Autoimmune Markers in Diabetes

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BACKGROUND: Type 1 diabetes (T1DM) results from cell-mediated autoimmune destruction of the β cells of the islets of Langerhans. Autoantibodies directed against the islets are useful clinical tools that allow the recognition and confirmation of β-cell autoimmunity.

CONTENT: In this review we define the term “islet autoantibody,” describe the pathogenesis of autoantibody generation, and explain the uses of islet autoantibodies in clinical medicine and in research studies that concern the interruption or prevention of T1DM. We also discuss the biology of islet autoantibodies and their rates of appearance at the time of onset of T1DM and their appearance before the development of T1DM.

SUMMARY: The presence of islet autoantibodies in persons with diabetes confirms an autoimmune etiology. In nondiabetic individuals, islet autoantibodies are strong predictors of the later development of T1DM.

“Islet autoantibody” is a generic term for any one of a group of autoantibodies that are directed against the islets of Langerhans or, in some circumstances, are directed specifically against autoantigens of the insulin-secreting β cells. β-Cell death that causes type 1A diabetes (T1DM)1 seems to result from a cell-mediated autoimmune process (1) initiated by yet-to-be-discovered environmental triggers (2) occurring in individuals with a genetic predisposition to the disease (3).

If destruction of the β cells by CD8 T-killer cells and macrophages is the "fire," the "smoke" (e.g., clinical evidence of β-cell autoreactivity) represents islet autoantibodies (4). Islet autoantibodies are commonly present at the onset of T1DM and persist for varying durations after onset. Most importantly, islet autoantibodies precede the onset of T1DM by months to many years (5). From the German BABY-DIAB study (6) and the Diabetes Autoimmunity Study in the Young (DAISY) study, islet autoantibodies can first appear very early in life and are predictive of the later onset of T1DM. Other similar studies are in progress [e.g., TEDDY (The Environmental Determinants of Diabetes in the Young) (7)].

Islet autoantibodies are considered unlikely to be the cause of T1DM. However, islet autoantibodies provide proof that in islet autoantibody-positive individuals certain islet antigens are recognized as foreign, resulting in a humoral immune response.

What Causes Islet Autoantibodies to Appear in the Sera of People with T1DM or before Their Development of T1DM?

Autoantibodies form because of a breakdown in tolerance (8, 9). For autoantibodies to appear, the autoantigen must become available (i.e., accessible) to the immune system so that an immunization event can occur. Immunization that results in an IgG autoantibody response requires switching of B-lymphocyte class, and therefore CD4 T cells must be involved in addition to naïve mature B cells. After the naïve mature B lymphocyte contacts the immunogen through surface IgM and/or IgD [with or without the B-lymphocyte CD21 (CR2), CD19, CD81 coreceptor interaction], help must be supplied by T-helper 1 or 2 cells to class switch to IgG (affinity maturation takes place as well). Other than insulin and carboxypeptidase H, all islet antigens are intracellular and are not normally secreted or expressed on the surface of the β cell. The release of intracellular antigens is possibly the result of cell-mediated autoimmune damage to β cells, which permits such otherwise sequestered self antigens access to naïve mature B lymphocytes and naïve CD4 T cells (10).

Several inborn errors in the β cell that affect the subunits of the inwardly rectifying potassium channel Kir6.2 [encoded by potassium inwardly-rectifying
channel, subfamily J, member 11 (*KCNJ11*) or SUR1 [encoded by ATP-binding cassette, sub-family C (CFTR/MRP), member 8 (*ABCC8*)] have been shown to cause neonatal diabetes (11). Recently, the appearance of islet autoantibodies has been described in older children who many years earlier had developed neonatal diabetes from *KCNJ11* gene mutations (12). In this situation, there was no a priori autoimmunity to islet cells (i.e., the β-cell defects were inherited); however, if the β cells were to die, β-cell death might have then led to subsequent islet autoantigen immunization. These observations provide evidence to support the sequestered-antigen theory of autoimmunity in T1DM as an explanation for the appearance of islet autoantibodies. Nonetheless, islet autoantibodies have not been detected in any other destructive form of diabetes such as cystic fibrosis or hemochromatosis-induced diabetes.

An alternative hypothesis (among many possible alternatives) to explain autoimmunity is that molecular mimicry occurs between an environmental agent, such as a viral or bacterial pathogen or other environmental molecule or chemical, and a primary β-cell antigen (13). If the immune system is not tolerant to the self antigen, because the self antigen is normally sequestered, the immunizing event resulting from the infection or some other environmental exposure leads to cross-reactive immunity to the self antigen with the appearance of islet autoantibodies (assuming that the immunoassay system is using an islet autoantigen as its target). If antibodies were sought against the molecule causing the mimicry, and not the cross-reactive autoantigen, the resulting antibodies would not be considered autoantibodies.

**What Islet Autoantibody Determinations Are Available for Clinical and Research Use?**

The list of islet autoantibodies and autoantigens to which islet autoantibodies have been detected is expansive (Table 1) (14–34). With the exclusion of islet-cell cytoplasmic autoantibodies (ICA), glutamic acid decarboxylase (GAD) autoantibodies (GADA), insulinoma 2 (IA-2)-associated autoantibodies (IA-2A), insulin autoantibodies (IAA), and zinc transporter 8 protein (ZnT8) islet autoantibody (ZnT8A), the other autoantibodies are difficult to measure and/or are not sufficiently sensitive or specific to warrant their use in present day studies of T1DM or its pathogenesis.

<table>
<thead>
<tr>
<th>Table 1. Selected autoantibodies in T1DM.</th>
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<tr>
<td><strong>Insulin, insulin processing and insulin storage</strong></td>
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<tr>
<td>Carboxypeptidase H autoantibodies (14)</td>
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<td>IAA (15)</td>
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<td>Proinsulin autoantibodies (16)</td>
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<td>ZnT8A (17)</td>
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<td>DNA topoisomerase II autoantibodies (22)</td>
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<td>GADA (23)</td>
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<td>51-kDa aromatic-L-amino-acid decarboxylase autoantibodies (24)</td>
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<td><strong>Miscellaneous</strong></td>
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<td>Aminoacyl-tRNA synthetase autoantibodies (25)</td>
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<td>Gli38 autoantibodies (26)</td>
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<td>GLUT2 autoantibodies (27)</td>
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<td>Glycolipid autoantibodies (28)</td>
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<td>GM2-1 islet ganglioside autoantibodies (29)</td>
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<td>Heat shock protein autoantibodies (30)</td>
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<td>Islet cell surface autoantibodies (ICSA) (31)</td>
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<td>ICA (32)</td>
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<td>Islet cell–specific 38-kDa autoantibodies (33)</td>
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<td>52-kDa RIN (rat insulinoma) autoantibodies (34)</td>
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Most major T1DM autoantigens, with the exception of insulin, are not unique to the β cell. Because of the early appearance of IAA in the pathogenesis of human and nonobese diabetic (NOD) mouse T1DM, insulin has been proposed as a primary autoantigenic target (e.g., loss of tolerance to insulin or failure to develop tolerance to insulin is the trigger to β-cell autoimmunity and eventual β-cell destruction) (35). The seminal findings of Pugliese and colleagues showed that variable-number tandem-repeat polymorphisms of the insulin gene, while not affecting the insulin molecule amino acid sequence, do affect the degree of insulin’s expression in the thymus (36). Insufficient thymic expression of insulin theoretically allows insulin-autoreactive clones of CD4 T cells and CD8 T cells to exit the thymus. Once the β cells are damaged, hypothetically, sequestered antigens are then released to which the immune system responds (e.g., GAD and IA-2) that may not be β-cell specific. Thus, over time, more islet autoantibodies appear and epitope spreading occurs (37).
The 4 major autoantibodies of clinical and research interest are ICA (32), GADA (23), IA-2A (18), and IAA (15). ZnT8A, a newly recognized ZnT8 islet autoantibody, may further improve the value of islet autoantibody testing (17).

ICA were first described in 1974 by Bottazzo and colleagues (32). The availability of an epifluorescent light source was the technical breakthrough that permitted the development of this indirect immunofluorescent technique. Patient sera are incubated on sections of human cryocut, blood-group O pancreas. After washing of the tissue section, a fluorescein-isothiocyanate–labeled, antihuman IgG conjugate is added. After another washing step, and after application of glycerol and a cover slip, the slide is carefully examined under the fluorescent microscope. If ICA are present, the islets fluoresce. By serially dilution of the patient’s serum to endpoint negativity with correlation to a standard serum, ICA are expressed in terms of JDF (Juvenile Diabetes Foundation) units. The lowest significant positive for ICA is 10 JDF units. ICA react against a sialoglycoconjugate, an insulinoma-associated autoantigen, and GAD. ICA are polyclonal.

ICA are the most difficult islet autoantibodies to measure because ICA assays are subject to variations in the pancreatic tissue, conjugate, incubation times, humidity, and biological-scientist interpretation. The measurement process is also very labor intensive; however, the disposable and reagent costs are relatively low.

ICA are detected in 70% to 80% of individuals with new-onset T1DM. ICA positivity declines after the onset of T1DM. After 10 years, few individuals remain ICA positive (approximately 5%). In the Diabetes Prevention Trial–Type 1 (DPT-1), nonaffectted relatives of people with T1DM were screened for ICA positivity and then found to have low first-phase insulin responses to intravenous glucose challenge had a 5-year risk for the development of T1DM of 60% and a projected 10-year risk near 90% (see below). In the DPT-1 (38) neither subcutaneous nor oral insulin prevented the development of T1DM in islet-autoantibody–positive relatives of probands with T1DM.

GADA, IA-2A, and IAA are collectively referred to as the “biochemical autoantibodies” because the islet autoantigens have been specifically identified and cloned. These autoantigens are used in immunoprecipitation (radiobinding) assays. \(^{3}H\) or \(^{35}S\)-methionine can be used as labels. These assays preserve the autoantigen in its native conformation, which is important to preserve the autoantigen epitopes that are recognized by the autoantibodies. In general, ELISA assays in which the autoantigen is directly adherent to the wall of the plate (with partial or complete autoantigen denaturation) are not predictive of T1DM (e.g., IAA ELISAs) (39).

GADA catalyzes the conversion of glutamic acid to the inhibitory neurotransmitter GABA (\(\gamma\)-amino butyric acid). The specific role of GABA in \(\beta\) cells is not known. In 1990, GAD was discovered to be the 64 000-Da molecular weight islet autoantigen that was immunoprecipitable by diabetic (but not nondiabetic) sera (23). GAD was known to be a major autoantigen recognized by sera from patients with stiff-person syndrome (40). Biochemical analysis has shown that GAD is found in a variety of tissues, with highest concentrations in the nervous system. GAD is an intracellular enzyme and thus it is not normally expressed on the surface of the \(\beta\) cell (41).

Although there are 2 major isoforms of GAD, GAD autoantibodies are more often found that are directed against GAD65 (65 000-Da molecular weight) than GAD67 (67 000-Da molecular weight). GADA are found at similar rates (70%–80%) as ICA in patients with new-onset T1DM. After the onset of T1DM, GADA are more persistent than ICA. For this reason, GADA testing is preferred over ICA testing when the diagnosis of latent autoimmune diabetes of adulthood (LADA) is sought in individuals with long-standing diabetes (42).

IA-2A was detected by screening an insulinoma expression library for reactivity with sera from T1DM patients. IA-2 is a member of the protein tyrosine phosphatase family and is a transmembrane protein. The predominant autoreactive epitopes are in its C-terminal region and are oriented intracellularly in a way that is consistent with a sequestered autoantigen. Autoreactivity to the C-terminal construct of IA-2A (ICA512) is known as ICA512 autoantibodies (ICA512A) (43). IA-2A is less common at the onset of T1DM (approximately 60%) than either ICA or GADA (44).

Insulin, as noted above, is a specific to \(\beta\)-cell autoantigen. Palmer et al. in 1983 described IAA in new-onset T1DM patients before institution of insulin therapy (15). IAA are more common in younger children with new-onset T1DM (approximately 60% positive) than in adults. Once insulin is exogenously administered (for >10 days) the IAA determination is no longer valid because exogenous insulin injection can elicit insulin antibody responses that cannot be distinguished from autoantibody production. However, the concentration of insulin antibodies is usually much higher than IAA. Of all the biochemical autoantibodies discussed, IAA are the most difficult to accurately and reproducibly measure. The original IAA assays used hundreds of microliters of sera (e.g., macroIAA assays). Presently most IAA assays have been redesigned to use only small volumes of sera for IAA measurement (microIAA).
We previously published the reported frequencies of islet autoantibodies at disease onset and their predictive values for the development of T1DM in nondiabetic individuals (45, 46). Unquestionably, as the number of islet autoantibodies expressed by a nondiabetic individual rises, their risk for T1DM also rises. Individuals positive for a single islet autoantibody are far less likely to develop T1DM than individuals who are positive for multiple islet autoantibodies. In general, the number of islet autoantibodies expressed by an individual is a more important predictor of T1DM than any specific combination of islet autoantibodies (47). In DPT-1 (38) per year of follow-up, T1DM developed in approximately 15% of unaffected first-degree relatives who were repeatedly positive for ICA and had persistent low insulin secretion in response to intravenous glucose.

In another analysis of DPT-1 data (47), the predictive values of ICA alone, GADA alone, and ICA512A alone were determined and were found to be similar: 3.9% of single-autoantibody–positive ICA-positive relatives developed T1DM vs 4.4% positive for single-autoantibody–positive GADA vs 4.6% for single-autoantibody–positive ICA512A. By itself, IAA did not predict T1DM. The addition of any other islet autoantibody to individuals with ICA, GADA, or IA-2A positivity significantly increased their risk for T1DM (risk for T1DM: ICA alone, 2.8%, vs ICA plus any other autoantibody, 17.9%; GADA alone, 2.3%, vs GADA plus any other autoantibody, 13.9%; and ICA512A alone, 3.0%, vs ICA512A plus any other autoantibody, 24.6%). The greater the number of islet autoantibodies present, the greater the risk of developing T1DM: the risk for T1DM in 4-autoantibody–positive individuals: 50%; the risk for T1DM in 3-autoantibody–positive individuals: 40.3%; the risk for T1DM in 2-autoantibody–positive individuals: 16.1%; the risk for T1DM in 1-autoantibody–positive individuals: 3.1%; and the risk for T1DM in 0-autoantibody–positive individuals: 0.5%. Higher ICA titers and higher concentrations of GADA were more powerful predictors of T1DM than lower titers and lower concentrations.

In the biochemical autoantibody assays, positivity is defined as signals that exceed the 99th percentile for the general population. In the ICA test, positivity is defined as islet fluorescence at a minimum sample dilution of 1–2 (1 part patient serum added to 1 part diluent). CVs for the GADA and IA-2A biochemical autoantibody assays are near 5%. For IAA determinations, the CVs are considerably larger (e.g., up to 20%–25%). With the recognition that ICA testing is performed via serial dilutions, ICA results within ±1 dilution step are observed in approximately 67% of repeated samples. ICA results within ±2 dilution steps are observed in 80% or more of repeated samples. The sensitivity and specificity of the 4 major islet autoantibodies for the diagnosis of T1DM are summarized in Table 2 (48, 49). None of the islet autoantibodies is sufficiently sensitive, by itself, to be used to diagnose T1DM or predict T1DM. However, for screening of at-risk relatives we recommend testing with the biochemical autoantibodies GAD and IA-2 as is done in the Type 1 Diabetes TrialNet Natural History Study. The GADA and IA-2A assays can be highly automated for screening purposes. In individuals positive for GADA and/or IA-2, ICA and IAA determinations are then carried out in search of multiple islet autoantibody positivity.

The discovery of autoantibodies to ZnT8, e.g., ZnT8A, is a recent, promising development (17). ZnT8A were first described in 2007, and ZnT8A have the potential to be the fourth major biochemical autoantibody and the fifth overall major islet autoantibody. The 369 amino acid, 6-transmembrane ZnT8 protein [encoded by solute carrier family 30 (zinc transporter), member 8 (SLC30A8)] is a member of the cation efflux family of which there are approximately 10 members (50). ZnT8 concentrates Zn in insulin secretory granules. Other ZnTs expressed in β cells include ZnT2, ZnT4, and ZnT5.

The gene for ZnT8 is located on chromosome 8q24.11. ZnT8 may be β-cell specific (51). Because both the N- and C- termini are intracellular, these domains are unlikely to be exposed on the surface of the β cell even with β-cell exocytosis of insulin.

Because of the novelty of ZnT8A, it has been reviewed in greater depth (17). The C-terminus of ZnT8 contains the epitope (or epitopes) recognized by ZnT8A. Alleles of the SLC30A8 gene influence susceptibility to type 2 diabetes mellitus (T2DM) (52), but SLC30A8 mutations are not a major cause of maturity-onset diabetes of youth (40).

In young patients with new-onset T1DM (53), 63% were positive for ZnT8A (vs 72% positive for GADA, 68% positive for IA-2A, and 55% positive for
IAA. Following the onset of T1DM, ZnT8A concentrations decline rapidly (54, 55).

In new-onset young patients with T1DM who were negative for ICA, GADA, IA-2A, and IAA, 26% were positive for ZnT8A (53). ZnT8A can also be observed in other autoimmune diseases: in Addison patients, 8.6% were positive for ZnT8A; in non-Addisonian individuals who were positive for 21-hydroxylase autoantibody, 13.3% were positive for ZnT8A; and in transglutaminase-positive individuals with a family history of T1DM, 30.8% were positive for ZnT8A. ZnT8A were not found in patients with systemic lupus erythematosus or in patients with rheumatoid arthritis.

Of new-onset T1DM patients tested for GADA, IA-2A, and IAA (53), 5.8% were negative for all 3 autoantibodies. However when ZnT8A testing was added to this panel, only 1.8% of new-onset T1DM patients were islet autoantibody negative. Whereas 72% of new-onset T1DM patients were positive for 2 or more autoantibodies when testing was limited to GADA, IA-2A, and IAA, the addition of ZnT8A testing increased the number of individuals positive for 2 or more autoantibodies to 82%. Whereas IAA prevalence at the onset of T1DM declines with increasing age of the patient, ZnT8A becomes more common at onset with increasing age. This finding argues in favor of testing for all 4 biochemical autoantibodies when a marker of islet autoimmunity is sought.

The predictive value of ZnT8A for the development of T1DM was evaluated in 43 individuals in the DAISY study (30 first-degree relatives of T1DM patients and 13 individuals from the general population; mean age at onset of T1DM: 6.8 years) (53). Based on HLA-DR, -DQ genotype, or family history, DAISY serially follows children at increased risk for T1DM. Comparable to other biochemical autoantibodies, ZnT8A were found in 62.9% of individuals before the development of T1DM (vs 70.3% positivity for GADA before T1DM onset; 51.8% for IA-2A, and 85.1% for IAA). Although there was no one reproducible order in which autoantibodies appeared, IAA were most commonly the first autoantibodies to be detected, followed by GADA, ZnT8A, and IA-2A. The later appearance of ZnT8A suggests that reactivity to ZnT8 may reflect progressive β-cell destruction. In 88 participants in the DAISY study who were more than 3 years old and were followed for more than 1 year, positivity for 1 biochemical autoantibody (excluding ZnT8A) yielded a 7.3% risk for T1DM. However, when ZnT8A were present together with GADA, IA-2A, or IAA, risk for T1DM rose approximately 5-fold to 36.8%.

As noted above, natural variants of ZnT8 exist. This polymorphism determines the ZnT8A specificity (56). Achenbach et al. showed that among ZnT8A-positive, initially nondiabetic relatives of T1DM patients, the rate of progression to T1DM was higher when rs13266634 was homozygous (CC or TT) (59% developed T1DM) than when rs13266634 was heterozygous (CT) (22% developed T1DM) (57).

When Should Islet Autoantibody Testing Be Ordered in Clinical Practice?

Having discussed the spectrum of islet autoantibodies, their significance and their clinical usefulness, we consider it prudent to state that the islet autoantigens recognized by islet autoantibodies do not appear to be altered or mutated self antigens. There are no data that suggest that islet autoantigens in people with T1DM differ in any way from islet autoantigens in people without T1DM.

The detection of islet autoantibodies in a diabetic individual indicates that the diabetes is of autoimmune origin (i.e., T1DM). This is true even if the initial phenotype is more like that of T2DM, producing LADA (58). In fact, 5% to 15% of patients whose initial diagnosis is T2DM most likely have T1DM (59), suggesting that there are approximately as many people with LADA as there are people with classic, acute-onset T1DM (60).

Islet autoantibody testing is indicated when the clinician cannot readily differentiate T1DM from T2DM (61). Differentiation of these conditions is critical because the early introduction of insulin has been shown to preserve β-cell function (62), and good glycemic control will delay the onset of microvascular and neuropathic complications in T1DM (63).

Other situations in which islet autoantibody testing would be helpful include: (a) acute-onset, ketotic, or ketoacidotic diabetes in an obese individual. T1DM with obesity should be distinguished from T2DM with ketosis or ketoacidosis, as can occur in minority teenagers with insulin-resistance and obesity; (b) nonketotic-diabetes onset in a lean individual. In this setting T1DM with very early onset should also be distinguished from monogenic diabetes. For intervention trials in new-onset T1DM, islet autoantibody positivity is required to establish the diagnosis of T1DM, especially when the intervention is immunologically based.

Although islet autoantibody testing for the development of T1DM in nondiabetic individuals is not yet clinically indicated, the predictive value of such testing makes it critical for the design of current research trials aimed at preventing T1DM. Presently, in the Type 1 Diabetes TrialNet investigations, entry criteria vary by study. For example, in the GAD-intervention protocol in new-onset patients with T1DM, the only islet autoantibody criterion is positivity for GADA. In the “Effects of Canakinumab On The Progression of Type 1
Diabetes In New Onset Subjects” protocol, at least 1 islet autoantibody (other than IAA) must be present in an individual for study inclusion. However, repeated positivity for IAA and at least 1 other islet autoantibody are required for entry into the oral insulin trial that will attempt to prevent the development of T1DM in relatives at risk for T1DM.

Because there are no proven preventative therapies, testing of nondiabetic individuals for islet autoantibodies should be limited to research studies (26). However, once safe, effective, and affordable preventative therapies are available, islet autoantibody testing will likely be in very high demand, given the high morbidity and early mortality caused by T1DM. In short, prevention is better for the individual, and better for society because overall costs will be reduced and disease-associated morbidity and premature death with loss of economic productivity will be averted.

If Islet Autoantibodies Do Not Cause T1DM, Do B Lymphocytes Have Any Role in the Pathogenesis of T1DM?

Whereas autoantibodies are excellent and predictive markers of β-cell autoimmunity, B lymphocytes may play a more important role as antigen-presenting cells (64) and/or regulatory cells in the genesis of T1DM (65–67). B lymphocytes (such as B10 cells) may produce regulatory cytokines such as interleukin-10 and transforming growth factor-β (68). T2-MZP (transitional 2-marginal zone precursor) B lymphocytes appear to play an immunoregulatory role in experimental arthritis (69).

Although T1DM can occur in humans in the absence of B lymphocytes on a congenital (70) or an acquired basis (71, 72), btk-deficient NOD mice that are antibody deficient are protected from T1DM (73). In humans, btk is the tyrosine kinase that is deficient in Bruton’s X-linked recessive agammaglobulinemia. Furthermore, NOD mice that are B-lymphocyte depleted by use of an anti-CD20 monoclonal antibody do not develop T1DM (74). In another study, administration of an anti-CD22 monoclonal antibody directed against mature B lymphocytes delayed the onset of T1DM in NOD mice (75). Recently, in new-onset T1DM patients, anti-CD20 monoclonal antibody (Rituximab®) therapy preserved C-peptide secretion for 1 year following diagnosis (76). These data suggest that B lymphocytes are important in the pathogenesis of T1DM in NOD mice (which is the most commonly used animal model of human T1DM) (77) and humans.

SUMMARY

The presence of islet autoantibodies in persons with diabetes confirms an autoimmune etiology (78). In nondiabetic individuals, islet autoantibodies are strong predictors of the later development of T1DM. The greater the number of islet autoantibodies detected, the greater is that individual’s risk for T1DM (79). Currently, measurements of the biochemical autoantibodies GADA and IA-2A are recommended for initial confirmation of the suspected diagnosis of T1DM or for the prediction of T1DM in research settings. For the diagnosis of T1DM, if GADA and IA-2A results are negative, testing for ICA and, in children, IAA should be pursued. In research settings in which GADA and/or IA-2A are positive, ICA and, in children, IAA testing are carried out when seeking to define multiple islet-autoantibody positivity. The newest major autoantibody, ZnT8A, improves our armamentarium to confirm and predict T1DM (17). With varying success, several autoantigens recognized by autoantibodies are now being administered in an effort to induce tolerance and modify the development of T1DM (80, 81).

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