Defective major histocompatibility complex class I expression on lymphoid cells in autoimmunity

Y. Fu, D.M. Nathan, F. Li, X. Li, D.L. Faustman

Immunobiology Laboratories of the Diabetes Unit and Medical Services, Massachusetts General Hospital and the Department of Medicine, Harvard Medical School, Boston, Massachusetts

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IN BRIEF

Hypothesis and aim

Lymphocytes from patients with insulin-dependent diabetes mellitus (IDDM), a chronic autoimmune disease, have recently been shown to have decreased surface expression of MHC class I antigens. Since IDDM and other autoimmune diseases share a strong genetic association with MHC class II genes, which may in turn be linked to genes that affect MHC class I expression, other autoimmune diseases have been studied to determine whether MHC class I expression is abnormal.

Experimental design and methods

Fresh PBLs were isolated from patients with IDDM (n=54), Hashimoto’s thyroiditis (n=16), Graves’ disease (n=36), systemic lupus erythematosus (n=14), rheumatoid arthritis (n=16), and Sjogren’s syndrome. Nondiabetic and non-insulin-dependent diabetes mellitus patients served as controls. MHC class I expression was measured with a conformationally dependent monoclonal antibody, W6/32.

Results

Freshly prepared PBLs from the autoimmune diseases studied and the corresponding fresh EBV-transformed B cell lines had decreased MHC class I expression compared with PBLs from normal volunteers and non-insulin-dependent (nonautoimmune) diabetic patients. Only 3 of more than 180 donors without IDDM or other clinically recognized autoimmune disease had persistently decreased MHC class I expression; one patient was treated with immunosuppressive drugs, and subsequent screening of the other two patients revealed high titers of autoantibodies, revealing clinically occult autoimmunity. Patients with nonautoimmune inflammation (osteomyelitis or tuberculosis) had normal MHC class I expression.

Messages and perspectives

Autoimmune diseases are characterized by decreased expression of MHC class I on lymphocytes. MHC class I expression may be necessary for self tolerance and abnormalities in such expression may lead to autoimmunity.

Comment by Jose Pinies and Luis Castaño

Faustman et al. have recently shown that MHC class I expression measured with a conformationally dependent monoclonal antibody (W6/32) is decreased in autoimmune diseases. Freshly prepared peripheral blood lymphocytes (PBLs) from patients with type I diabetes and other autoimmune diseases and the corresponding fresh EBV-transformed B cell lines had faulty MHC class I expression compared
with PBLs from normal volunteers and non-insulin dependent diabetic patients. The authors propose that the concomitant defect in antigen presentation may impair the development of self tolerance, which could result in autoimmune disease.

Insulin-dependent (type 1) diabetes mellitus is an autoimmune disorder in which immunological tolerance for a component of self, pancreatic β cell, is lost. Although it is now generally recognized that genetic susceptibility plays a major role in the etiology of type I diabetes, this knowledge has not been easily developed. The potential interaction of genetic and environmental factors, the lack of knowledge of the basic defect, the reduced penetrance of the disorder, and the existence of genetic heterogeneity are some of the obstacles to analyze the genetics of type I diabetes. Over the past 20 years a large number of studies have consistently found an increased frequency of HLA antigens B8 and B15 (MHC class 1), and more prominently DR3 and DR4 (MHC class II), among Caucasian type I diabetic patients. These molecules, encoded by MHC class I and II genes on chromosome 6, are required for normal antigen processing. Intracellular and extracellular antigens present quite different challenges to the immune system, both in terms of recognition and appropriate response. It is not surprising, therefore, that parallel systems have evolved to meet this challenge. Extracellular antigen-derived peptides are presented to CD4+ T cells by the MHC class II molecules found on specialized antigen-presenting cells while peptides derived from intracellular antigens are generally presented to CD8+ T cells by MHC class I molecules, which are expressed on virtually all cells. Assembly of the class I heavy chain (encoded in the MHC class I region) with β2 microglobulin occurs within the endoplasmic reticulum (ER). Endogenous peptides arising from protein degradation within the cytosol are delivered into the ER to assembling class I molecules by transporter proteins (TAP 1 and TAP 2) encoded in the MHC class II region between the DPA and DQB genes.

Classically, very strong immunogenetic association links type I diabetes with the DQ class II locus, specifically with the HLA DQ 3,2 gene. This gene appears to account for the DR4 association. The aminoacid occupying position 57 in the β chain of this molecule has been identified as playing a particular critical role in delimiting susceptibility to type I diabetes among Caucasians. An aspartate residue at this position exerts a strong protective effect. It is thought that properly configured class II molecules could facilitate the presentation of an autoantigen peptide fragment to the immune system and initiate the disease process. Although the association of MHC class II haplotype with type I diabetes risk is both substantial and teleologically appealing it remains an association without a fully defined mechanism.

Fautsman and associates proposed that the connection between type I diabetes and the MHC actually represents faulty surface expression of class I molecules. These molecules present fragments of endogenous proteins to the immune system; the concomitant defect in antigen presentation may impair the development of self tolerance, which could result in autoimmune disease. Previously, the authors had observed a defective MHC class I surface expression on splenocytes (lymphocytes) from prediabetic and diabetic NOD mice compared with H-2 cogenic and noncogenic mouse strains. Furthermore, transgenic mice with faulty MHC class I expression caused by a deficiency of β2 microglobulin were reported to develop both insulitis and hyperglycemia. A defect within TAP gene region was found in NOD mice, proposing these genes as candidates for both the genetic basis of impaired MHC class I expression and as the MHC class II linked gene that confers diabetes susceptibility in the NOD mouse.

In the present work the authors analyzed MHC class I expression in PBLs isolated from patients with type I diabetes (n=54) and other autoimmune diseases (Hashimoto’s thyroiditis, Graves’s disease, systemic lupus erythematosus, rheumatoid arthritis and Sjögren’s syndrome). Because many in vivo factors other than genetics could be influencing MHC class I expression, newly transformed EBV cells were produced from patients for each of the autoimmune disease. MHC class I expression was measured by flow cytometry analysis showing binding of conformationally dependent mAb W6/32 (anti HLA A, B, and C). MHC class I expression on PBLs as well as on EBV cell lines from patients with type I diabetes and other autoimmune diseases were consistently depressed compared with controls. On the other hand, lymphocytes from NIDDM patients had a similar MHC class I expression compared with nondiabetic controls. Interestingly, 3 NIDDM patients were considered to have abnormal MHC class I expression. One of the 3 was treated with high dose glucocorticoids as well as immunosuppressive drugs. The other 2 NIDDM patients were studied for clinically silent autoimmunity that revealed high titers of anti-smooth-muscle antibodies in one patient and thyroid-colloid, antimicrosomal and antinuclear antibodies in the other, suggesting underlying autoimmunity in these