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EDITORIAL

Autoantibodies against multiple tissues in type 1 diabetes

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Diabetes mellitus type 1 (DM1) results from a T-cell mediated destruction of the insulin-producing β-cells in the pancreatic islets of Langerhans. The role of autoantibodies in the pathogenesis of this disease is unclear.[1] Whether islet autoantibodies count as 'smoke or fire' in β-cell destruction remains a question. Approximately 20% of DM1 patients are seronegative for islet autoantibodies, indicating that autoantibodies are not required for the development of DM1, whereas the vast majority of subjects with islet autoantibodies remain nondiabetic. The targets of islet autoantibodies including insulin, glutamic acid decarboxylase-65 (GAD65) and the tyrosine phosphatase insulinoma antigen-2 (IA-2) are not tissue specific, while autoantibodies against these are not disease specific. Yet islet autoantibodies are the most apt predictors of clinical manifestation of DM1 in first-degree relatives of patients. In particular, high titres of multiple autoantibodies are considered synonymous with preclinical diabetes.

In their contribution in this issue of the journal, De Graaff, Smit and Radder studied the literature on autoantibodies with specificity for other target tissues than pancreatic islets, with possible clinical implications.[2] Indeed, DM1 is frequently associated with multiple autoimmune features that are not limited to pancreatic islets.[3,4] Autoantibodies against thyroid tissue (thyroglobulin (Tg) and thyroid peroxidase (TPO)), parietal cells in the stomach (PCA), adrenal cortex (adrenocortical antibodies, ACA) or gut (endomysium, EMA) occur in widely diverse frequencies in different cohorts of DM1 patients, even though this is not accompanied with associated clinical symptoms in the majority of cases.

What is the cause of the occurrence of non-islet autoantibodies and comorbidity of autoimmune diseases in DM1? First, the genetic predisposition to DM1 is shared with other autoimmune diseases. Polymorphisms of the human leucocyte antigen (HLA) are perhaps most important in this regard. Indeed, HLA-DR3 predisposes to a variety of autoimmune diseases including DM1, thyroiditis and coeliac disease. Recently, it was shown that development of DM1 is associated with impaired function of the regulatory T cells, in spite of equivalent frequencies of these immune suppressors in the blood of patients compared with nondiabetic control subjects.[5] It is conceivable that an impaired capacity of the immune system to keep immune abnormalities in check may lead to loss of immune tolerance to other tissues.

A prominent observation by De Graaff and colleagues involves the considerable degree of inconsistency between the reports in their literature study. An important confounder is HLA predisposing to many autoimmune diseases. A caveat is therefore that the probability of developing any type of autoantibody or autoimmune disease may be associated with genetic predisposition, rather than the development of DM1. Since the frequency of HLA-DR3 differs considerably across Europe (coincident with the local incidence of DM1), it may not be unexpected that the frequencies of autoantibodies in the control populations differed between the reports. Some of the supposed increased frequencies of autoantibodies in DM1 patients compared with nondiabetic control subjects will be confounded by inappropriate matching for HLA: the frequency of EMA autoantibodies often appears to be quite similar in DM1 patients to that of HLA-DR3 positive nondiabetic control subjects. As the authors noticed, the prevalence of several tissue-specific autoantibodies increases with age, and with the disparities in age of the cohorts compared here, the frequencies of autoantibodies will vary. Consistency between the various reports will further suffer from the small sizes of the study cohorts and ascertainment bias.

There are some striking differences between islet autoantibodies and autoantibodies against other tissues. With age, islet autoantibodies become less frequent, whereas those against the thyroid and possibly parietal cells increase. Furthermore, while a gender bias in DM1 is negligible, there is a female preponderance for

autoantibodies against the thyroid and possibly the adrenals. Disparities between reports may again be attributed to insufficient matching between patient and control populations for age, gender and HLA.

What are the clinical consequences of autoantibody positivity? As indicated above, the presence of islet autoantibodies has not yet been shown to be pathogenic. There is no evidence that islet autoantibodies impair β-cell function. Intriguingly, changes in autoantibody titres during experimental immunotherapy are discordant with clinical benefit, while immunointervention strategies targeting B-cells or antibodies (e.g., plasmapheresis, intravenous immunologlobulin therapy) have failed thus far.[1] Remarkably, transplacental transfer of maternal islet autoantibodies from diabetic mothers appears to prevent rather than precipitate DM1 in the offspring. This is in contrast to the situation in preclinical animal models of the disease. Indeed, the nonobese diabetic mouse spontaneously develops an immune mediated β-cell destruction that is clearly B-cell dependent. This may represent yet another case where animal models may be misleading. As every model represents an inbred population, this underscores the appropriateness of De Graaff and colleagues to exclude case reports in their literature study.[6] A clinical trial in progress assessing the effect of anti-B-cell therapy (rituximab) may shed light on the role of B cells in the pathogenesis of DM1 (see www.diabetestrialnet.org for details).

For several other tissue-specific autoantibodies, the evidence supporting a role in the disease process is more compelling. Antibodies against thyroid, gastric parietal cells and adrenal cortex have unequivocally been shown to affect target tissue function. EMA autoantibodies are very strongly associated with villous atrophy in biopsies of the small intestine, even in cases where clinical symptoms of coeliac disease are lacking. Interestingly, an important target of EMA autoantibodies is the enzyme tissue transglutaminase (tTG). This enzyme is critically important in the pathogenesis of coeliac disease, as it modifies gluten components by deamidation, introducing epitopes of pathogenic T cells in coeliac disease. Despite the striking discovery that tTG is the main target of autoantibodies in coeliac disease, it remains to be elucidated whether, and if so, how they contribute to disease. Given the exceptionally strong similarities between coeliac disease and DM1 that include comorbidity, epidemiology, rise in incidence, genetic predisposition and gluten as environmental risk factor, it is conceivable that autoimmune components contribute to dietary triggering of the symptoms of coeliac disease.

Even though clinical symptoms are often lacking, the recommendation by De Graaff and colleagues to monitor for subclinical autoimmune disease associated with autoantibodies against tissues other than islets is warranted and worthy of implementation in diabetes care.

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