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Molecular Mimicry in Multiple Sclerosis: Role of MHC-Altered Peptide Ligands (MAPL)

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Multiple sclerosis (MS) is a chronic inflammatory illness affecting the CNS white matter that can lead to progressive neurologic dysfunction. Together with other organ-specific autoimmune diseases such as type 1 diabetes mellitus and rheumatoid arthritis, MS is thought to be mediated by autoreactive T cells that recognize CNS self-antigens. Supporting evidence for the autoimmune basis of MS includes the inflammatory nature of the CNS lesions, the genetic linkage to the MHC region, similarities to the animal model experimental autoimmune encephalomyelitis (EAE), and the therapeutic effects of immunomodulatory drugs [1]. Data from animal studies in the EAE model established that CD4+ Th1 cells specific to myelin antigens can play a central role in the induction and progression of autoimmune demyelinating disease [2, 3]. This finding has fueled efforts to dissect the antigenic specificity and functional characteristics of myelin-reactive CD4+ T cells in the peripheral blood and cerebrospinal fluid of patients with MS.

Several peptide epitopes derived from myelin proteins have been found to activate CD4+ T cells in the circulation of patients with MS. Among them, MBP (myelin basic protein) 84–102 and MBP148–162 have been classified as immunodominant epitopes in the context of HLA-DR2 haplotype [4–6]. However, CD4+ T cells reactive to these self-peptides have also been detected in healthy persons, suggesting that the presence of myelin-reactive T cells is not sufficient for the development of MS. While resting autoreactive T cells are a part of normal T cell repertoire, the activation status of these cells is different in patients than in healthy individuals. Consistent with the properties of pre-activated T cells, myelin-reactive T cells recovered from patients are less dependent on costimulation for activation and express activation markers, such as IL-2R, on their cell surfaces [7–9]. These findings lead to the question of what induces the activation of myelin-reactive T lymphocytes in patients with MS. One attractive hypothesis is based on the role of microbial infections in the activation of self-reactive T cells. If invading microorganisms contain protein antigens with sufficient structural homology to human proteins, infection itself may be sufficient to activate pre-existing self-reactive T cells. This is the basic concept of molecular mimicry. Several clinical and epidemiological studies support the hypothesis of mimicry as a mechanism of autoimmunity. According to the original observation by Fujinami and Oldstone [10], rabbits immunized with a hepatitis B polymerase peptide that shared six amino acids with the MBP sequence developed CNS lesions reminiscent of EAE. In humans, upper respiratory infections often precede MS exacerbations. The original concept of molecular mimicry evolved from the recent understanding of the degenerative recognition of antigens by the T cell receptor (TCR). In examining the immune response to MBP, we found that complementary mutations in an antigenic peptide allow for cross-reactivity of autoreactive T cell clones that may be related to shifts of the TCR structure itself [11]. Using combinatorial libraries, Hemmer and co-workers [12] demonstrated that totally unrelated peptides also activate autoreactive T cells. Furthermore, recent data suggest that even different MHC molecules complexed
with diverse peptides can activate MBP-reactive T lymphocytes in an agonistic or antagonistic fashion. In the following sections, we will describe examples of this broader concept of molecular mimicry and its clinical relevance in MS.

1. RELATIONSHIP BETWEEN MICROBIAL INFECTIONS AND MS

Since 1894, when Pierre Marie proposed that infection is the cause of MS, many reports have supported the possible involvement of infectious pathogens. Epidemiological studies have formulated a list of suspicious microbes, including Borrelia burgdorferi, Chlamydia pneumoniae, measles virus, rabies virus, paramyxovirus, coronavirus, Epstein-Barr virus, cytomegalovirus, varicella-zoster virus, herpes simplex virus, human herpes virus 6, rubella virus, mumps virus, Marek's disease virus, Semliki Forest virus, human retroviruses, and human lymphoma virus type 1 [13]. So far, none of these infectious agents have been found to be specific for MS, although an MS-specific agent may yet be discovered. The apparent absence of an MS-specific infectious agent and the autoimmune nature of MS suggest another role of infection in the development of this disease. Three mechanisms have been proposed to explain the association of microbial infection and MS. One is the molecular mimicry theory, which has received a great deal of attention and will be discussed in detail in the following sections. Another is bystander activation, including epitope spreading [14]. Infections can activate autoreactive T cells through the release of sequestered myelin proteins as a result of infection-related tissue damage, activation of antigen-presenting cells (APCs), and induction of secretion of inflammatory cytokines and chemokines, irrespective of the particular microbial determinants. The third is superantigenic T cell activation. Several bacterial and viral products are able to cross-link TCR and MHC molecules independent of specific antigen recognition through the TCR. Cross-linking leads to activation of T cells with particular Vβ families of TCR. Myelin-reactive T cells with a particular TCR Vβ chain can be activated after infection with microbes whose superantigen recognizes this specific Vβ chain. Again, many studies have failed to reveal signs of superantigenic activation of myelin-reactive T cells in MS. Thus, molecular mimicry is still a very attractive theory to explain the frequent association of microbial infection with the development or exacerbation of MS.

2. MOLECULAR MIMICRY ASSOCIATED WITH SEQUENCE HOMOLOGY

Molecular mimicry describes a situation whereby a foreign antigen can initiate an immune response in which a T or B cell component cross-recognizes self. The previous concept for the antigen specificity of T cells predicted that the presence of strict sequence homology between the microbial antigens and self-peptide was necessary to induce autoimmunity (Fig. 1, top A). There are two approaches to determining the foreign microbial antigens that are cross-reactive to self-antigens. One is the initial identification of causative microbes and their major antigenic epitopes and subsequent demonstration of their cross-reactivity to self-antigens. This approach was applied successfully to reveal that two autoimmune diseases are caused by a molecular mimicry mechanism. Autoimmune Lyme arthritis is preceded by infection with B. burgdorferi and is associated with hLFA-1-reactive T cells that were initially primed and expanded by the OspA(165–173) peptide of this spirochete [15]. Herpetic stromal keratitis (HSK) follows infection of the eye with herpes simplex virus 1 and is caused by the activation of autoreactive cells by viral UL6(299–314) peptide [16]. However, it is difficult to apply this strategy for the study of molecular mimicry in MS because, as mentioned previously, no microbial agent has been directly associated with the disease.

The other approach is to first identify T cell determinants capable of inducing autoimmunity and then search for the microbial antigens with sequences homologous to those determinants. An initial study adapting this latter strategy successfully demonstrated that a peptide from hepatitis B virus polymerase (HBVP) with six consecutive amino acids in common with an encephalitogenic determinant of MBP (ICGYGLPQE in HBVP vs TTHYGSLPQK in MBP) could induce subclinical EAE in rabbits [10]. However, proteins sharing a sequence of more than six amino acids are not
Molecular mimicry

A. Extensive sequence homology

B. Minimal sequence homology

C. Entirely unrelated peptide

Variant molecular mimicry

A. Different MHC/same peptide

B. Different MHC/different peptide

Figure 1. Schematic representation of molecular mimicry. Top: Classical molecular mimicry occurs by the sequence homology between self and microbial peptide (A). Expanded molecular mimicry can occur either by peptides with minimal sequence homology (B) or even by entirely unrelated peptides complexed with cognate MHC molecule (C). Bottom: Variant molecular mimicry means the cross-recognition of a different MHC/same (A) or different peptide (B) by the identical TCR.

common in nature, and this type of homologous foreign peptides has not yet been identified in human MS.

Extensive biochemical and structural characterization of the recognition of MHC/peptide ligand by TCR in humans has greatly influenced the identification of cross-reactive epitopes for the given TCR. While a few amino acid residues of a peptide are important for binding to the MHC molecule, the other one or two amino acid residues serve as critical residues for the recognition by the TCR (Fig. 1, top B). Specifically, in the immunodo-
minant peptide ligand (MBP85–99) presented by DRβ*1501, two hydrophobic residues (Val-89 and Phe-92) serve as the primary anchors to the HLA-DR2 molecule, while Phe-91 and Lys-93 have been defined as the primary TCR contact residues for a MBP85–99-specific T cell clone. Mutations in other amino acid residues are tolerated with respect to recognition by the TCR [17]. On the basis of this information, Wucherpfennig and Strominger [18] developed an efficient strategy to search for peptides that share these critical contact motives rather than sequence homology. This search yielded seven viral and one bacterial peptides derived from herpes simplex virus, adenovirus, human papillomavirus, Epstein-Barr virus, influenza type A virus, reovirus type 3, and Pseudomonas that efficiently activated T cell clones. Interestingly, only one of them has been identified as a molecular mimic by sequence alignment. These data clearly indicated that more foreign peptides may act as molecular mimics than was previously thought.

3. MOLECULAR MIMICRY WITHOUT SEQUENCE HOMOLOGY

Conservation of critical MHC and TCR contact residues appears to be a general rule for activation by the peptide of a specific T cell. However, several peptide sequences with no sequence homology have been shown to be able to activate identical T cells (Fig. 1, top C) [19, 20]. In addition, the use of synthetic peptide combinatorial libraries has clearly illustrated the extreme degeneracy of TCR recognition of antigen. Hemmer et al [12] examined the response of CD4+ T cell clones specific for MBP86–96 to a set of 220 11-mer peptide sublibraries, each containing 10 degenerated amino acids and one defined amino acid in the positional scanning format. The new knowledge obtained from this study was 1) that of highly degenerative recognition of peptides by autoreactive CD4+ T cells, including identification of stimulatory ligands not sharing a single amino acid in corresponding positions with the antigen used to establish the T cell clone and 2) the identification of more potent agonistic peptides than cognate self-peptide. From the database search for natural proteins with deduced peptide sequences, they found four self and three microbial proteins as stimulatory ligands to this T cell clone. Most interestingly, one self-peptide (protein-glutamine gamma-glutamyltransferase, 675–685) and two microbial peptides (human CMV UL71, 166–176; UDP-N-acetylenolpyruvoyl-glucosamine reductase of Salmonella typhimurium, 227–237) were defined as even more potent agonists than MBP86–96. This strategy opened the way for the identification of molecular mimics if relevant autoreactive T cells are defined in MS.

4. VARIANT MOLECULAR MIMICRY: MHC-ALTERED PEPTIDE LIGAND

The studies discussed above focused on the molecular mimics with respect to the peptide portion of TCR ligand. Since TCRs recognize MHC/peptide as a single unit and exhibit greatly degenerative recognition of their ligands, they might recognize a different MHC combined with a cognate or even a different peptide as an agonist (Fig. 1, bottom). Since most people are heterozygous for the HLA-DR locus, this type of molecular mimicry is likely to occur in physiological situations. It has been shown that the human MBP peptide 84–102 binds to several different DR molecules and that T cells recognize this peptide presented by these different HLA-DR2 molecules [21]. We systematically examined this type of cross-reaction using a panel of CD8+ T cell clones specific to Tax1–19 peptide of HTLV-1 in the context of HLA-A*0201 [22]. When CD8+ T cells were stimulated with cognate Tax1–19 peptide presented by different HLA-A2 subtype alleles, which have one to four amino acid differences at specific positions (Table 1), they showed a diverse pattern of T cell function, encompassing agonistic, weak agonistic, or partial agonistic, depending on the individual T cell clones (Fig. 2). This is similar to the effects induced by antigenic altered peptide ligands (APL). In addition, atypical partial agonistic T cell function was observed; i.e., a number of CD8+ T cell clones proliferated in response to Tax11–19 presented by the HLA-A*0205 subtype even though they did not exhibit any cytotoxic activity. The analysis of the structural interaction between the TCR and MHC/peptide complex indicated that polymorphic amino acids in the HLA-A2 peptide-binding groove, especially the D-pocket, rather than the dif-
Table 1. Summary of amino acid sequences at polymorphic HLA-a2 positions

| HLA-A2 subtype | Amino acid sequence at specific position |
|----------------|-----------------------------------------|
|                | α1 domain | α2 domain |
|                | 9 43      | 95 149  152 156 |
| A*0201         | F Q V A V L |
| A*0202         | F R L A V W |
| A*0203         | F Q V T E W |
| A*0205         | Y R L A V W |
| A*0206         | Y Q V A V L |

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ferences on the MHC residues in direct contact with the TCR, were responsible for this partial agonism (Fig. 3A). This was supported by the finding that reciprocal mutations of the Tax peptide side chain that engaged the D-pocket restored the agonist functions of the MHC/peptide complex (Fig. 3B). Thus, our study clearly demonstrated that MHC molecules play an important role in T cell activation not only by restricting antigen element but also by altering the antigenic nature of peptide. We termed this type of TCR ligand MHC-altered peptide ligand (MAPL).

CD4+ T cell can also exhibit MAPL effects on the recognition of variant MHC class II molecules. Germain and colleagues [23] previously suggested that a peptide presented on a mutant MHC class II molecule induces a response different from the response induced with the native MHC molecule. We also recently examined the modulation of T cell responses induced by stimulation with different MHC class II/peptide complexes, demonstrating the existence of significant cross-reactivity of autoreactive CD4+ T cells in the context of the distinct MHC class II molecules. The Ob1A12 T cell clone is reactive to the immunodominant MBP peptide, MBP85–99, presented by HLA-DRA/DRB*1501 and was generated from peripheral blood mononuclear cells of a patient with MS [24]. Characterization of this T cell clone showed that it recognizes several single amino acid substitutes of MBP85–99 presented by DRB1*1501 in a degenerative fashion. Moreover, when the responses of this T cell to APLs in the context of the other self-DR allele (DRA/DRB1*0401) were examined, the Ob1A12 T cell clone responded to the MBP85–99 88V->K APL, even though it did not recognize the MBP85–99 presented by this allele (Fig. 4, [25]). These data indicate that APL-induced cross-reactivity provides a further degree of T cell receptor degeneracy among different DR molecules. It should be noted that the functional outcome of this type of cross-reaction could be agonistic, partial agonistic, or even antagonistic depending on the specific combination of MHC molecules and peptides.

The cross-reaction induced by MAPLs containing cognate, altered, or even irrelevant peptides has not been well appreciated as a potential mechanism of molecular mimicry. However, our data generated from the systemic analyses in vitro, as mentioned above, and the increasing awareness of the highly degenerative nature of TCR recognition strongly predict that this type of molecular mimicry might effect the activation of autoreactive T cells. In fact, a recent report provides a good example for this type of molecular mimicry by showing that T cells derived from a patients with MS recognized an Epstein-Barr virus DNA polymerase peptide in the context of DRB5*0101 as well as the immunodominant MBP85–99 epitope in the context of DRB1*1501 [26]. The structural similarity in TCR contact surfaces between these two MHC/peptide complexes explains this cross-reactivity. If this type of molecular mimicry is frequent, the chances for autoreactive T cell activation would be higher than previously thought, while the identification of mimicry peptides would be more complicated. This means that we need to consider both the peptide epitopes and MHC class II alleles to carry out an exhaustive study of the molecular mimics.

5. THE RELEVANCE OF MOLECULAR MIMICRY IN MS

It is important to define whether molecular mimicry induces the initiation of autoimmune responses or contributes only to the exacerbation of existing autoimmune responses. Unfortunately, no convincing evidence is currently available for a role of molecular mimicry in the initiation of any autoimm-
Figure 2. Summary of CD8⁺ T cell clone functions with Tax11-19 presentation by different HLA-A2 subtype molecules. Lymphoblastoid cell lines expressing different HLA-A2 subtypes were loaded with 50 µM Tax11-19 and used as target cells or APCs. Cytotoxicity was tested by ⁵¹Cr releases assay at an E/T ratio of 10:1. Interferon-γ was measured in culture supernatants by ELISA after 48 h of incubation. Proliferation was determined by an 18 h-[³H]thymidine incorporation assay at the end of a 72-h culture and expressed as the stimulation index (S.I.). N.D., not determined. Individual T cells can recognize the different MHC/same peptide ligand as an agonist, weak agonist, or partial agonist. Reproduced from Ref. [22] by copyright permission of the Rockefeller University Press.
Figure 3. Polymorphic amino acids located in the HLA-A2 peptide-binding groove alter peptide ligands to induce atypical partial agonistic T cell function. (A) Location of HLA-A2 subtype polymorphic residues. The HLA-A2/Tax11-19 complex viewed from above the peptide-binding groove. Residue 156 is located in D-pocket of the groove and is within the Van der Waals radius of the P3 side chain of the Tax peptide. Thus, the substitution of Leu for a bulky Trp in HLA-A*0205 is most likely to affect TCR recognition by the structural change in peptide bound in the MHC molecule. (B) Cytotoxicity and proliferative responses of T cell clone to Tax11-19 peptide analogues with single amino acid substitutions at P3 position presented by HLA-A*0201 or A*0205. Reciprocal mutation (Phe to Asn) of the Tax peptide side chain engaging the D-pocket restores the agonist function of MHC/peptide complex. Reproduced from Ref. [22] by copyright permission of the Rockefeller University Press.
Figure 4. Cross-reaction of human autoreactive T-cell receptor with APLs in the absence of reaction to cognate peptide presented by different MHC class II molecules. (A) The MBP85–99 peptide was substituted in the core recognition region and presented by either DRB1*1501 or DRB1*0401. The responses of Ob1A12.TCR hybridoma to these ligands were analyzed by HT.2 assay measuring the interleukin-2 production. (B) As the MBP 88K peptide was recognized in the context of DRB1*0401, a series of MBP85–99 peptide with substitutions at position 88 were synthesized and tested for their ability to activate Ob1A12.TCR hybridoma.

Figure 4. Cross-reaction of human autoreactive T-cell receptor with APLs in the absence of reaction to cognate peptide presented by different MHC class II molecules. (A) The MBP85–99 peptide was substituted in the core recognition region and presented by either DRB1*1501 or DRB1*0401. The responses of Ob1A12.TCR hybridoma to these ligands were analyzed by HT.2 assay measuring the interleukin-2 production. (B) As the MBP 88K peptide was recognized in the context of DRB1*0401, a series of MBP85–99 peptide with substitutions at position 88 were synthesized and tested for their ability to activate Ob1A12.TCR hybridoma.

It should be emphasized that all the cross-reactive foreign peptides have been defined by their stimulatory capacity and selected from protein databases or screening based on the role of individual amino acid residues. Therefore, it is not clear whether these peptides can be processed by and presented on APCs after microbial infection. If they can be, it still remains to be defined whether or not cross-reactive T cells can be successfully activated and expanded sufficiently to attack self. Even though epidemiological studies suggested that several viral and bacterial infections often precede the exacerbation of MS [27], it is difficult to discriminate between two potential mechanisms for this effect: the molecular mimicry described here and the bystander activation of autoreactive T cells. The latter includes the effect of inflammation, epitope spreading, or a superantigenic effect of invading microbes. In addition, a chronologic relationship is difficult to establish because the starting point of the disease is usually unknown and most suspicious microbes induce persistent infection. The lack of an
animal model of spontaneous development of MS is another obstacle to finding answers to these questions. Thus, although a great deal of fragmentary evidence is available, a definitive role for molecular mimicry in the pathogenesis of MS has not been proven.

Potential evidence for the role of molecular mimicry in human MS has recently emerged from a clinical trial of altered peptide ligand therapy [28, 29]. In vitro and animal studies found that APLs can inhibit the response of T cells to agonistic autoantigen and can block EAE [30, 31]. Furthermore, APLs could induce a novel, APL-reactive T cell population that had a Th2 phenotype and cross-reacted with native MBP antigens [32]. These data supported the use of APLs as a therapeutic agent for MS. Unfortunately, unexpected detrimental side effects, including a hypersensitivity reaction to APLs and exacerbation of disease, necessitated the premature termination of all the trials before completion. An immunological study suggested that the latter side effect came from the expansion of APL-specific T cells with pro-inflammatory phenotype, which cross-reacted with MBP [30]. This finding is perhaps the strongest argument that, in some situations, molecular mimicry indeed can play a role in the pathogenesis of MS. Considering the highly degenerative nature of T cell recognition, it can be proposed that APLs may be presented by any of the HLA class II molecules and activate the pro-inflammatory T cells, which cross-react with myelin antigens presented either by APL-restricting or another class II molecule. However, the previous studies employed a single HLA-DR molecule for the selection of the APLs. Since the majority of patients are heterozygous for HLA-DR locus, the effect of APLs should be considered in conjunction with the individual's entire HLA class II haplotype. Actually, we recently observed that one APL (88V→K) of MBP85–99 could stimulate the Ob1A12 TCR in the context of both DRB*1501 and DRB1*0401, whereas the original MBP85–99 peptide could not be recognized in the context of DRB*0401 [25]. Therefore, stricter criteria, considering all the self-MHC class II molecules as potential restriction elements, should be applied for the selection of APLs.

6. CONCLUDING REMARKS

Molecular mimicry still remains an attractive hypothesis to explain the initiation and maintenance of MS lesions. Epidemiological and immunological studies support this theory. Indeed, several microbial peptides that cross-react with self myelin proteins have been identified. In addition, more microbial peptides will be identified in the near future if the MAPL concept is considered during screening for cross-reacting antigens. However, as mentioned previously, not all the available data can be taken as direct evidence that this molecular mechanism is at work in the pathogenesis of MS. Considering the highly degenerative nature of TCR recognition and the presence of self-reactive T cells in a normal repertoire, why do only a small percentage of people suffer from MS after microbial infections? One possible explanation is the multifactorial origin of MS. A recent twin study convincingly showed the importance of genetic traits as a risk factor [33]. If genetically predisposed individuals suffer from infections, they may develop MS due to molecular mimicry.

Recently, there has been a conceptual movement in the MS field that MS is not a single disease entity but rather a syndrome composed of different disorders with different causes [34]. In addition, major pathogenic mechanisms might differ depending on the disease stage. Therefore, the molecular mimicry hypothesis should be re-evaluated according to the new concept of the complexity of T cell cross-reactivity as well as the disease entity.

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