Commentary

Major Histocompatibility Complex–linked Control of Autoimmunity

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Although the MHC is a key genetic component in autoimmune disease, our knowledge of the mechanisms by which the molecules encoded within the MHC influence autoimmune processes remains incomplete. Because of the linkage disequilibrium that exists among the class I, II, and III genes within the HLA complex in humans and the homologous MHC complex in rodents, the absolute contribution of the individual loci has been difficult to dissect. However, it is clear from association and linkage studies of autoimmune diseases in humans as well as from various forms of analyses in the mouse and rat for diseases such as spontaneous autoimmune diabetes and experimentally induced encephalomyelitis, arthritis, and thyroiditis, that class II molecules are a primary (but not always the sole) basis of the HLA–MHC association. One area of intense investigation and speculation has been stimulated by the demonstration that particular class II molecules have positive, neutral, or negative association with human autoimmune diabetes (1, 2).

Much of the experimental work to understand the contribution of class II alleles to autoimmunity has used the nonobese diabetic (NOD) mouse, a model of spontaneous diabetes. Although analysis of the few intra-MHC recombinants available has pointed to the importance of the class II region in autoimmune diabetes (3), transgenic introduction of class II molecules into the NOD mouse has provided the most persuasive evidence of the essential role of particular class II molecules in the autoimmune process (4–7). In addition, the disease diminution that has been afforded by the introduction of nondiabetogenic I-E or I-A class II molecules has created models that are hoped to mimic the protection observed in human autoimmune diabetes by certain HLA class II molecules that are negatively associated with disease. However, the mechanism by which the introduced nondiabetogenic class II molecules prevent diabetes remains a point of controversy. Originally, one leading hypothesis was that the introduced class II molecule led to the deletion of self-reactive cells. However, evidence to support this hypothesis was not found, leading several groups to dismiss this possibility (8–12). In particular, Mathis et al. (9) introduced by transgenesis into the NOD mouse an islet-specific, I-A^{g7}–restricted TCR derived from a pathogenic clone, BDC2.5 (13). Such TCR-transgenic NOD mice became diabetic with increased frequency and at a somewhat earlier time than normal NOD mice. Introduction of the Eα transgene, which protects NOD mice from disease, failed to alter the disease course in the BDC2.5 TCR-transgenic mice.

Other hypotheses were also put forth to explain the experimental results of disease protection. As reviewed by Tisch and McDevitt (14), the presence or absence of an aspartic acid at residue 57 of the β chain alters both the peptide binding motif of a particular class II molecule as well as its association with diabetes. This polymorphism would therefore greatly influence the peptides presented during an autoimmune response. Some studies documented a shift in the balance of Th1 and Th2 in the presence of protective class II molecules (14, 15). A different mechanism of disease association has been suggested by Unanue et al. who have presented evidence that the I-A^{g7} molecule is relatively unstable, which leads to poor peptide binding (16). They hypothesized that such poor binding causes inadequate presentation of self peptides in the thymus, which then leads to a greater number of self-reactive cells in the periphery. Data consistent with this hypothesis have been presented by Fathman et al. who observed an abnormal reactivity to self proteins in NOD mice (17). Poor stability of a diabetes-associated human class II molecule has also been reported (18).

With these and many other studies not detailed here, the stage is set for the study by Schmidt et al. (19) in the current issue. Using a newly created TCR transgenic mouse, the authors come to the surprising conclusion that thymic deletion mediated by protective class II alleles, a mechanism thought to have been ruled out previously, appears to be a major factor in disease protection. The striking disparity between the current study and that described above (9) where the TCR derived from the BDC2.5 T cell clone was analyzed, may well be due to a difference in the molecular specificities of the two TCRs, both of which are still unknown. Schmidt et al. use a TCR derived from a pathogenic clone, NY4.1, isolated by Nagata and Yoon (20). The NY4.1 transgenic mice display a more aggressive disease course than the BDC2.5 transgenic mice, thus making the reduction of insulitis and diabetes by disease-resistant class II molecules even more striking. Other findings detailed in the study suggest that non-MHC genes influence the development and activity of the transgenic T cells. If this can be substantiated in further studies, the NY4.1 TCR may more closely represent the autoimmune T cells

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that are essential for the initiation and progression of disease in the nontransgenic NOD mouse, T cells whose generation and activity are controlled by both MHC-linked and non–MHC-linked diabetes-susceptibility loci (21). Such non–MHC-linked loci might include genes that affect the activation threshold of the T cells within the thymus and the periphery, as well as genes which function in the many pathways that result in the apoptosis of self-reactive cells.

Finally, hypotheses that attempt to explain the association of the MHC with a particular autoimmune disease must incorporate the fact that class II molecules are disease specific. One particular class II allele is not associated with many different autoimmune diseases, arguing that a diabetes-associated allele, for example, does not produce a globally abnormal class II molecule, but rather encodes a functional variant which somehow favors the production of islet-specific T cells as compared with other alleles that are not diabetes associated (22). The normal functionality of disease-associated alleles is further emphasized by the fact that disease-susceptible class II molecules cannot mediate disease in the absence of additional non–MHC-linked susceptibility genes (23). One example of the ability of the MHC to direct the autoimmune response in conjunction with non-MHC autoimmune susceptibility genes is the situation where the B10.*H2*^{g7} (I-A^{g7}) and B10.A(4R) (I-A^{k}) strains are both nonautoimmune, whereas the NOD (I-A^{g7}) and NOD.*H2*^{h4} (I-A^{k}) strains are both autoimmune prone but with different specificities. Although NOD mice develop diabetes, only a small percentage of mice from this strain display mild infiltrates of the thyroid gland. In contrast, NOD.*H2*^{h4} mice are free of diabetes (24), but display extensive infiltration of the thyroid gland, especially in the presence of increased dietary iodine (21, 25). The propensity of NOD.*H2*^{h4} mice to develop thryoiditis is especially interesting since I-A^{k} is the class II molecule required for the induction of autoimmune thyroiditis after injection of thyroglobulin (26). In addition, although the *H2*^{b} haplotype is protective in regard to diabetes (27), destructive sialitis leading to a diminution of secretory function is observed in both NOD and NOD.*H2*^{b} mice (28). Thus, MHC-linked and non–MHC-linked genes act in concert to cause a breakdown in tolerance: specific class II molecules are necessary for the positive selection of what will eventually be organ-specific pathogenic T cell clones (with protective alleles potentially causing their deletion), whereas the activity of products of non-MHC autoimmunity genes enable these "forbidden clones" to escape normal tolerance induction mechanisms that could potentially stop their development into effectors of autoimmune destruction.

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