CD8+ T Cells in Multiple Sclerosis

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1 Genetic Basis for an Association of MS With Different T Cell Subsets

Autoimmune diseases such as multiple sclerosis (MS) are common and are thought to result from complex interactions of susceptibility genes at multiple loci, environmental factors, and stochastic events. During the last decade there has been great interest in testing candidate genomic regions or genes for associations with particular autoimmune diseases. This is complicated by the difficulties of distinguishing between true and false associations and demonstrating causality. Furthermore, for complex diseases many genes usually influence the disease in only a modest way, underlining that autoimmune diseases occur owing to a combination of certain genes. Therefore, identification of these genes ultimately relies on functional studies that link the gene or gene combinations and phenotype. The most extensively studied genetic region is the major histocompatibility
complex (MHC), which shows associations in almost all autoimmune diseases (Rioux and Abbas, 2005). Insulin-dependent diabetes mellitus is associated with alleles belonging to the HLA-DR3 and HLA-DR4 haplotypes (Nepom and Erlich, 1991), rheumatoid arthritis with HLA-DR4 alleles (Stastny, 1978), and celiac disease with HLA-DQ2 and HLA-DQ8 alleles (Solliid et al., 1989; Solliid and Thorsby, 1993). Familial aggregation of MS indicates that this disease also has a significant genetic component (Ebers et al., 1995). In particular, it associates with the HLA-DR2 haplotype, which contains three alleles: DRB1*1501, DRB5*0101, and DQB1*0602. HLA-DR2 confers a fourfold relative risk in northern European Caucasian patients, of whom about two-thirds are HLA-DR2+ (Olerup and Hillert, 1991). Although MS most commonly associates with the HLA-DR2 haplotype, this can vary among populations. In the Sardinian population, for example, it is associated with the HLA-DR3 (DRB1*0301–DQA1*0501–DQB1*0201) and HLA-DR4 (DRB1*0405–DQA1*0501–DQB1*0301) haplotypes (Marrosu et al., 1997) in addition to HLA-DR2 (Marrosu et al., 2001).

There is also evidence implicating MHC loci other than DRB1 and DQB1; in the Sardinian MS population, there are additional associations with the HLA class II DPB1 locus and a microsatellite in the HLA class I region (Marrosu et al., 2001). Other studies have also documented associations with MHC class I (MHC I) microsatellites (Ebers et al., 1996; Rubio et al., 2002), and two recent studies have shown that HLA-A*0301 increases the risk of MS independently of HLA-DR2 (Fogdell-Hahn et al., 2000; Harbo et al., 2004). Indeed, the first reported associations were with this allele (Naito et al., 1972) or possibly with the linked HLA-B7 (Jersild et al., 1972). Whereas the previously recorded association with HLA-B7 (B*0702) proved to be secondary to that with the linked HLA-DR2 allele, more refined methods in larger series have now convincingly shown that HLA-A3 (A*0301) roughly doubles the risk of developing MS and does so independently of the HLA-DR2 alleles (Fogdell-Hahn et al., 2000; Harbo et al., 2004). Indeed, subjects with both HLA-A*0301 and HLA-DR2 have a more than additive risk of developing MS. In contrast, HLA-A2 (A*0201) confers some protection against MS, approximately halving the relative risk (Fogdell-Hahn et al., 2000; Harbo et al., 2004). Another study supports these findings (Boon et al., 2001), although the protective MHC I region locus has not yet been mapped precisely.

Therefore, MS is positively and independently associated with HLA-A*0301 and HLA-DR2 genes. The relative risk is increased substantially by HLA-A3 and HLA-DR2 but not by HLA-B7. This association can be partly overridden by the protective allele HLA-A*0201.

2 Evidence from Animal Models of MS for Contributions by Different T Cell Subsets

Although these association studies imply an important role for CD4+ helper T cells (which interact with MHC II molecules), they also suggest that CD8+ T cells (interacting with MHC I molecules) could be involved in the disease