Autoimmunity Reviews 15 (2016) 644–648

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Type 1 diabetes associated autoimmunity

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ARTICLE INFO

Article history:
Received 13 February 2016
Accepted 15 February 2016
Available online 20 February 2016

Keywords:
Type 1 diabetes
Endocrine autoimmunity
Autoimmune thyroid disease

ABSTRACT

Diabetes mellitus is increasing in prevalence worldwide. The economic costs are considerable given the cardiovascular complications and co-morbidities that it may entail. Type 1 diabetes (T1D) is a chronic autoimmune disease characterized by the loss of insulin-producing pancreatic β-cells. The pathogenesis of T1D is complex and multifactorial and involves a genetic susceptibility that predisposes to abnormal immune responses in the presence of ill-defined environmental insults to the pancreatic islets. Genetic background may affect the risk for autoimmune disease and patients with T1D exhibit an increased risk of other autoimmune disorders such as autoimmune thyroid disease, Addison's disease, autoimmune gastritis, coeliac disease and vitiligo. Approximately 20%–25% of patients with T1D have thyroid antibodies, and up to 50% of such patients progress to clinical autoimmune thyroid disease. Approximately 0.5% of diabetic patients have concomitant Addison's disease and 4% have coeliac disease. The prevalence of autoimmune gastritis and pernicious anemia is 5% to 10% and 2.6% to 4%, respectively. Early detection of antibodies and latent organ-specific dysfunction is advocated to alert physicians to take appropriate action in order to prevent full-blown disease. Patients and family members should be educated to be able to recognize signs and symptoms of underlying disease.

Contents

1. Introduction and clinical phenotype . . . 644
2. Pancreatic autoimmunity . . . 645
3. Immunogenetics . . . 645
4. Organ-specific autoimmunity . . . 646
5. Own findings in type 1 diabetes-associated endocrine autoimmunity . . . 646
6. Summary and perspectives . . . 647
Disclosure . . . 647
Take-home messages . . . 647
References . . . 647

1. Introduction and clinical phenotype

Diabetes mellitus is increasing in prevalence worldwide. The economic costs and burden of the disease are considerable given the cardiovascular complications and co-morbidities that it may entail. Two major groups of diabetes mellitus have been defined, type 1, or immune-based, and type 2. In recent years, other subgroups have been described in-between these major groups. Correct classification of the disease is crucial in order to ascribe the most efficient preventive, diagnostic and treatment strategies for each patient [1].

Type 1 diabetes (T1D) is an autoimmune disease characterized by the loss of insulin-producing pancreatic β-cells. The pathogenesis of T1D is multifactorial and involves a genetic susceptibility that predisposes to abnormal immune responses in the presence of ill-defined environmental insults to the pancreatic islets [2]. Adaptive immunoregulatory T cells contribute to the modulation of the development and evolution of T1D [3]. T1D results from autoimmune destruction of insulin-producing β cells and is characterized by the presence of insulitis and β-cell autoantibodies (Ab). The model of T1D begins with environmental triggers in genetically susceptible persons, progressing to autoimmunity with the appearance of β-cell Ab, further

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http://dx.doi.org/10.1016/j.autrev.2016.02.017
1568-9972/

evolving towards metabolic dysregulation with loss of first-phase insulin response, increasing glycosylating hemoglobin within the normal range, impaired fasting glycemia or impaired glucose tolerance and finally resulting in overt T1D and loss of C-peptide [4–5]. The first-phase insulin response measured by intravenous glucose tolerance testing is the sum of insulin levels the first and third minute after administration of an intravenous glucose load. Many subjects with T1D had a low first-phase before the diagnosis of T1D and this may persist for years before clinical disease onset. These data suggest that subjects go through a phase of decreasing β-cell mass. The exact β-cell mass at diagnosis is poorly defined. For patients with long-term T1D, it is usually decreased to less than 1% of normal. Residual β-cell function can also be analyzed according to the measurement of C-peptide release as induced by a hyperglycemic clamp procedure. Low first phase C-peptide response specifically predicts impending T1D while a low second phase response probably reflects an earlier disease stage. A typical de novo T1D patient presents with hyperglycemia and polyuria, polydipsia and weight loss. Ketoacidosis is common and Ab status at the moment of T1D diagnosis should be verified [6].

T1D and autoimmune thyroid diseases (AITD) frequently occur in the same individual, suggesting a strong shared genetic susceptibility. The co-occurrence of T1D + AITD in the same individual is classified as autoimmune polyglandular syndrome (APS) type 3 [7–9]. Fifteen to 30% of T1D subjects have AITD, Hashimoto's (HT) or Graves' disease (GD), 0.5% have Addison's disease (AD), 5% to 10% are diagnosed with autoimmune gastritis and/or pernicious anemia, 4% to 9% present with celiac disease (CD), and 2% to 10% show vitiligo. Up to one-third of T1D patients develop an APS. Children and adolescents with T1D may also develop organ-specific multiple autoimmunity in the context of APS. The most frequently encountered associated autoimmune disorders in children with T1D are AITD, followed by CD, autoimmune gastric disease and other rare autoimmune conditions [8]. These diseases are characterized by the presence of Ab to certain antigens of the gland, mostly intracellular enzymes, which appear in the blood. These include thyroid peroxidase (for HT), thyroid stimulating hormone (TSH) receptor (for GD), 21-hydroxylase (for AD), parietal cell or intrinsic factor (for autoimmune gastritis/ pernicious anemia) and tissue transglutaminase (for CD). The role of such Ab remains unclear, but they are important as diagnostic messengers and appear commonly before clinical hormone deficiency. Early detection of Ab and latent organ-specific dysfunction is advocated to alert physicians to take appropriate action in order to prevent full-blown disease. Thus, screening for these Ab allows early detection and the potential to prevent significant morbidity related to unrecognized disease. However, the frequency of screening for and follow-up of patients with positive Ab remain controversial. Hashimoto's hypothyroidism may cause weight gain, hyperlipidemia, goiter and may affect diabetes control, menses and pregnancy outcome. In contrast, Graves' hyperthyroidism may induce weight loss, atrial fibrillation, heat intolerance and ophthalmopathy. Adrenal insufficiency may cause vomiting, anorexia, hypoglycemia, malaise, fatigue, muscular weakness, hyperkalemia, hypotension and generalized hyperpigmentation. Autoimmune gastritis may manifest via iron deficiency or vitamin B_{12} deficiency anemia with fatigue and painful neuropathy. Clinical features of CD include abdominal discomfort, growth abnormalities, infertility, low bone mineralization and iron deficiency anemia.

2. Pancreatic autoimmunity

T1D is characterized by the appearance of insulitis and the presence of β-cell Ab. Several lines of evidence support the autoimmune nature of the β-cell-destructive process: (a) infiltration of the pancreatic islets by lymphocytes and macrophages (insulitis); (b) presence of Ab to islet cell antigens (ICA), tyrosine phosphatase (IA2), glutamic acid decarboxylase-65 (GAD), insulin (IAA) and zinc transporter ZnT8 (Slc30A8); (c) a preferential occurrence of T1D in persons carrying specific allelic combinations at immune response loci within the HLA gene complex; (d) increased prevalence of organ-specific autoimmune disorders in T1D; (e) the disease can be transferred by spleen or bone marrow cells and finally (f) animal models of T1D that show a defect in immunoregulation contributing to the onset of disease [10].

One or more β-cell Ab is present in approximately 90% of new-onset patients with T1D. They appear to develop sequentially. Insulin-Ab is often the first expressed, especially in younger children. GAD-Ab positivity is suggested to represent a propensity for general autoimmunity, while IA2-Ab positivity may be a more specific marker of β-cell destruction. Beta-cell Ab also represents important preclinical markers of the disease as they may be present for years before T1D diagnosis. The risk of T1D for a first-degree relative depends on the number and type of Ab that are present. Family members who express insulin, GAD and IA2-Ab have a 75% risk of developing T1D within the next five years, as compared with a 10% to 25% five-year risk in those expressing only one of the Ab. The general five-year risk for T1D is 34% in subjects positive for ≥ three Ab. Progression to T1D amounted to 12% within five years among siblings positive for IAA, 20% for ICA, 19% for GAD but 59% for IA-2-Ab. IA-2-Ab were detected in 1.7% of all siblings and in 56% of the prediabetic subjects on first sampling [4–6].

T1D was one of the earliest disorders to be associated with the phenomenon of autoimmunity and is one of the most studied organ-specific autoimmune diseases at the epidemiologic, immunologic and genetic level [11]. Despite this, and the emergence of a plethora of strategies for trying to intervene in, or prevent the disease, it remains at some distance from being reliably and safely tractable by immunotherapy, a source of great frustration in this research field. The key concepts that might impact upon this lack of success in the clinic going forward include new insights into autoreactive CD4 and CD8 T-cell biology and a discussion of the concept of disease heterogeneity as it applies to T1D. The onset of disease is characterized by a delicate equilibrium of proinflammatory and regulatory T cells, which are termed “balanced autoreactive set-point”, and which may be amenable to antigen-specific immunotherapies that alter the rate of disease progression. Advances in the characterization of T cells, especially at the single cell level, could be rewarding, notably from the vantage point of biomarker and surrogate discovery. A better understanding of T-cell targeting, autoantigen processing and the β-cell-immune interface is also needed, although access to diseased tissues is a major limitation in this effort. Finally, recent findings demonstrate that MicroRNAs (miRNAs), which regulate T-cell development and function and, whose disruption in natural regulatory CD4 + FOXP3 + T cells (nTreg) leads to autoimmune disease in mice, are markers of risk and T cell dysfunction in T1D when differentially expressed in CD4 + T cell subsets [12].

3. Immunogenetics

Among genes associated with T1D, the HLA gene complex on chromosome 6p21 is the genetic factor with the strongest association [13]. Another gene located on chromosome 11p15 in the upstream region of the insulin gene also confers susceptibility to T1D. Multiple additional genes also contribute to T1D susceptibility. One of these is IDDM12 on chromosome 2q33, which contains two autoimmune disease candidate genes: cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and CD28, encoding for T-cell receptors involved in controlling T-cell proliferation. Other important genes include the MHC I-related gene A (MIC-A) and the protein tyrosine phosphatase non-receptor type 22 (PTPN22). Ninety percent of Caucasian T1D patients express the HLA DR3 and/or DR4 alleles [14]. These HLA alleles are expressed in 30-40% of the general white population. Expression of HLA DR2 is decreased in persons with T1D. Certain combinations of HLA alleles are found with a frequency greater than expected and are thus not randomly distributed within the general population. This phenomenon is called linkage disequilibrium. Particularly, HLA DQA1*0301-DQB1*0302 (in linkage disequilibrium with DR4) and DQA1*0501-B1*0201 (in linkage disequilibrium with DR3) haplotypes confer a high diabetic risk. The absolute risk of a