JCI The Journal of Clinical Investigation

DR, DQ, and you: MHC alleles and autoimmunity

Grete Sønderstrup, Hugh O. McDevitt

J Clin Invest. 2001;107(7):795-796. https://doi.org/10.1172/JCI12634.

Commentary

It has mystified immunologists for decades that antigen-specific T-cell clones obtained from human peripheral blood are, almost without exception, restricted by MHC class II molecules of the HLA-DR type, rather than by HLA-DQ molecules (1, 2). This is particularly surprising in that HLA-DQ alleles strongly influence susceptibility to many autoimmune diseases, including type 1 diabetes mellitus (T1DM) (3, 4). Thus, in humans, the HLA-DQB*0602 and HLA-DRB1*0403 alleles confer strong protection against T1DM (4, 5). The basis of this protective effect is undoubtedly complex and has proved difficult to study in humans. Unlike mice, where a number of inbred laboratory strains lack expression of H-2 IE (the murine equivalent to HLA-DR), humans always express both HLA-DR and HLA-DQ, usually a different set from each parent. In humans, it is therefore difficult to study the function of a single HLA class II allele in isolation, and in vivo experimentation with human subjects has many other constraints. These problems are further complicated by the strong linkage disequilibrium in the MHC class II region, which makes it difficult to distinguish the effects of individual HLA-DR alleles from the effects of linked HLA-DQ alleles, since particular DR/DQ allelic combinations tend to persist, with very little recombination. For these reasons, several laboratories have developed HLA class II transgenic mice to serve as an experimental surrogate for […]

DR, DQ, and you: MHC alleles and autoimmunity

Commentary

See related article, pages 871–880.

Grete Sønderstrup and Hugh O. McDevitt

Department of Microbiology and Immunology, Stanford University School of Medicine, Stanford, California, USA

Address correspondence to: Grete Sønderstrup, Department of Microbiology and Immunology, Stanford University School of Medicine, Stanford, California 94305-5124, USA. Phone: (650) 723-5893; Fax: (650) 723-9180; E-mail: gretes@stanford.edu.

It has mystified immunologists for decades that antigen-specific T-cell clones obtained from human peripheral blood are, almost without exception, restricted by MHC class II molecules of the HLA-DR type, rather than by HLA-DQ molecules (1, 2). This is particularly surprising in that HLA-DQ alleles strongly influence susceptibility to many autoimmune diseases, including type 1 diabetes mellitus (T1DM) (3, 4). Thus, in humans, the HLA-DQB*0602 and HLA-DRB1*0403 alleles confer strong protection against T1DM (4, 5).

The basis of this protective effect is undoubtedly complex and has proved difficult to study in humans. Unlike mice, where a number of inbred laboratory strains lack expression of H-2 IE (the murine equivalent to HLA-DR), humans always express both HLA-DR and HLA-DQ, usually a different set from each parent. In humans, it is therefore difficult to study the function of a single HLA class II allele in isolation, and in vivo experimentation with human subjects has many other constraints. These problems are further complicated by the strong linkage disequilibrium in the MHC class II region, which makes it difficult to distinguish the effects of individual HLA-DR alleles from the effects of linked HLA-DQ alleles, since particular DR/DQ allelic combinations tend to persist, with very little recombination. For these reasons, several laboratories have developed HLA class II transgenic mice to serve as an experimental surrogate for the $CD4^+$ T-cell compartment of normal human subjects (6).

David and his colleagues have produced HLA class II transgenic mice, which they and others have used to model human autoimmune diseases (7–9). By studying the influence of different combinations of coexpression of DR3, DQ8, DR2, and/or DQ6 alleles, and comparing these with HLA transgenic mice carrying only a single HLA allele, these authors found that coexpression of DR3 can modify the manifestations of an experimental arthritis associated with expression of DQ8 (7). DQ8 also increases the severity of other experimentally induced autoimmune diseases in this model system (8), whereas the DQ6 allele can prevent the spontaneous loss of tolerance to the pancreatic autoantigen GAD65 and the insulitis that are otherwise seen in HLA-DR3, DQ8 transgenic mice (9).

In this issue of the *JCI*, Wen et al. wished to explore the influence of coexpression of HLA-DR alleles on the diabetes susceptibility conferred by the DQ8 allele (10). The HLA-DRB1*0401, DQ8 haplotype, the most common HLA haplotype in Caucasian T1DM patients, was therefore a logical candidate for this study (5). Because HLA-DQ8 transgenic mice do not develop diabetes spontaneously, the authors crossed them with a diabetes-prone transgenic strain, RIP-B7, which lacks endogenous MHC class II molecules and overexpresses the costimulatory molecule B7 specifically in the islet cells of the pancreas (11). When these RIP-B7 transgenic animals also carry the human HLA-DQ8 transgene, they develop spontaneous diabetes at a frequency of 73% (10, 11). Remarkably, a congenic RIP-B7 transgenic line carrying the DR4 (B1*0401) allele develops diabetes at a frequency of only 25%. To model the case of humans expressing the HLA-DR4, DQ8 haplotype, the authors then produced mice expressing both DR4 and DQ8 and found that the incidence of disease in these HLA double transgenic mice is almost identical to that of the DR4 transgenic mice (10). This suggests that DR4 can partly cancel the disease-promoting effect of DQ8.

Following up on this finding, Wen and colleagues purified splenic $CD4^+$ T cells from the diabetes-prone DQ8/RIP-B7 animals and from the other, relatively disease-insensitive strains (10). In vitro cytokine production by cells from DQ8/RIP-B7 mice produced mainly IFN-γ, compatible with a Th1 cytokine pattern. In contrast, cells from the DR4/RIP-B7 and the DQ8DR4/RIP-B7 mice produced IL-4 but very little IFN-γ, suggesting a Th2 cytokine pattern (10). However as the authors point out, the mechanisms of the HLA-DR4 effect are not clear (10).

Similar HLA class II transgenic mice have been used to study the T-cell receptor (TCR) repertoire after immunization with recombinant GAD65 (12). These studies, using several DR/DR as well as DR/DQ combinations, have revealed that certain immunodominant GAD65-specific TCRs are all but absent in the repertoire of HLA class II double transgenic mice, if the diabetes-protective DRB1*0403 allele is present. This elimination of potentially pathogenic T cells occurs through still-unidentified mechanisms, operating at least in part at the level of intracellular antigen processing. Similarly, human antigen-presenting cells (APCs) carrying both the diabetes-protective DRB1*0403 allele and a second, diabetes-conducive DR4 allele (DRB1*0405) fail to present these processed immunodominant GAD65 epitopes to T cells (S. Parry and G.

Elimination of potentially pathogenic T cells may account for the protective effect of specific HLA class II alleles that prevent autoimmune disease in humans.

Sønderstrup, unpublished results), although they are perfectly capable of presenting these epitopes if they are provided as synthetic peptides. Further, these same human APCs can process and present other GAD65 epitopes normally to T cells that recognize these epitopes in the context of the DRB1*0405 molecule (S. Parry and G. Sønderstrup, unpublished results). This result indicates that this is a selective epitope-specific phenomenon. The ability to eliminate potentially pathogenic T cells presented by coexpressed HLA class II molecules, HLA-DR or DQ, may be responsible for the disease-protective effect of the HLA-DRB1*0403 allele and may therefore represent yet another mechanism for preventing autoimmunity in humans.

The study of Wen et al. (10) and the results described above illustrate how HLA class II transgenic mice can provide a blueprint for unraveling DR/DQ allelic interactions in autoimmunity. This information should also provide new insight into pathogenesis and inspire novel strategies to prevent autoimmune disease.

1. Mølvig, J., et al. 1989. Characterization of PPD specific T cell lines generated in type I (insulin dependent) diabetic and healthy individuals. *Scand. J. Immunol.* **30**:615–639.
2. Endl, J., et al. 1997. Identification of naturally processed T cell epitopes from glutamic acid decarboxylase presented in the context of HLA-DR alleles by T lymphocytes of recent onset IDDM patients. *J. Clin. Invest.* **99**:2405–2415.
3. Todd, J., Bell, J.I., and McDevitt, H.O. 1987. HLA-DQβ gene contributes to susceptibility and resistance to insulin-dependent diabetes mellitus. *Nature.* **329**:599–604.
4. McDevitt, H.O. 1998. The role of MHC class II molecules in susceptibility and resistance to autoimmunity. *Curr. Opin. Immunol.* **10**:677–681.
5. Undlien, D.E., et al. 1997. HLA-encoded genetic predisposition in IDDM: DR4 subtypes may be associated with different degrees of protection. *Diabetes.* **46**:143–149.
6. Sønderstrup, G., et al. 1999. HLA class II transgenic mice: models of the human CD4+ T-cell immune response. *Immunol. Rev.* **172**:335–343.
7. Taneja, V., Griffiths, M.M., Luthra, H., and David, C.S. 1998. Modulation of HLA-DO-restricted collagen-induced arthritis by HLA-DRB1 polymorphism. *Int. Immunol.* **10**:1449–1457.
8. Das, P., et al. 2000. Complementation between specific HLA-DR and HLA-DQ genes in transgenic mice determines susceptibility to experimental autoimmune encephalomyelitis. *Hum. Immunol.* **61**:279–289.
9. Abraham, R.S., Kudva, Y.C., Wilson, S.B., Strominger, J.L., and David, C.S. 2000. Co-expression of HLA DR3 and DQ8 results in the development of spontaneous insulitis and loss of tolerance to GAD65 in transgenic mice. *Diabetes.* **49**:548–554.
10. Wen, L., Chen, N.-Y., Tang, J., Sherwin, R., and Wong, F.S. 2001. The regulatory role of DR4 in a spontaneous diabetes DQ8 transgenic model. *J. Clin. Invest.* **107**:871–880.
11. Wen, L., et al. 2000. In vivo evidence for the contribution of human histocompatibility leucocyte antigen (HLA)-DQ molecules to the development of diabetes. *J. Exp. Med.* **191**:97–104.
12. Patel, S., Congia, M., Cope, A.P., Fugger, L., and Sønderstrup-McDevitt, G. 1997. Identification of immunodominant T cell epitopes of human glutamic acid decarboxylase 65 using HLA-DR (α1*0101, β1*0401) transgenic mice. *Proc. Natl. Acad. Sci. USA.* **94**:8082–8087.