide evidence of autoreactive T cell–B cell interactions. Each B cell recognizes a single antigenic site, or epitope, on folded proteins via the antibody variable (V) region of its B-cell receptors (BCRs), internalizes the protein, and processes it into peptides for presentation on MHC class II (MHCII) to T cells (Fig. 1). Thus, autoreactive B cells are uniquely suited to activate autoreactive T cells. Likewise, T cells provide help to B cells, driving antigen-specific germinal center (GC) formation and differentiation into plasma cells that secrete autoantibodies identical to the BCR. Transgenic models provide evidence that B cells must be autoantigen specific to support T1D: anti-insulin B cells present antigen, activate T cells, and promote T1D in nonobese diabetic (NOD) mice (5,6,8). Conversely, NOD mice with transgenic B cells that do not recognize an autoantigen fail to develop diabetes (5,9). While there are multiple T1D-related autoantibodies in humans, to date, insulin has been the only reliable T1D-predictive autoantigen in NOD mice. In this issue of Diabetes, Leeth et al. (10) report on a new transgenic model in which B cells recognize peripherin, a neuronal antigen, and are able to support diabetes development.

Peripherin is expressed in peri-insular areas of islets, and in central and peripheral nervous system cells, similar to the important human autoantigen GAD65. The BCR transgene, designated PerIg, was developed from a BCR cloned from islet-invading B cells in NOD mice (10–13). NOD.PerIg mice expressing the BCR heavy chain, the BCR light chain, or both develop diabetes at higher rates than wild-type NOD counterparts. As expected, disease outcome is T cell dependent.

PerIg B cells have many features that suggest that they escape central tolerance mechanisms in a functionally defective state termed anergy. They do not produce antibody or proliferate well when stimulated. They are significantly increased in number at the early transitional (T1) stage, which is a tolerance checkpoint, and have decreased mature follicular numbers, suggesting that these cells are developmentally blocked and culled at the T1 stage. They are increased in the marginal zone compartment, which depends on low-affinity antigen-dependent selection and is enriched for autoreactive specificities, but do not populate the similar B1a compartment. PerIg B cells also have altered maturation profiles in the bone marrow and engraft poorly under a variety of conditions. Many of these characteristics are shared with anergic anti-insulin (125Tg) B cells, indicating that B-cell tolerance need not be broken for them to play this role (6). In fact, it suggests the possibility that the residual functions of anergic B cells may somehow be especially well suited to present antigen and support T cell–mediated T1D.

Despite having dysfunctional properties, PerIg B cells invade islets well, where they show evidence of proliferation (Ki67+) and even differentiation into plasma cells (CD138+). CD86 expression is higher on PerIg B cells in islets than on their WT NOD counterparts, suggesting increased capacity for T-cell activation. Consistent with this, GC reactions are increased in draining pancreatic lymph nodes (PLNs), as characterized by Fas+/GL7+ GC B cells and CXCR5+/ICOS+ T follicular helper cells. However, BCR sequencing from PLNs shows no somatic hypermutation, which normally increases affinity and is the final end point of GC reactions, and anti-peripherin antibody is not found in serum. This may reflect functional status of these cells or may simply be due to the unknown integration site of the transgene. Nevertheless, the presence of GCs in PLNs strongly suggests that anti-peripherin T cells are available to activate PerIg B cells and vice versa.

Of note, highly activated GC B cells do have increased ability to present antigens beyond those recognized by their BCRs, can cross present antigen to CD8+ T cells, and also produce inflammatory cytokines (14,15). It is also possible, as stated by Leeth et al. (10), that the PerIg BCR cross-reacts...
with β-cell antigens or that β-cell antigens form complexes with peripherin that are internalized by the anti-peripherin BCR. These scenarios would promote epitope-spreading and widespread β-cell destruction by T cells that recognize autoantigens beyond peripherin. This concept could be tested in the future by examining the frequency of β-cell destruction by T cells that recognize the same antigen. Each B cell recognizes a single antigen via the antibody component of BCRs. The BCR specifically binds its target autoantigen and then internalizes it into the B cell for processing. The protein antigen is cleaved into short peptides that are loaded into MHCII molecules. MHCII then moves to the surface of the B cell and presents the peptide to T cells that recognize the same antigen. The T cell further activates the B cell, driving it into germinal centers, where it differentiates into memory B cells and plasma cells that then secrete large amounts of antibody identical to the BCR. The antigen-presenting B cell also provides a critical costimulatory signal (CD86 to CD28) to activate the T cell. Activated autoreactive T cells destroy insulin-producing β-cells, while the autoreactive B cells serve as markers of autoimmune activity and can reveal the autoantigens that are recognized by pathogenic T cells. These processes may occur in draining pancreatic lymph nodes or in inflamed islets. The inset shows immunohistochemical staining of T cells (blue) and B cells (red) infiltrating an islet from an NOD mouse.

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