Isotypes of Anti-Islet Autoantibodies

In this issue of Diabetes Care, Hawa et al. (1) conclude that “the pathogenesis of antigen-specific antibodies in type 1 diabetes and type 2 diabetes is similar and probably involves a chronic nonrandom antigen-driven polyclonal B-cell activation that is consistent with a Th1-type immune response.” The data presented also indicate that what are now standard anti-islet autoantibody assays are not improved by the use of antibody subclass specific reagents. These are reasonable conclusions concerning both autoimmune T- and B-cells and are derived from the study of GAD65 and IA-2 (ICA512) autoantibodies. Some conclusions are naturally firmer than others. For instance, the finding that autoantibodies express both κ and λ immunoglobulin light chains is convincing evidence of a polyclonal immune response. Each B-cell clone produces either λ or κ antibodies.

The finding that prediabetic subjects, new-onset type 1 diabetic patients, and patients with type 1 diabetes presenting as adults with “non-insulin-dependent diabetes” all express predominantly IgG1 antibodies is consistent with reports of a predominance of IgG1 antibodies in young infants (2). The lack of changes in the subclass of the autoantibodies may be influenced by the stage of disease analyzed. When anti-islet autoantibodies first appear, there is reported variation in subclass expression (2). A lack of change in antibody subclasses at the onset of diabetes compared with several years before onset is consistent with chronic progression to type 1 diabetes. To date, there is little evidence of an immunologic change at the time of presentation of diabetes. In humans, diabetes probably results from progressive immune destruction of β-cells (3). In animal models, there is controversy as to whether β-cell destruction is chronic (4) or acute (5).

It is noteworthy that autoantibodies were measured to ascertain whether the T-cells orchestrating an immune response are predominantly Th1-like (producing lymphokines such as γ-interferon and interleukin [IL]-2) or Th2-like (producing lymphokines such as IL-4 and IL-10). Antibodies are being measured because they are something we can now measure well. The presence of anti-islet antibodies reacting with defined antigens such as GAD65, IA-2, or insulin is the best parameter for distinguishing type 1A (immune-mediated) from type 1B, or type 2 diabetes (6). At onset of diabetes, it might be the only parameter of utility because C-peptide levels frequently overlap normal ranges. Many children (particularly in U.S. minority populations) are now developing type 2 diabetes (7), and as illustrated in the article by Hawa et al., many adults have type 1A diabetes. Presence of autoantibodies reacting with multiple islet antigens is highly predictive of progression to diabetes and insulin dependence (8,9).

The subclasses of antibodies, especially in humans, however, are an imprecise reflection of T-cell lymphokine production (10). Measuring autoimmune T-cell responses is just beyond the limits of current technology (11). We will likely have to wait for better technologies for analyzing autoimmune T-cells. For example, specific reagents labeling autoimmune T-cell receptors (e.g., HLA tetramers [12]) are now used in animal models.

Though there are excellent assays for autoantibodies (13), there is evidence that antibodies do not cause diabetes but are “footprints” reflecting the presence of T-cells, which are destroying islet β-cells. In the future, both autoantibodies and autoimmune T-cells should be accessible to analysis. This should further our understanding of disease pathogenesis and provide better diagnostic and prognostic information.

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Editorial

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