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Molecular Mimicry and Antigen-Specific T Cell Responses in Multiple Sclerosis and Chronic CNS Lyme Disease

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The concept of molecular mimicry provides and elegant framework as to how cross-reactivity between antigens from a foreign agent with self proteins may trigger autoimmune diseases. While it was previously thought that sequence and structural homology between foreign and self proteins or the sharing of T cell receptor (TCR) and MHC-binding motifs are required for molecular mimicry to occur, we have shown that even completely unrelated peptide sequences may lead to cross-recognition by T cells. The use of synthetic combinatorial peptide libraries in the positional scanning format (PS-SCL) together with novel biometric prediction approaches has allowed us to describe the recognition profiles of individual autoreactive T cell clones (TCC) with unprecedented accuracy. Through studies of myelin-specific TCC as well as clones from the nervous system of patients suffering from chronic central nervous (CNS) Lyme disease it has become clear that at least some T cells are more degenerate than previously anticipated. These data will not only help us to redefine what constitutes specific T cell recognition, but also allow us to study in more detail the biological role of molecular mimicry. A recent clinical trial with an altered peptide ligand (APL) of one of the candidate myelin basic protein (MBP) epitopes in MS (amino acids 83–99) has shown that such a modified MBP peptide may not only have therapeutic efficacy, but also bears the potential to exacerbate disease. Thus, we provide firm evidence that the basic principles of cross-recognition and their pathogenetic significance are relevant in MS.

Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) with various degrees of axonal damage [1–3]. Young adults between the ages of 20 and 40 years are most often affected, and MS leads to substantial disability in more than 50% of patients. It is believed that a T cell-mediated autoimmune process against CNS myelin underlies its pathogenesis [1]. This concept is based on the inflammatory nature of MS plaques [4, 5], on parallels to an animal model, experimental allergic encephalomyelitis (EAE) [1, 6–8], on the response to immunomodulatory and -suppressive therapies, and also on genetic factors, particularly HLA genes [9–12]. $CD4^+$ pro-inflammatory (T helper-1; Th1 cells secreting interferon-gamme (IFN-γ) have a central role for the induction and perpetuation of the disease while they may be less important as effector cells that damage myelin and/or axons [1, 8, 13]. Numerous studies have therefore chacterized in detail the specificity, TCR expression, MHC/HLA-restriction and functional profile of myelin-reactive T cells in EAE as well as in human peripheral blood derived from MS patients. Consequently, EAE has become the best-examined model for any human autoimmune disease, and similarly extensive knowledge exists about T cell reactivity to myelin components in MS [8].

Epidemiological studies demonstrate that viral infections often precede MS exacerbations [14, 15], and it is thought that such infections with foreign agents either activate myelin-specific T cells by molecular mimicry, i.e. cross-recognition of a viral and a myelin peptide [16], or by bystander activation, e.g. via inflammatory cytokines [17]. The concept of molecular mimicry has undergone a substantial evolution

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during the last two decades. While it was initially held that molecular mimicry only occurs if stretches of amino acid sequences are identical or shared between e.g. a viral and a myelin peptide [16], the better understanding of T cell recognition has led to a redefinition of this phenomenon in recent years [18]. We will briefly summarize these new developments and what we believe is required for molecular mimicry. Furthermore, we will provide an example that documents the biological relevance of T cell cross-recognition for MS disease exacerbations during a clinical trial with an altered peptide ligand (APL).

The Changing Concept of T Cell Activation by Molecular Mimicry

When molecular mimicry was introduced almost two decades ago, it was believed that activation of autoreactive T cells only occurs if a self antigen shares entire stretches of amino acids with an antigen that is expressed by a virus or other foreign agent. An elegant example was provided by Fujinami and Oldstone who demonstrated that injection of a hepatitis B virus polymerase peptide which shared a sequence stretch of six amino acids with MBP into rabbits could induce an encephalomyelitis (Figure 1) [16]. Subsequent studies followed this example and searched for homologous sequences between foreign agents and autoantigens. Since sequence sharing of six or more amino acids is a relatively rare event even if large protein data bases are screened, it was no surprise that not too many examples were found. During the last few years, experiments of T cell immunologists showed, however, that only a few critical amino acids need to be shared by two antigenic peptides in order to elicit cross-reactivity [19–21]. These residues were amino acids that contacted either the TCR (TCR contacts) or were important for embedding the antigenic peptide in the peptide binding groove of the presenting MHC/HLA molecule (MHC anchors) [19–21]. Thus, it was concluded that similarities or homologies in this contact-motif are critical, whereas other amino acids are not important for cross-recognition. Wucherpfennig and Strominger employed this knowledge and developed an efficient strategy to search for sharing of this contact motif rather than sequence homology between foreign and self proteins. They were able to identify a number of molecular mimics from various viruses and bacteria and a T cell epitope (amino acids 84–102) of MBP [18] (Figure 1). Their data not only extrapolated from the basic rules of T cell recognition to molecular mimicry, but also indicated that cross-recognition is probably occurring more often than previously thought.

These observations were taken even further by our own experiments with systematical studies of single- or multiple amino acid-substituted peptides or synthetic combinatorial peptide libraries in the positional scanning format (PS-SCL) [22–25]. The results demonstrated that every single amino acid in the epitope interface between TCR and MHC contributes independently and in an additive fashion to T cell recognition (Figure 1). This was confirmed by creating peptides for an MBP (83–99)-specific TCC that combined a number of amino acids that were different from the native peptide in each position and had either positive or negative influences on T cell stimulation. Pushing this concept to the extreme, we showed that no single amino acid needs to be shared between cross-reactive peptides as long as the stimulatory potency for a given TCC is above a critical

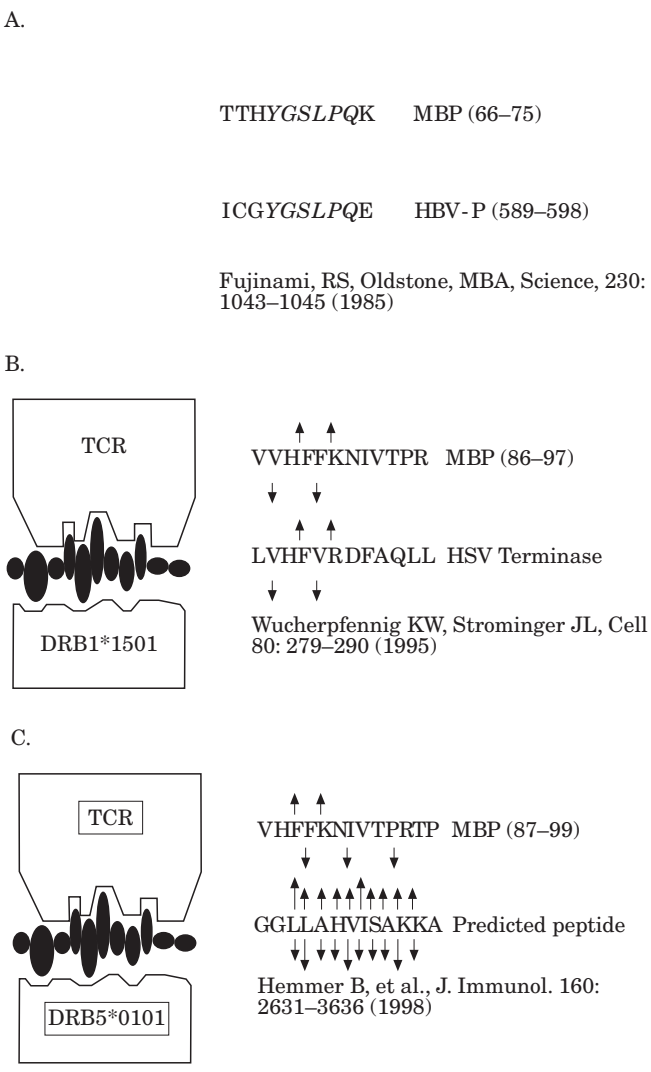

Figure 1. Schematic representation of the changing concept of molecular mimicry. (A) A hepatitis B virus polymerase peptide and a myelin basic protein peptide share six amino acids in sequence. Immunization of rabbits with the hepatitis B virus peptide leads to encephalomyelitis via molecular mimicry. (B) Knowledge of the T cell receptor- and MHC anchor amino acids led Wucherpfennig and Strominger (1995) to use this motif of four amino acids to search for molecular mimics in data bases. (C) Molecular mimicry can even occur with peptides that share no single amino acid as long as the additive stimulatory potency of all amino acids surpasses a stimulatory threshold (from Hemmer, B., *et al.* 1998).

threshold [24, 26]. Two important conclusions were drawn from these data: (a) T cell recognition is much more degenerate than previously thought, and each TCC can probably recognize large numbers of peptides, and (b) molecular mimicry is most likely a frequent event and usually physiological for selecting and maintaining the T cell repertoire. One would expect that it is only in the right context such as a pro-inflammatory environment that an autoimmune disease is triggered and/or perpetuated by molecular mimicry. The fact that completely non-homologous peptides may result in molecular mimicry also posed a dilemma, i.e. how does one identify in a systematic way which peptides may be cross-reactive for a given TCC without testing large sets of modified peptides. The solution of this problem came from a combination of applying PS-SCL for testing TCC specificity and from biometric approaches. The latter allowed to take data from the T cell assays with PS-SCL to calculate the stimulatory score of a peptide, and employ this score matrix-based system for large scale data base searches for potential molecular mimics. As a next step the peptides were ranked according to stimulatory score and finally synthesized to test whether the above hypotheses were met [25].

This strategy was already successfully applied in MS patients and myelin-specific TCC, but also in foreign antigen-specific TCC, and showed the unprecedented efficacy in translating the peptide library data to protein data base searches and epitope prediction [25, 27, 28]. This technique provides a clear advantage over strategies that only use the MHC binding-motifs to predict e.g. candidate myelin peptides [29]. In our case, the data is derived from PS-SCL testing with individual clones, then creating a score matrix and subsequently survey the largest available protein- and DNA-sequence databases for potential mimics. We already utilized this search strategy for the identification of both *Borrelia burgdorferi*-derived sequences, the causative agent of Lyme disease, and to human proteins, for a clone (CSF-3) that was isolated from the cerebrospinal fluid (CSF) of a patient with chronic CNS Lyme disease [25]. Our data highlighted a number of important points: (1) Despite the fact that TCC CSF-3 responded to multiple *Borrelia* peptides and thus was degenerate in its specificity, it recognized the *Borrelia* peptides at considerably lower antigen concentrations compared to molecular mimics from self- or viral proteins. Thus, specificity is maintained, even though the TCR of CSF-3 was able to interact with multiple peptides. (2) Consequently, by testing PS-SCL which are composed of trillions of peptides and combining this strategy with sophisticated biometric data analysis allowed us to search the entire set of known peptides and identify efficiently both antigens derived from the pathogenic organism, but also from multiple candidate autoantigens. (3) In principle, these techniques are useful not only for the identification of novel vaccines, but also to delineate the specificity of tumor-infiltrating lymphocytes or of potentially autoreactive clones that are isolated from an affected tissue, e.g. the joint in rheumatoid arthritis.

Is Molecular Mimicry and Cross-reactivity with Autoantigens of Pathogenetic Relevance?

From the summary of the above observations, we conclude that molecular mimicry is likely to be a frequent event. It may even serve physiological roles by selecting a diverse, foreign antigen-specific T cell repertoire on a limited set of self peptides in the thymus and by maintaining this repertoire via supporting T cell survival in the periphery. It is therefore probably the context of T cell activation, i.e. upregulation of adhesion- and co-stimulatory molecules, upregulation of MHC, and the secretion of proinflammatory cytokines, that determines the fate of a developing immune response, whether it is pro- or anti-inflammatory, contained at a certain site, and more.

What does this changed concept of molecular mimicry mean for the elicitation of autoimmunity and autoimmune diseases? Despite some elegant examples of molecular mimicry in animal systems [16, 30, 31], convincing evidence for its *in vivo* relevance is still sparse. In MS, it is well known that exacerbations are often preceded by viral infections [14, 15]. Furthermore, acute demyelinating encephalopathies after measles infections demonstrate that demyelination can be initiated by viruses [32]. While this evidence is compelling, it could either mean that the exacerbation was due to molecular mimicry or caused by bystander activation of myelin-reactive cells.

We obtained more direct evidence for the pathogenetic role of molecular mimicry during a recent clinical trial with an altered peptide ligand of one immunodominant MBP peptide, MBP (83–99) [13]. Based on *in vitro* experiments with such modified peptides it was demonstrated that modifications of immunogenic peptides in either MHC- or TCR-contact positions of a peptide epitope can result in alterations of T cell activation such as partial agonism (not all T cell functions are activated compared with the agonist peptide) or T cell receptor antagonism (the APL inhibits the response to the agonist, if both are present at the same time) [19, 20, 33–36]. This knowledge was rapidly translated to *in vivo* experimental systems, and multiple groups showed that APL peptides can block EAE [37–40]. Furthermore, it was noted that APL occur as natural mutants of viral or parasitic pathogens and allow these either to escape T cell priming or evade ongoing protective immune responses, e.g. in HIV-infected patients [41–43]. The most interesting mechanism for the inhibition of EAE was, however, neither TCR antagonism nor partial agonism, but the induction of a novel, APL-reactive T cell population that showed a Th2 phenotype and cross-reacted with the native myelin peptide in a system of PLP (139–151)-induced EAE in SJL mice [39]. The investigators elegantly dissected this mechanism and thus provided a system that could be expected not only to shut down the Th1-mediated and pathogenic immune response against the parental myelin peptide, but also against other myelin

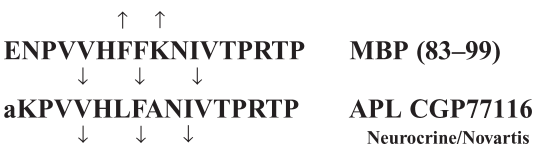

Figure 2. An altered peptide ligand based on MBP amino acids (83–99), CGP77116 (or NBI-5788) incorporates amino acid exchanges in the two major T cell receptor contact positions.

components that might become targets via epitope spreading [44].

In MS, the situation is complicated by the fact that we are not dealing with an induced disease, but rather a process that is already ongoing for a long time before it is diagnosed and directed against multiple, usually unknown epitopes. Based on these considerations and the complexity of human immune reactivity, e.g. against even single MBP epitopes in MS [45, 46], we speculated that TCR antagonism and partial agonism are unlikely to be effective therapies. However, the potential to induce bystander suppression with an APL appeared attractive, and consequently an APL was designed based on a very well characterized candidate myelin peptide, the immunodominant MBP peptide MBP (83–99) [13, 47]. As shown in Figure 2, two major TCR contacts were modified to create an APL that was considered safe and expected to induce a cross-reactive T cell population with a different phenotype than typical MBP-specific T cells which are often Th1 or Th0 in MS patients. Phase I clinical testing showed that the peptide was indeed safe, immunogenic *in vivo* [48], and, at least at the lower doses, capable of inducing Th2-like, APL-specific cells. Due to these promising data, APL CGP 77116 was tested in two phase II trials [13, 47]. One of these was oriented towards showing the safety and tolerability as well as its potential efficacy on inhibiting MRI activity in a small cohort of patients with active disease [13], whereas the other, much larger multicenter study aimed at demonstrating clinical efficacy [47]. The first trial that was conducted at NIH employed only a high dose, i.e. 50 mg of APL subcutaneously, weekly for 9 months, whereas the larger study incorporated a placebo arm and three different doses (5, 20 and 50 mg sc/weekly for 4 months). Without going in detail over the different trial designs and all the considerations regarding MRI, clinical and immunological testing, we will briefly summarize the main results from these studies below.

Both trials were stopped before completion, the NIH study because of unexpected exacerbations that could be linked to APL treatment in two out of three patients, the multicenter trial primarily because of hypersensitivity reactions in 9% of the treated individuals [47]. Elaborate immunological experiments in the NIH trial during the time of exacerbations as well as the entire study, led to the following conclusions: (1) Different from APL stimulation *in vitro*, the peptide was highly immunogenic *in vivo* and led to the sensitization and expansion of APL-specific T cells in every individual, (2) CGP 77116 at the high dose was not well tolerated and resulted in local reactions in all patients, hypersensitivity in one out of eight, and exacerbations in three of eight treated patients, (3) in two of three patients the exacerbations could be linked to the expansion of APL-specific T cells with a pro-rather than anti-inflammatory phenotype and various patterns of cross-reactivity with the native MBP peptide. The occurrence of these cross-reactive T cells at more than thousand-fold higher frequencies and further enriched in the CSF strongly argued for their relevance for the disease relapses [13]. Thus, it demonstrated that cross-reactivity with the APL, which may be considered a molecular mimic of MBP (83–99), was elicited by APL immunization with the high dose. (4) We concluded further that the high dose and frequent administration had likely played an important role for these observations, i.e. the Th1 skewing of the APL-specific immune response. Support for this notion comes from data of the large, multi-center phase II trial. While only a very small number of patients was studied immunologically, the MRI data as well as the phenotyping of APL-specific T cells indicated a Th2-biasing effect and the induction of bystander suppression in the 5 mg dose group [47]. These data show not only that the pathogenetic concepts that have largely been deduced from EAE experiments are likely to be valid in MS as well and that we need to reconsider the concept of specific immunotherapies by APL at least with respect to dose and timing of the immunization regimen. However, the results of the NIH APL trial also provides very strong evidence for a pathogenetic role of molecular mimicry or cross-reactivity as inducers of myelin reactivity. To exploit the potential of APL peptides further in the future, we need more information how to administer them safely with respect to timing and dose.

Summary

Induction of autoreactivity and autoimmune diseases via molecular mimicry remains an intriguing concept. Our advances in understanding the rules of T cell activation as well as the application of combinatorial peptide chemistry have allowed a better and broader definition of the requirements for cross-reactivity to occur. The discovery that T cell recognition is more degenerate than previously thought also implied that molecular mimicry is in most instances a physiological process that serves to maintain a broad peripheral T cell repertoire. Only under certain circumstances such as addition of adjuvant in EAE or the immunization with very high doses of an immunogenic molecular mimics, or co-activation, e.g. by a viral infection, carry the risk of inducing pathogenic molecular mimicry in specific target tissues such as the CNS. Such a context is unlikely to occur during vaccinations with protein antigens or inactivated viruses or bacterial antigens because these do not induce damage in the target tissue. Strong support that molecular mimicry and cross-reactivity can indeed exacerbate autoimmune diseases in humans

stems from the above-described trial with an altered peptide ligand in MS.

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