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Review

Immunogenetics of type 1 diabetes mellitus

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ABSTRACT

Type 1 diabetes mellitus (T1DM) is an autoimmune disease arising through a complex interaction of both genetic and immunologic factors. Similar to the majority of autoimmune diseases, T1DM usually has a relapsing remitting disease course with autoantibody and T cellular responses to islet autoantigens, which precede the clinical onset of the disease process. The immunological diagnosis of autoimmune diseases relies primarily on the detection of autoantibodies in the serum of T1DM patients. Although their pathogenic significance remains uncertain, they have the practical advantage of serving as surrogate biomarkers for predicting the clinical onset of T1DM. Type 1 diabetes is a polygenic disease with a small number of genes having large effects (i.e. HLA), and a large number of genes having small effects. Risk of T1DM progression is conferred by specific HLA DR/DQ alleles [e.g., DRB1*03-DQB1*0201 (DR3) or DRB1*04-DQB1*0302 (DR4)]. In addition, HLA alleles such as DQB1*0602 are associated with dominant protection from T1DM in multiple populations.

A discordance rate of greater than 50% between monozygotic twins indicates a potential involvement of environmental factors on disease development. Viral infections may play a role in the chain of events leading to disease, albeit conclusive evidence linking infections with T1DM remains to be firmly established. Two syndromes have been described in which an immune-mediated form of diabetes occurs as the result of a single gene defect. These syndromes are termed autoimmune polyglandular syndrome type I (APS-I) or autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), and X-linked poyendocrinopathy, immune dysfunction and diarrhea (XPID). These two syndromes are unique models to understand the mechanisms involved in the loss of tolerance to self-antigens in autoimmune diabetes and its associated organ-specific autoimmune disorders. A growing number of animal models of these diseases have greatly helped elucidate the immunologic mechanisms leading to autoimmune diabetes.

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1. Introduction

Type 1 diabetes mellitus is a chronic autoimmune disease in which endogenous insulin production is severely compromised as a result of an immune-mediated injury of pancreatic β-cells (Eisenbarth, 1986). Genetic analyses of T1DM have linked the HLA complex, mainly class II alleles, to susceptibility to T1DM (Morel et al., 1988; Todd et al., 1987). Viral antigens may also play a role in the generation of beta cell autoimmunity (Lonnrot et al., 2000). The latter observations are supported by the increasing seasonal incidence of T1DM in many Western countries (Orchard et al., 1986) and that enteroviruses may be involved in the autoimmune pathogenesis of T1DM (Hyoty, 2002; Lonnrot et al., 2000; Zipris et al., 2007).

Type 1 diabetes was not always considered as the classical organ-specific disease it is now known to be. Insulin-dependent diabetes was known to occasionally occur in the Autoimmune Polyendocrine Syndrome I (APS I), a classic autoimmune syndrome with T-cell and B-cell antibody abnormalities directed at adrenal, parathyroid, gonadal, thyroid and other tissues. However, diabetes mellitus is not a constant, necessary or sufficient feature of APS I (Eisenbarth and Gottlieb, 2004). This condition is now known to be caused by mutations in the autoimmune regulator gene (AIRE) (Husebye and Anderson, 2010). Bottazzo et al. (1974) reported that sections of human pancreas treated with sera of diabetic patients who also had Addison's disease and myxedema, showed cytoplasmic fluorescence in the islets of Langerhans. This response was termed cytoplasmic islet cell antibodies (ICA) (Bottazzo et al., 1974). Furthermore, the existence of insulin autoantibodies and other autoantibodies against various islet proteins was not uncovered until years later. It was in 1983 that insulin autoantibodies were reported in sera of newly diagnosed patients with T1DM, before any treatment with exogenous insulin (Palmer et al., 1983). In this finding, improvements of the sensitivity of the insulin antibody assay were instrumental for the determination that about one-half of newly diagnosed patients had autoantibodies that bound ^{125}I-labeled insulin.

Type 1 diabetes is primarily a T-cell mediated disease. Following the early discoveries on humoral autoimmunity in T1DM, there has been a remarkable expansion in the detection of T1DM-associated autoantibodies as well as in the characterization of the molecular basis of the antigenicity of their target proteins (Atkinson and Eisenbarth, 2001; Pietropaolo and Eisenbarth, 2001). This expansion has led to the uncovering of specific antigenic determinants, the development of biochemically defined immunoassays and also to coordinated efforts to standardize assays across laboratories (Bonifacio et al., 2010).

2. Association with other autoimmune diseases

For reasons not fully understood, patients with an organ-specific autoimmune disease have increased risks of developing autoimmune responses against other organs/tissues (Jaberi-Douraki et al., 2014; Pietropaolo et al., 2012). Patients with T1DM are at increased risk for developing other autoimmune diseases, most commonly autoimmune thyroiditis and celiac disease. Thyroid autoimmunity is particularly common among patients with type 1A diabetes, affecting more than one-fourth of individuals, and 2 to 5 percent of patients with type 1 diabetes develop autoimmune hypothyroidism. Transglutaminase autoantibodies are present in approximately 10 percent of patients, and half of these patients have high levels of these autoantibodies and celiac disease on biopsy (Hoffenberg et al., 2004; Jaeger et al., 2001). In addition, certain alleles (e.g., HLA haplotype DR3-DQ2 or DR4-DQ8 PTPN2, CTLA4, RGS1) confer a genetic susceptibility to both T1DM and celiac disease, suggesting a common biological pathway (Liu et al., 2014; Smyth et al., 2008a). Fewer than 1 percent of children with T1DM have autoimmune adrenalitis. In one study, it was reported that 11 of 629 patients (1.7 percent) with type 1 diabetes but none of the 239 normal subjects had antibodies directed against 21-hydroxylase, a common autoantigen in primary adrenal insufficiency (Brewer et al., 1997). A total of 3 out of 8 patients with anti-21-hydroxylase antibodies had adrenal insufficiency.

Type 1 diabetes can be seen with polyglandular autoimmune disease, especially type II, in which adrenal insufficiency, autoimmune thyroid disease, and gonadal insufficiency are the other major components. Rare syndromes associated with T1DM have shed important light on pathogenesis. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is associated with neonates developing T1DM. These infants usually die of