Molecular Mimicry and Multiple Sclerosis: Degenerate T-Cell Recognition and the Induction of Autoimmunity

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Various mechanisms have been proposed for the initiation of autoimmune responses by autoreactive T-cell clones. One of these, the molecular mimicry hypothesis, postulates that myelin-reactive T-cell clones are activated by foreign antigens. Until recently, sequence homology between self- and foreign antigens was considered necessary for cross-recognition to occur in multiple sclerosis. This article reviews current progress in T-cell receptor immunology that led to modify this view and proposes a role for degenerate T-cell antigen recognition in the induction of autoimmunity.

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Both clinical and experimental evidence supports the hypothesis that immune mechanisms are involved in the pathogenesis of inflammatory demyelination in multiple sclerosis (MS) and that autoreactive T lymphocytes initiate the process of central nervous system (CNS) myelin damage. Molecular mimicry has been proposed as a way by which an autoimmune response to myelin antigens may be initiated. According to this model, self-reactive T cells may be activated by cross-reactivity with infectious agents that “mimic” or share immunological epitopes with the autoantigen. Sequence homology between a self-antigen such as myelin basic protein (MBP) and a foreign antigen such as a viral protein was initially considered a requirement for such cross-recognition. Recent studies on the mechanisms of T-cell activation have shown that, at least for some T-cell clones, antigen recognition is much more “degenerate” than previously appreciated, and that sequence homology is not necessary for cross-reactivity. This article will focus on current advances in basic T-cell receptor immunology that bear on the occurrence of autoimmunity in the CNS.

Evidence for Immunopathogenesis Comes from Different Lines of Research

Various fields of research, such as pathology, epidemiology, immunogenetics, pharmacology, brain imaging, and studies of experimental autoimmune encephalomyelitis (EAE), an animal model resembling MS, have contributed complementary evidence that MS is an immune-mediated disease. The presence of perivenous inflammatory infiltrates of CD4+, CD8+, and γδ T-cell receptor+ (TCR+) T lymphocytes, plasma cells, and macrophages suggests that these cell types contribute to myelin damage in MS lesions. The association with certain alleles of MHC class II genes (ie, DR15 Dw2 and DQw6 in whites, DR2 and DR6 in Japanese, and DR4 in Sardinians) suggests a role of immunogenetic background in MS susceptibility, and was recently supported by two of three large-scale genome screenings. This suggests a possible role of major histocompatibility locus (MHC) class II-dependent T-cell responses in the pathogenesis of MS. Immune system involvement is also suggested by the clinical and biological response to immunomodulatory and immunosuppressive treatments as well as worsening of the disease by interferon-γ. Although the combined evidence points to an immunological basis for MS, the origin of autoreactivity has remained uncertain. The molecular mimicry hypothesis, an important conceptual framework for how autoreactivity could be initiated, was first tested in experimental allergic encephalomyelitis (EAE), an animal model of
EAE, MS, and Molecular Mimicry

Discussing the immunology of MS is difficult without briefly recapitulating the relevant findings that have emerged from EAE research. EAE can be induced in susceptible animals by active immunization with brain homogenate, myelin antigens such as MBP or proteolipid protein (PLP) or peptides derived from these antigens. Because EAE resembles MS and is induced by CD4⁺ T cells, it has stimulated research efforts to clarify the role of CD4⁺ T cells in MS. This disease model has provided insight into the pathogenic “steps” that may be relevant to MS, including (1) genetic susceptibility, (2) priming and activation of myelin-specific T cells, (3) interaction of autoreactive T cells with endothelium and migration into the CNS, and (4) recognition of myelin antigens and initiation of inflammatory or demyelinating damage (Fig 1). Autoreactive T cells have been shown to be part of the mature immune repertoire of healthy, nonimmunized animals. Genetic control of the frequency and function of such T cells in different animal strains may play an important role in disease susceptibility. For potential autoreactivity to become overt autoimmunity, however, myelin-reactive T cells must be activated by immunization with myelin antigens or strong unspecific stimuli such as bacterial superantigens. The molecular mimicry hypothesis of autoimmunity proposes that cross-reactive foreign antigens can activate autoimmune T cells, and subsequently mediate pathological and clinical damage (Fig 2). Once activated in the periphery, autoreactive T cells can cross the blood–brain barrier (BBB), infiltrate the CNS, recognize myelin antigens, and damage oligodendrocytes and the myelin sheath by various effector mechanisms.

With the exception of active immunization, similar pathogenic steps have been proposed for MS. Indeed, the presence of MBP- and PLP-reactive T cells has been extensively documented in the mature repertoire of both MS patients and healthy controls. Based on epidemiological data linking viral infections to MS exacerbations and possibly also to the cause of the disease, viral antigens are attractive candidates for initiating autoimmune mechanisms through molecular mimicry. Although it is as yet unknown how exactly a virus initiates autoimmunity, the molecular mimicry hypothesis provides an elegant conceptual framework for how autoreactivity may be triggered and will therefore be discussed herein.

Antigen Recognition by T Cells

One cannot understand molecular mimicry without describing the mechanisms underlying antigen recognition by T lymphocytes. Unlike antibodies, which react with complex protein or polysaccharide structures in particulate form or in solution, the TCR recognizes short peptide fragments derived from larger proteins in the context of self-MHC. T lymphocytes respond to short peptides generated by intracellular proteolytic degradation of antigenic proteins by antigen-presenting cells (APCs). Ten- to 16-amino acid–long peptides are loaded onto MHC molecules and transported to the surface of APCs where they can be recognized as a complex by specific CD4⁺ T cells (class II MHC-
restricted antigen recognition)\(^\text{33}\) (Fig 3). After recognition of antigen/MHC, T cells become activated, undergo clonal expansion, and acquire effector functions such as cytokine production and cytotoxicity.\(^\text{34}\) The production of cytokines such as interferon-\(\gamma\) and tumor necrosis factor-\(\alpha\) and \(\beta\) by a subset of CD4\(^+\) T cells (T-helper type 1 cells) may be important in mediating part of the immunological damage in MS.\(^\text{35}\) After clonal expansion, subpopulations of the expanded cell clones enter the pool of circulating memory T cells, whose requirements for subsequent activation by antigenic challenge appear to be lower than those of naive T cells.\(^\text{36}\)

**Evolution of the Concept of Molecular Mimicry**

Does molecular mimicry play a role in activating autoreactive T cells? Fujinami and Oldstone\(^\text{2}\) observed that rabbits immunized with a hepatitis B polymerase peptide (ICGYGLSPQ; one-letter code) that shared six amino acids with the sequence of MBP (TTHYGSLPQK) developed an antibody response to MBP and, in some cases, CNS lesions reminiscent of EAE. Quite recently, Gautam and colleagues\(^\text{37}\) induced clinical EAE by immunizing susceptible mice with a herpesvirus saimiri peptide (AAQRPSRFA) that has five amino acids of discontinuous sequence homology to MBP (1–11 peptide, ASQKRPSQRHG). Studies conducted in other animal models of autoimmune diseases such as adjuvant arthritis confirmed that mimicry of host antigens by infectious agents could lead to the development of disease by inducing cellular as well as humoral autoimmune responses.\(^\text{38,39}\)

What is the molecular basis of mimicry and what extent of sequence homology is required? The TCR, the antigenic peptide, and the MHC molecule form the trimolecular complex of T-cell antigen recognition (see Fig 3). Antigenic peptide and MHC molecule form the ligand that is recognized by antigen-specific T cells via their TCR. "Pockets" in the MHC peptide-binding groove preferentially "anchor" amino acids with certain chemical properties in specific positions of the antigenic peptides. Outside of the pockets, amino acid side chains that do not fit the MHC groove may have a strong negative influence and thus hinder binding.\(^\text{33,40}\) When peptide–MHC complexes are formed based on such "MHC-binding motifs" and exposed on the surface of APCs, both components will be recognized by a specific TCR (see Fig 3). Certain amino acid positions in the peptide sequence are more critical than others for the interaction with the TCR. Allen and co-workers proposed that one amino acid residue in the antigenic peptide sequence is strictly required (primary TCR contact), so that even a conservative amino acid substitution at this position will abolish recognition. Amino acids in other TCR contact positions (secondary TCR contacts) modulate the interaction and can be substituted with amino acids that are
similar in charge, polarity, or size. Thus, the antigenic peptide interacts with both MHC and TCR, and certain amino acids may be more important for contact in either direction. The MHC–TCR interface (ie, contacts formed between TCR and MHC directly rather than between TCR and peptide) is also crucial. In fact, the outcome of thymic selection of the mature T-cell repertoire is strongly influenced by the affinity of TCRs for self-MHC displayed on thymic epithelium.

Based on this theoretical background, amino acid residues critical for binding to the MS-associated class II molecules DR2 and DQ1 (MHC contacts), as well as for recognition by specific TCR (TCR contacts), have been defined for the MBP peptide preferentially recognized in the context of DR2. Molecular mimicry motifs that would satisfy both MHC binding and recognition by specific TCR were used by Wucherpfennig and Strominger to identify microbial peptides that were effective in activating three MBP-specific T-cell clones (TCCs) derived from MS patients (Table 1). Thus, experimental data confirmed the theoretical prediction that sequence homology was not required for cross-recognition of self- and foreign antigens. Indeed, only one of the stimulatory peptides could have been identified as a molecular mimic by sequence alignment, as opposed to structural criteria.

A further development of the molecular mimicry model originated from studies conducted in our laboratory to systematically dissect T-cell recognition of the above-mentioned immunodominant peptide MBP (83–99). Single amino acid substitutions in each position of the sequence were used to analyze the response to altered peptide ligands derived from MBP (83–99) that bind MHC with approximately the same strength. As expected, some substitutions were tolerated (they did not change the functional response of the clone) whereas others caused a reduction or abolition of the response. A new and intriguing finding was that certain amino acid substitutions were not only tolerated, but actually generated superagonist peptides that were even more potent stimulators of TCC functions (proliferation, cytokine production, cytotoxicity, and early TCR-signaling events) than the native MBP peptide.

Thus, at least for some autoreactive TCCs, the immunodominant MBP peptide used to grow and expand the TCCs was not the optimal ligand. When multiple amino acid substitutions were introduced in the antigenic peptide, their combined effect on T-cell antigen recognition was largely predictable by the additive effect (ie, positive or negative) of single amino acid modifications. The effect of “negative” substitutions in virtually any position of the peptide sequence (those leading to a reduced functional response) could be compensated by “positive” substitutions in other positions (leading to more potent responses).

Table 1

| Antigens | Cross-Reactive Peptides | References |
|----------|--------------------------|------------|
| MBP (66–75) | TTHYGS LPQK | 2 |
| HBV-P (589–598) | ICGYGSLPOE | |
| MBP (83–97) | ENP VHFKNVTPR | 46 |
| EBV-P (627–641) | TGCVHFKHKVHES | |
| MBP (83–97) | ENP VHFKNVTPR | 46 |
| HSV-T (153–167) | FRQVYHFRDFQALL | |
| HSV (87–99) | VHFKNIVTPR | 49 |
| Predicted peptide | GLLAHVISAKKA | |
| Predicted peptide | FFKNIVTPR | 49 |
| Predicted peptide | WYALLPSCKG | |

Amino acid sequences of cross-reacting peptides are reported by using the one-letter code. Sequence homology, ie, identical amino acids in corresponding positions of cross-reacting peptides, are shown in boldface underlined characters.

MBP = myelin basic protein; HBV-P = hepatitis B virus polymerase; EBV-P = Epstein-Barr virus DNA polymerase; HSV-T = herpes simplex virus terminase.

Extensive Dissection of TCR Antigen Recognition by Synthetic Peptide Combinatorial Libraries

The use of synthetic peptide combinatorial libraries has provided a novel, unbiased tool to further investigate the degeneracy of TCR antigen interactions. Synthetic peptide combinatorial libraries are highly complex mixtures of peptides in which the 20 natural amino acids occur in completely randomized order at each position in the sequence. For a given peptide length, they represent the complete set of peptides that can theoretically be built with the 20 naturally occurring amino acids (except cysteine to avoid secondary structures). For example, a completely randomized decapeptide library is made of 19 different individual peptides. For the purpose of analyzing T-cell antigen recognition, the positional scanning approach was chosen. Sets of “sublibraries” were used that are completely randomized, except for one defined position in the sequence. In the example of a decamer library, 200 sublibraries (20 amino acids × 10 positions in the sequence)
Degenerate TCR Antigen Recognition and T-Cell Development

How does this dissection of T-cell specificities help us to understand the induction of autoimmune diseases? Recognition of antigen by CD4+ T cells is considered a crucial check point for the development of any kind of immune response. This is because of not only the specificity of interaction (a feature that also characterizes B-cell antigen recognition) but also the helper function that CD4+ T cells exert on other cells of the immune system. The concept of T-cell antigen recognition has evolved from high specificity into high flexibility and, at least in some cases, extreme degeneracy. The affinity between TCR and MHC–peptide ligands is crucial to understanding the implications of their interactions. As demonstrated for some autoreactive TCCs, ligands can be found that are several orders of magnitude lower than the MBP peptide.53,54

By extending the observations made with amino acid substitutions to their theoretical limits, the combinatorial chemistry approach supports a previously unrecognized level of TCR cross-reactivity.53,54 It is noteworthy that this new concept is supported by other lines of experimental evidence (for review, see Mason55).

Degeneracy of TCR recognition may have relevance for the process of thymic selection, which may set the stage for the occurrence of autoimmune responses by shaping the immune repertoire.59 The process involves the positive selection of T cells that are able to recognize a pool of self-peptides presented by self-MHC molecules. What appears to be crucial at this stage is the capacity to recognize such MHC–peptide ligands with a degree of affinity that is not extreme. T cells with very high affinity for self-MHC–peptide complexes are deleted by programmed cell death (ie, negative selection), whereas T cells with very low affinity do not expand (death by neglect; Fig 5).60–63 Positive selection seems to occur at intermediate levels of affinity. The nature of the peptides displayed on thymic epithelial cells and their precise role in mediating the positive selection of the mature T-cell repertoire is currently under intense investigation.64 Peptides derived from MHC class II molecules and other proteins abundantly available in the endocytic compartment have been eluted from thymic epithelial cells as well as other APCs in different organs.44,65 It is noteworthy that a variety of self-antigens involved in the pathogenesis of autoimmune disease that were thought to be only expressed extrathymically, including MBP,66–68 PLP,67 uveitogenic retinal proteins,69 and other proteins that are not “sequestered” by blood–organ barriers (thyroglobulin,68,70 insulin, and glutamic acid decarboxylase68), have been shown to be expressed at the mRNA or protein level by thymic epithelial cells. These find-
ings suggest that thymic presentation of peptides derived from these antigens may participate in shaping the mature immune repertoire by both negative and positive selection. In some instances, thymic presentation of autoantigens correlates with resistance to autoimmune disease, suggesting that resistant animal strains effectively establish central tolerance to such antigens. On the other hand, presentation of self-peptides in the thymus may also explain why autoreactive T cells are part of the normal mature immune system. In fact, incomplete clonal deletion may cause the “escape” of autoreactive clones from the thymus. Although the importance of individual peptides in positive selection of T cells in the thymus is not yet completely understood, it is clear that degenerate interactions between TCR and MHC–peptide ligands play an important role. Indeed, animals that express a single MHC–peptide ligand select a remarkably diverse T-cell repertoire. Conversely, different self-peptides have the capacity to promote the selection of a single TCR. These mechanisms may ensure that the selected repertoire is diverse enough to respond to virtually any foreign antigen encountered in the periphery, but may also impose a risk for reactivity against self.

Another potential role for T-cell cross-reactivity is in the maintenance of the mature T-cell repertoire. If a high number of self-antigenic ligands are recognized with low affinity by mature T-cell clones, these ligands may provide the low degree of stimulation that is required for T-cell survival in the periphery.

**T-Cell Cross-Reactivity and Autoimmunity: A New Perspective**

Results obtained with the use of peptide combinatorial libraries and other experimental approaches suggest that a certain degree of degeneracy in recognition of antigens by the TCR is a normal feature of the immune system. A very important implication is that the potential for autoreactivity is very high, and any concept about autoimmunity must explain not only how autoreactivity is initiated, but also why it is rare. A model for how cross-recognition of foreign and self-peptides could initiate autoimmune responses is proposed, based on two fundamental requirements, the activation of cross-reactive T cells in the periphery, and the recognition of myelin antigens in the CNS. It is clear from the above considerations as well as from data obtained in other autoimmune diseases that autoreactive T cells will always be part of the normal mature repertoire. Based on our current understanding of TCR antigen recognition, a subset of such cells is expected, for statistical reasons, to be cross-reactive to foreign antigens. In the course of infections, viral antigens may often activate cross-reactive T cells in the periphery. A fraction of such T cells may then cross the BBB and enter the CNS parenchyma. If the viral peptide is a more potent agonist than the myelin antigen peptide, several other factors may be required to facilitate recognition of a myelin antigen that would normally be “seen” with lower affinity (Table 2). T-cell factors may include the increased expression of adhesion molecules and coreceptors that characterize...
Table 2. Critical Factors in the Activation of Autoreactive T Cells in the CNS

| Factor                                             | References |
|----------------------------------------------------|------------|
| Effector/memory phenotype of infiltrating T cells   | 36, 79, 89 |
| Up-regulation of adhesion molecules and coreceptors| 90         |
| Up-regulation of MHC and costimulatory molecules   | 91         |
| Expression of viral antigens in the CNS            | 83         |
| Release of self-antigens after initiation of tissue damage | 92, 93    |

CNS = central nervous system; MHC = major histocompatibility locus; APCs = antigen-presenting cells.

The memory/effectort phenotype. In addition, up-regulation of MHC and costimulatory molecules on APCs in the CNS will increase the avidity of interaction with T cells. It is interesting that the viral infection itself may cause local inflammation that will facilitate autoreactivity in the target organ. This has clearly been shown in a murine model of autoimmune diabetes, in which “bystander activation” of transgenic, β-islet antigen-specific T cells by local infection with coxsackievirus was sufficient to initiate pancreatic damage. Although the viral infection is eventually cleared, the local release of self-antigen may lead to a self-perpetuating chronic inflammation.

Another possibility is that peripheral activation of T cells by viral peptides may lead to cross-recognition of myelin antigens with the same or even higher affinity. In the scenario of highly degenerate TCR cross-recognition, this is indeed a possible event. However, we favor the view that it may occur less frequently in vivo. In fact, consistent with the negative selection of the high-affinity autoreactive T-cell repertoire, myelin-specific TCCs generated from both MS patients and healthy subjects are usually characterized by a relatively low affinity for their myelin peptide ligands (Martin and colleagues, unpublished data). Taken together, these considerations suggest that the concurrent effect of several factors may be required for “physiological cross-recognition” to become “dangerous mimicry” and frank autoimmunity. It is the need for several events to occur simultaneously that may help explain why autoimmune diseases are relatively rare. Compared with other target organs, the CNS may be protected from immune-mediated damage by the high selectivity of the BBB and the very low expression of MHC molecules. Elegant studies of transgenic expression of viral peptides in the β-islet cell of the pancreas (viral peptides expressed as self) have shown that infection with the same virus is required to initiate autoimmunity even if most peripheral T cells are specific for “viral self” peptides. When the same viral antigens were expressed as transgenes on oligodendrocytes, tissue damage induced by viral infection was less severe than in the pancreas, and only a second infection caused demyelination and obvious motor deficits. This elegant work also showed that the exacerbating effect of the second infection could be caused by an unrelated virus, a situation reminiscent of MS, where different viruses may play a role in disease exacerbations, but no single agent has been consistently associated with the disease.

In summary, the data discussed in this article suggest that although the conceptual framework of molecular mimicry remains a valid hypothesis for the occurrence of autoimmunity, the requirements for cross-reactivity are more flexible than previously appreciated. New powerful tools are available for the study of these interactions. The application of these methods to T cells isolated from the CNS compartment will be important to obtain more direct evidence for a role of molecular mimicry in the induction of CNS autoimmunity in MS.

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