Bridging the gap between mouse and humans: Development of novel therapies for MS in “humanized” HLA-DR transgenic mice.

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Multiple sclerosis (MS) is believed to be mediated by pathogenic T cells attacking and destroying the myelin sheaths surrounding neuronal axons in the central nervous system (CNS). The strongest genetic association for MS is with genes of the human major histocompatibility gene complex (MHC, HLA), but the function of these genes in the disease process has remained unresolved. We have investigated the role of MS-associated MHC class II molecules for the formation and function of pathogenic T cells in “humanized” mice expressing HLA-DRB1*1501, HLA-DRB5*0101, and HLA-DRB1*0401 molecules.
We found that these MS-associated MHC class II molecules are highly efficient at inducing T cell tolerance to high-affinity MHC-binding T cell epitope, whereas autoreactive T cells specific for the low-affinity MHC-binding epitopes and “type B” T cells can escape the induction of T cell tolerance and may promote MS. Using this information, we are developing novel approaches to silencing pathogenic T cells as a treatment for MS.