Acta Medica et Biologica
Vol. 38, No. 4, 151-158, 1990

Molecular Basis of Susceptibility to Multiple Sclerosis

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Received March 23, 1990

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disorder of the central nervous system (CNS).[1-3] New guidelines indicate that clinically definite MS shall be diagnosed with a history of two attacks and clinical evidence of two separate lesions or clinical evidence of a single lesion and paraclinical evidence such as CT, MRI scan or evoked responses for another. There is no diagnostic test that is specific for MS.[4]

Several epidemiological studies have shown that MS susceptibility differs considerably among races. In northern Europe between 65° and 45° north latitude and in the northern United States and southern Canada, as well as in southern Australia and New Zealand, MS is the most common (30 to 80 cases per 100,000 population) cause of nontraumatic neurologic disability arising in early adulthood. In contrast, these studies have also shown areas of low risk (5 or fewer cases per 100,000) as being most of Asia and Africa. The Bantu, Yakuts, Hutterites, and Inuit are quite low in susceptibility.[5]

Family studies have indicated that the susceptibility to MS is inherited. Familial aggregation is known to occur, and there is an increased risk among first-degree relatives. Several twin studies have shown a higher concordance rate among monozygotic twins than dizygotic twins.[6] Although the cause of MS is not known, an immunologic process is generally considered to be an important element in the pathogenesis of the disease: activated T cells infiltrate in the demyelinating lesions, activated T cells appear in the CSF or abnormal T cell subsets in the blood of active MS patients. Treatment with corticosteroid or immunosuppressants are beneficial; chronic relapsing experimental allergic encephalomyelitis (EAE) mediated by T cells sensitized with myelin basic protein (MBP) resembles MS.[7,8]

Immune response gene

During the induction of an immune response, an antigen is taken up by macrophages or other antigen-presenting cells (APC), processed, and co-expressed with Class II Major Histocompatibility Complex (MHC) molecules. $CD4^+$ T cells usually recognize a complex of Class II molecules and processed antigen with a T cell receptor and CD3 complex on the surface of the T cells. When $CD8^+$ T cells recognize antigens on target cells, they bind Class I molecules (Fig. 1).[9] These molecules are members of immunoglobulin gene superfamily.[10] The specificity of the immune response is based on the polymorphism of variable regions of HLA or T cell receptors (TCR) that may explain MS susceptibility.

The potential roles of MHC Class II molecules in EAE

The T cells sensitized with some antigens of CNS reach the brain and recognize a complex of processed antigen and MHC Class II (Ia) molecules on the surface of APC in the CNS such as astrocytes, microglia or endothelial cells.[11] These cells do not show any MHC molecules on their surface, if not be stimulated.[12] The presentation of antigens by APC in the CNS requires the expression of Ia molecules which can be induced by interferon (IFN)-γ.[12] The potential role of these Ia-positive APC in clinical disease is suggested by observations that: 1) the induction of EAE can be prevented by treatment with anti-Ia antibody[13]; 2) EAE is mediated by Class II-restricted T cells[14]; 3) Ia antigen-positive macrophages, astrocytes and endothelial cells become detectable in brain tissue during the development of EAE[15,16]; and 4) hyperinducibility of Ia antigens on

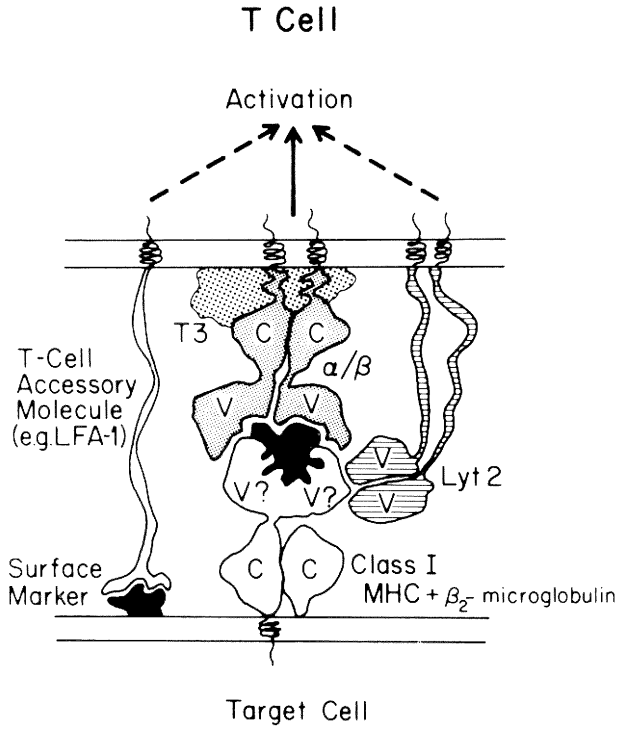

Fig. 1. A processed antigen and variable region (V) of MHC Class II molecules recognized by T cells via a T cell receptor variable region (V).[9] The T cell receptor forms a complex with T3 (CD3). Accessory molecules such as LFA-1 or L3T4 (CD4) participate in T cell recognition.

astrocytes[17] or endothelial cells[18] correlates with strain-specific susceptibility to EAE. For these reasons, the regulation of Ia expression influences the clinical course of T cell-mediated diseases such as MS or EAE. IFN-γ is generally the potent Ia inducer.[19] IL-4,[20] or the tumor necrosis factor (TNF)-α,[21] can augment Ia expression by IFN-γ. Ia molecules can be induced by virus infection.[22] IFN-α/β,[23] a transforming growth factor β1,[24] prostaglandin E,[25] glucocorticoids,[26] norepinephrine,[27] immune complex,[28] lipopolysaccharide,[29] and serotonin[30] can inhibit Ia induction by IFN-γ. The effect of TNF-α on brain cells related to Ia expression is not uniform. TNF-α can augment the Ia expression by INF-γ on astrocytes, but also inhibit it on endothelial cells from CNS microvessels of SJL.[31]

As shown in Fig. 1, there is a close relationship between the antigen and MHC molecules. EAE appears to be MHC specific since SJL mice (I-A^s) or PL mice (I-A^u) are susceptible but BALB/c (I-A^d) mice are relatively resistant.[17] The encephalitogenic peptide of MBP is not the same among mouse strains with different MHC molecules. T cell lines or clones capable of causing EAE from a Ia^u mouse (PL/J) react with the acetylated nine amino acid residues of the N-terminal,[32] and those from the SJL/J mouse (Ia^s) specifically react with MBP peptide (90-101).[33]

HLA in MS

MS is known to show different clinical courses such as relapsing remitting and chronic progressive types. The primarily chronic progressive form has been shown to be an immunogenetically distinct entity from the relapsing/remitting type since *Taq*-1 DQ beta allelic restriction fragment patterns from patients with relapsing/remitting MS are different from those of the primarily chronic progressive form.[34] Primarily chronic progressive MS is extremely rare in Japan.

MS has been reported to be associated with DR2/D_w2,[2] DQ_w1.[35] To study MS susceptibility, HLA Class II gene polymorphism has been investigated. The same restriction fragment length polymorphism (RFLP) profile of the HLA DR2/D_w2 was found in all six MS patients examined, but another investigation[37] could not comfirm these results. HLA DQ, another type of HLA Class II molecule, is partially linked to HLA DR. Some $DR2^+$ MS patients have showed a 3.25 kb fragment after digestion with *Msp* 1 and hybridization to DQα, this being extremely rare in normal controls.[38] More than 95% of Norwegian MS patients show at least one of the HLA DR2, DR4 or DR_w6. They carry DR2, DR4 or DR_w6-associated HLA DQ B_1 genes which encode shared polymorphic amino acid sequences.[39]

HLA DP, one of three HLA Class II antigens, has also been investigated in MS patients. The associations with DR and DP are independent of each other in MS.[40] The synergism between DP and DR gene products may play a role in the genetic susceptibility to MS since the combined presence of DP_w4 and DR2 gives a significantly higher risk than either antigen alone.[40] That the HLA gene is related to MS susceptibility has not yet been established and further investigations are needed.

Detailed analyses of HLA association with diseases using molecular techniques have been investigated in insulin-dependent diabetes mellitus.[41] One particular residue, at codon 57 of the DQβ gene, has been highly correlated with disease susceptibility. In most Caucasian HLA haplotypes associated with diabetes, codon 57 encodes an amino acid other than aspartate, which is the residue in most Class II β genes at position 57. This remarkable homology

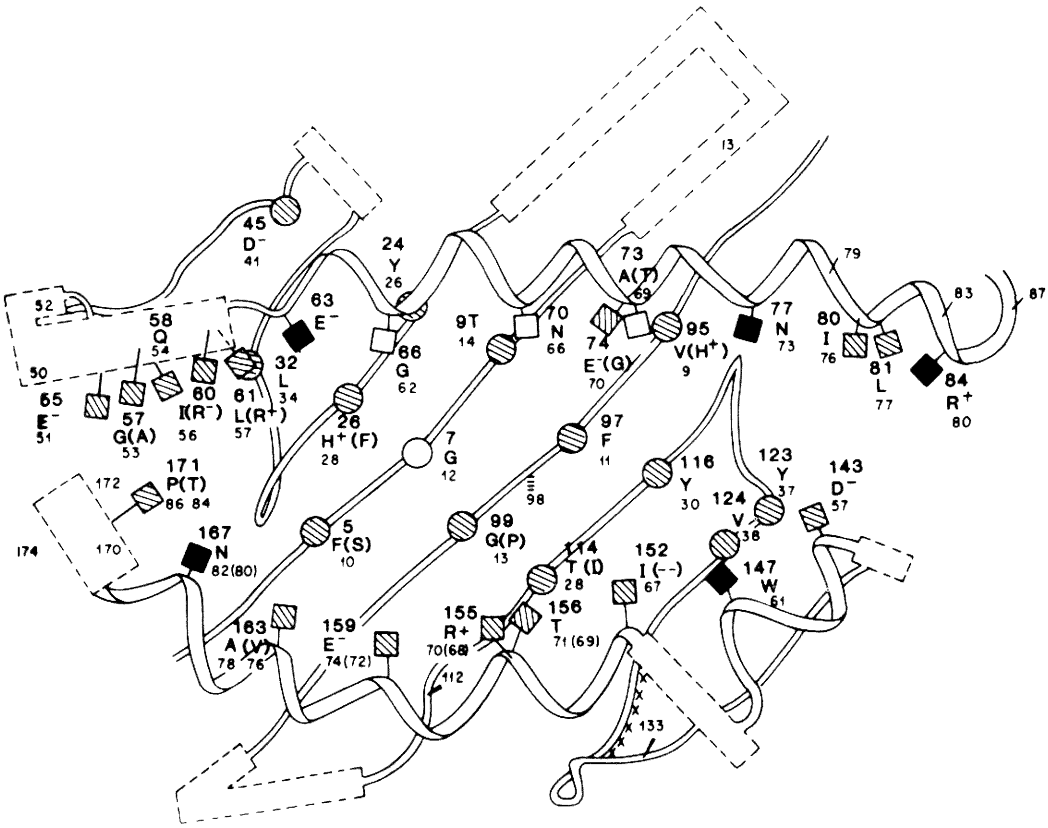

Fig. 2. Hypothelical class II foreign antigen binding cleft as viewed from above. The floor of the cleft is composed of four beta strands, two from each class II chain. The sides of the cleft are formed by two largely uninterrupted stretches of alpha helix.[69] (square=helix, circle=beta-strand) Numbering: bild, HLA-A2; regular, I-A^d; parenthesis, I-A^k.

supports the hypothesis that this residue may play some role in the function of the DQ gene in pathogenesis. Such an association has not been confirmed in Japanese patients.[42]

Another molecular approach is undertaken in Japanese rheumatoid arthritis (RA) patients.[43] A strong association between DR4 and RA has been reported in many countries. Researchers have found that a particular sequence encoding amino acids Gln^{70}-Arg^{71}-Arg^{72}-Ala^{73}-Ala^{74} shows a strong association with RA. This region may participate in the antigen binding as shown in Fig. 2.

T cell receptor

MS susceptibility is also affected by the polymorphism of TCR. TCR forms two different heterodimers, $\alpha:\beta$ and $\gamma:\delta$, that consist of N-terminal domains (V or variable domains) and constant domains (C) such as an immunoglobulin as shown in Fig. 1. TCR genes employ far fewer V gene segments than do immunoglobulins, as many as 100 Vα sequences; the combinatorial diversity (V$\alpha \times$Vβ) in these antigen receptor molecules shows an even greater disparity when compared to immunoglobulins.[44]

Autoimmune susceptible murine strains including NZB, SJL, SWR, PL/J and NOD have been shown to share a common Vα haplotype.[45] However, the strains carrying other Vα haplotypes are also susceptible to many of the same autoimmune diseases, indicating that autoreactive Vα genes are not restricted to any single Vα haplotype. Unlike Vβ as detailed below, the deletion of entire Vα subfamilies has not been observed.[45]

Most encephalitogenic T cells in Lewis rats express TCR Vα2 genes.[46] Fourteen of 18 (78%) N-terminal MBP specific T cell clones from the PL/J mouse have been shown to express a member of the TCR Vβ8 subfamily.[47] A surprising observation is the restricted TCR Vβ usage in the autoimmune T cell response to the dominant encephalitogenic N-terminal epitope of the MBP. The same TCR Vβ is also used in Lewis rat encephalitogenic T cells specific to the 68-88 peptide of MBP.[48] When thirty-

three T cell clones specific for MBP inducing EAE in B10. PL mice were examined in detail,[49] two Vα genes such as 61% of Vα2.3 and 39% of Vα4.2, the same Jα gene, Jα39, and two Vβ-Jβ gene complex, 79% of Vβ8.2 Jβ2.6 and 21% Vβ13 Jβ2.2 were found. The TCR genes of MBP specific T cells are summarized in Table 1. In summary, two different species such as rats and mice use similar V genes, both Vα2/4 and Vβ8.2, to recognize different MHC Class II antigens and different peptides.

Encephalitogenic T cells from SJL mice were examined for their TCR using Southern analysis, which indicated that four of five T cells from a spinal cord with EAE share a 14.5 kb rearranged TCR $\alpha\beta$ band; PPD or ovalbumin reactive T cell lines did not, however, show this 14.5 kb band.[50]

As mentioned above, Vβ8 predominantly expressed in encephalitogenic T cell clones from PL/J mice was lacking in SJL/J mice that also showed Vβ5, 9, 11, 12 and 13 deletion.[51] Sasai et al.,[52] have found that about half of the independently derived 89-101 specific T cell clones are KJ23a$^+$ (TCR Vβ17a), and that KJ23a$^-$ T cells are also encephalitogenic. Expression of the TCR Vβ17a gene occurs in strains such as SWR/SuJ, SJL/J or C57L mice, which do not express any I-E molecules.[52] KJ23a$^+$ T cells are not found in I-E$^+$ mice, and this negative selection in the thymus may be caused by a clonal deletion of T cells reacting with a self I-E molecule.[53] It is interesting that Vβ17a$^+$CD4$^+$ T cells in SJL expand to react with spontaneous reticulum cell sarcoma in SJL and so provide further evidence that the stimulatory antigens on the reticulum cell sarcoma are I-E or "I-E like" molecules.[54]

The usage of restricted TCR V domains is also found in other antigen specific T cell clones (Table 1). In particular, the TCR V region seems to be selected by antigen.[55] It may be possible that some autoimmune diseases are caused by the disease specific TCR V region.

Only a few papers have reported any association between MS and TCR haplotypes. MS susceptibility genes may be located in the region of the TCRβ chain gene complex, since siblings with MS share a TCRβ chain gene haplotype,[56] or the distribution of TCR haplotypes in MS patients is different from that in DR2$^+$ healthy controls.[57] Another investigator has found significant differences in the frequency of the polymorphic Vα and Cα markers between MS patients and healthy individuals; however, this is also found in patients with other diseases.[58]

From the evidence from mice and rats, it is possible that MS may also be a V region disease. T cells from MS patients's CSF, although they are not reactive to MBP, have been shown to share TCR gene rearrangements.[59] This suggests that the inactivation of T cells with anti-disease specific TCR may be a specific therapy for MS.

Table 1. Restricted usage of T cell receptor variable domains in antigen specific T cell clones[55]

Antigen	HHC	TCR Vα/Vβ
Myelin basic protein	I-A^u	4/8.2
Myelin basic protein	I-A^u	2 & 4/8.2 & 13
Myelin basic protein	RAT RT-1	2/8.2
Cytochrome C	I-E^k	11/3
Cytochrome C	I-E	11/3
γ repressor	I-E	3/1

Approaches for antigen specific treatment in experimental autoimmune diseases

T cell recognition has been used as the target for immune intervention[60]; namely, 1) inhibiting MHC recognition with an anti-MHC antibody; 2) inhibiting T cell activation with anti-TCR or anti-CD4 antibody; or 3) competing for antigen binding (Fig. 3). Since anti-MHC or anti-CD4 antibody therapy is nonspecific, the general immune response should be suppressed. The prevention or treatment of EAE with an anti-Vβ8 monoclonal antibody has been achieved in the Lewis rat[61] or PL/J mice[49,62] for their restricted use of TCR V genes of MBP specific T cell clones. But anti-TCR antibody therapy is not adequate for SJL mice which show a deletion of Vβ8 and unrestricted use of TCR Vβ genes.[52] Whole T cell vaccination to modulate the idiotype of encephalitogenic T cells has been reported,[63] but this induces immune response to T cell determinants other than those that confer protection. Immunization of Lewis rats with a synthetic peptide representing a hypervariable region of the TCR Vβ8 molecule can prevent the induction of EAE.[64,65] Vaccination with TCR peptide is preferable to monoclonal antibody infusion because persistent, active immunity is induced.

Three groups have used synthetic peptides to explore the recognition of MBP peptide by I-A^U restricted encephalitogenic T cells. Peptides modified at position 4 has been shown to bind class II MHC molecules much more strongly than the native peptide, potently stimulating encephalitogenic clones but not inducing diseases *in vivo*.[66] The second group found that encephalitogenic T cells could not be

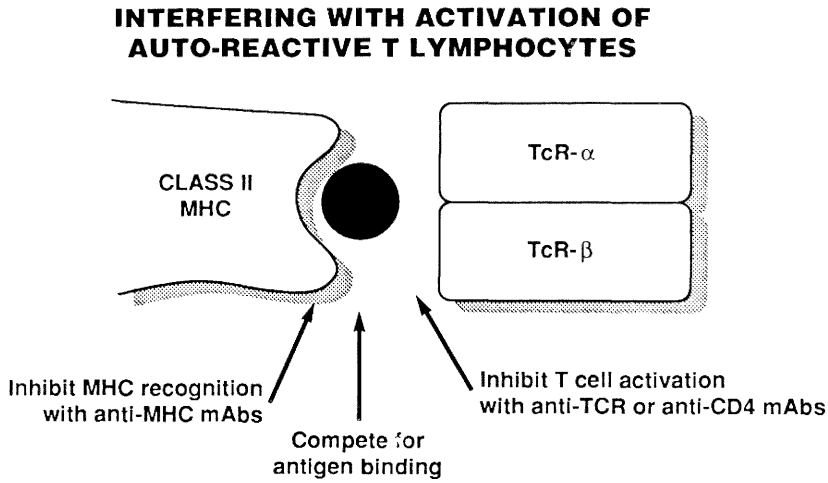

Fig. 3. T cell recognition as the target for immune intervention in autoimmune disease.[60]

activated by peptides modified at position 3.[67] Both repored that modified peptides prevented EAE induced by native MBP peptide. The modified peptides bind class II MHC molecules (I-A^u) strongly but no longer interact with the TCR. The third group showed that unacetylated p1-20 could inhibt the induction of EAE by actylated p1-11.[60] The mechanism is not known, but most probably it reflects the ability of unacetylated 1-20 to inhibit the binding of acetylated p1-11 to those I-A^u molecules competitively.

These elegant studies in MS susceptibility depend upon recently acquired knowledge in fundamental immunology using molecular biological techniques. More detailed studies are required to develop disease specific therapy through an analysis of T cell recognition.

Acknowledgements. The author would like to express his thanks to Prof. T. Miyatake (Dept. Neurol., Niigata Univ.), Dr, R. M. McCarron (Lab. Neuropathol. Neuroanat. Sci., NIH) and Dr. D. E. McFarlin (Neuroimmunol. Branch, NIH) for their valuable discussion.

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