Transgenic mice as a model of multiple sclerosis

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The PhD dissertation was accepted by the Faculty of Health Sciences of the University of Aarhus, and defended on December 16, 2004.

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Dan Med Bull 2005;52:26.

ABSTRACT

Type 1 diabetes, rheumatoid arthritis and multiple sclerosis (MS) are all examples of diseases to which susceptibility is associated with certain major histocompatibility complex (MHC) class II genes. This association suggests an autoimmune etiology. Presumably, the disease associated MHC (HLA in humans) class II molecules triggers disease through the presentation of autoantigenic peptides, which are recognized by T-cell receptors (TCRs) on autoaggressive CD4+ T-cells. Activation of such T-cells will enable them to mediate the inflammation and tissue destruction associated with the diseases.

Multiple sclerosis is associated with the HLA class II genes DRB1*1501, DRB5*0101 and DQB1*0602 which encode the molecules DR15, DR51 and DQ6. The primary association is probably through DR15/DR51, but because of strong linkage disequilibrium of the genes, it has been very difficult through population studies to determine the individual roles in MS pathogenesis. To study this, transgenic mice expressing DR15, DR51 and both together were crossed with myelin basic protein (MBP) TCR transgenic mice. MBP is a major MS candidate autoantigen. The transgenic TCRs recognize MBP in the context of DR15. Two TCRs were examined; one which recognizes peptides when presented solely through DR15 (non-cross-reactive), and another which also recognizes peptides trough DR51 (cross-reactive). All TCR transgenic mice which express DR15 developed MS-like disease/EAE either spontaneously when bred on the immunodeficient $Rag2^{-/-}$ background or after immunization with MBP. The addition of DR51 protected the cross-reactive TCR transgenic mice from disease by decreasing the frequency of autoaggressive T-cells and decreasing the response to MBP. The DR51-dependent protection was not seen in non-cross-reactive TCR transgenic mice. Protection was associated by a decrease in the frequency of autoaggressive T-cells and a decrease in the response to MBP (84-102). Through adoptive transfer studies it was shown that DR51 modifies the peripheral repertoire of cross-reactive T-cells.

The study emphasizes the importance of recognizing epistatic interactions between different MHC molecules and the consequences of TCR cross-reactivity in order to understand the etiology and the course of autoimmune diseases better. It also shows the great value of using gene-modified mice to improve our knowledge of such complex diseases.