Autoimmunity provoked by infection: how good is the case for T cell epitope mimicry?

Christophe Benoist and Diane Mathis

Autoimmune diseases remain one of the mysteries that perplex immunologists. What makes the immune system, which has evolved to protect an organism from foreign invaders, turn on the organism itself? A popular answer to this question involves the lymphoid network's primordial function: autoimmunity is a by-product of the immune response to microbial infection. For decades there have been tantalizing associations between infectious agents and autoimmunity: β-hemolytic streptococci and rheumatic fever; B3 Coxsackieviruses and myocarditis; *Trypanosoma cruzi* and Chagas' disease; diverse viruses and multiple sclerosis; *Borrelia burgdorfii* and Lyme arthritis; and B4 Coxsackievirus, cytomegalovirus or rubella and type 1 diabetes, to name the most frequently cited examples[1]. In addition, animal models have provided direct evidence that infection with a particular microbe can incite a particular autoimmune disease[2]. Nonetheless, many of the associations appear less than convincing and, even for those that seem to be on solid footing, there is no real understanding of the underlying mechanism(s).

Any explanation of how microbial infections might set off autoimmune diseases must take into account the observation that all individuals appear to harbor potentially autoreactive lymphocytes, but that these cells remain innocuous unless somehow activated. Mechanisms by which infectious agents might activate these cells fall into two major classes: antigen-specific and antigen-nonspecific. The cornerstone of the antigen-specific theory is epitope mimicry: an antigenic determinant on one of the microbe's proteins is structurally similar to a determinant on one of the proteins made by the host, although different enough to be recognized as foreign by the host's immune system (**Fig. 1**). For T cells, the focus of this Review, the determinants involved would be linear peptide stretches of about 8–15 amino acids (aa) long. The immune response to the microbial determinant would then cross-react with host tissue and eventually result in autoimmune destruction. The antigen-nonspecific theory has several variants: they are grouped loosely under the term "bystander activation". For all these mechanisms, no particular microbial determinant is implicated. For example, infection might cause host cell destruction, which results in the release of large quantities of normally sequestered proteins. These could then be trafficked to the draining lymph nodes or presented at the invasion site. Alternatively, or in addition, microbial insult could alter the phenotype of professional or nonprofessional antigen-presenting cells (APCs), rendering them more effective by enhancing antigen-processing machinery, display of major histocompatibility complex (MHC) molecules at the cell surface or expression of costimulatory molecules. Such an insult could also induce the synthesis of inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin 1 (IL-1), whose activities include activation of APCs and modification of lymphocyte migration patterns. Finally, infection might provoke polyclonal lymphocyte activation *via* either a mitogen or a superantigen effect.

Of late, epitope mimicry has been the favored explanation for the proclivity of microbial infection to precipitate an autoimmune reaction. This is partly due to increasing awareness that T cell receptor (TCR) recognition of MHC-peptide complexes is extremely degenerate, and does not even require primary structure homology between two peptides presented by a given MHC molecule[3,4]. Yet, careful review of the evidence for epitope mimicry leaves one with the impression that the case is far from proven. Before discussing some of this evidence, it may be worthwhile to state what criteria an "air-tight" case should satisfy. We propose the following five criteria, which are similar to those presented previously[1,5].

(i) As a prelude, an association between the particular microbial infection and the particular inflammatory state should be sought. This might be correlative, showing a temporal relationship between the two or demonstrating that the severity of the inflammation is influenced by the strength of the infection. Or it might be causal, directly showing, usually in an animal model, that the specified infection precipitates the specified inflammatory state. To establish the autoimmune nature of the inflammation, it is important to show that it persists in the absence of the inciting microbe. This criterion may be challenging to satisfy in some cases: the microbe may have been cleared too long before disease manifestation to have been noted; it may be a common infecting agent, provoking disease only in combination with more rare genetic or environmental elements; or it may just prime the immune system, the immediate disease-provoking stimulus being a second virus or some nonspecific "adjuvant"[6,7].

(ii) The responsible microbial and self-proteins should be identified: more specifically, the culprit epitopes. The microbial epitope

Section on Immunology and Immunogenetics, Joslin Diabetes Center, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, One Joslin Place, Boston, MA, USA. Correspondence should be addressed to D. M. (cbdm@joslin.harvard.edu).

(and protein) should be able to elicit a T cell response that is cross-reactive to the self-epitope (and protein). As discussed below, difficulties in satisfying this criterion may arise because of the increasingly appreciated degeneracy of the T cell repertoire[8–12].

(iii) The relevance of the microbial and self-epitopes, and the cross-reactive response to them, needs to be established because they are involved in the evolution of both the infection and the autoimmune disease. Can APCs that display these epitopes be found within the infectious-autoimmune lesion or the draining lymph nodes? Are cross-reactive T cells a significant component of the immune response elicited by the infection? Are they expanded during the autoimmune disease? Answers to the last two questions should be more forthcoming as the use of MHC-peptide tetramer technology becomes more widespread.

(iv) A requirement for both the microbial and self-epitopes in the development of the autoimmune disease should be demonstrated. This can be done by assessing the effect of deleting or altering the epitopes of the microbial and self-proteins. Of course, care needs to be taken to rule out the possibility that mutation of the microbial protein in question does not change other relevant properties of the microbe, for example, infectivity or replication.

(v) It must be established that T cells elicited by the microbe and cross-reactive to the microbial and self-epitopes can, and are necessary to, provoke the autoimmune disease. This can be achieved with adoptive-transfer experiments, a TCR-transgenic mouse system or a combination of the two.

These criteria have been designed to stringently distinguish between a mechanism that involves epitope mimicry and the diverse mechanisms that rely on the different variants of bystander activation. Within this framework, we will next examine two of the most often cited examples of epitope mimicry.

OspA–LFA-1 and antibiotic-resistant Lyme arthritis

Lyme disease is a multisystem illness that results from infection by the tick-borne spirochete *Borrelia burgdorferi*[13,14]. A prominent late manifestation, particularly in North America where the species *B. burgdorferi sensu stricto* predominates, is an inflammatory joint disorder that resembles rheumatoid arthritis. In about 10% of patients with Lyme arthritis, joint inflammation resists extended antibiotic therapy. After drug treatment, no spirochetal DNA has ever been detected in the synovial tissue or fluid of such patients, although it is easily found before administration. This has provoked the hypothesis that antibiotic-resistant borrelial arthritis is an autoimmune disease.

Support for the theory that autoimmunity underlies Lyme arthritis has come from observations of an MHC association and an anti-borrelia immune response associated in time and severity with the arthritis symptoms. The majority of individuals with the treatment-resistant disease have the HLA-DRB1*0401 or HLA-DRB1*0101 alleles which, interestingly, are also more frequent in rheumatoid arthritis patients[15,16]. Also characteristic of many individuals, and appearing coincidentally with the onset of a prolonged arthritis episode, is a high titer of immunoglobulin G (IgG) antibodies that recognize the outer surface protein A (OspA) of *B. burgdorferi*[16,17]. T helper 1 (T_H1) cells reactive to OspA are often found as well[18–20]. Finally, immunization with recombinant OspA has been effective in preventing Lyme disease in two clinical trials[21,22] and is now available as a vaccine. These findings suggest that an HLA-DRB1*0401- or HLA-DRB1*0101-restricted immune response that is OspA-specific somehow precipitates joint-specific autoimmunity.

A breakthrough came when the immunodominant HLA-DRB1*0401-restricted peptide of OspA was identified[23]. With the use of a computer alogarithm[24], the nine-residue peptide OspA(165–173) was predicted to be the peptide most effectively bound by HLA-DRB1*0401; this was confirmed experimentally in competitive binding assays. In addition, when injected with OspA protein, mice that were transgenic for HLA-DRB1*0401 responded primarily to the OspA(165–173) peptide, as did T cells from an HLA-DRB1*0401$^+$ antibiotic-resistant patient with Lyme arthritis, which were challenged *in vitro*. A search of the Genbank Database identified one human protein, leukocyte function–associated antigen 1α (hLFA-1α), which contains the peptide hLFA-1α(L332–340). hLFA-1α(L332–340) has homology to the dominant epitope of OspA and was predicted to bind strongly to HLA-DRB1*0401 (which was eventually confirmed experimentally)[23]. Most importantly, synovial fluid T cells from patients with antibiotic-resistant arthritis, but not antibiotic-sensitive or other inflammatory arthritides, could respond to both OspA(165–173) and hLFA-1α[25]. Tetramer technology has now been applied to this field and has permitted direct enumeration of HLA-DRB1*0401-restricted T cells that are OspA(164–175)-specific. It has identified increased numbers of these cells in the synovial fluid compared to in the blood of treatment-resistant arthritis patients[26]. It has also allowed the demonstration of OspA(165–184) and hLFA-1α(L326–345) cross-reactivity at the single cell level, although for only 10% of OspA(165–184)-reactive clones and with a markedly lower hLFA-1α(L326–345) response[27].

These observations suggested the following epitope mimicry scenario. *B. burgdorferi sensu stricto* infects the host and disseminates to multiple tissues, including the joints. Some time later, often after several months, an inflammatory immune reaction begins in the joints; it is characterized in HLA-DR4B1*0401 individuals by an anti-OspA IgG response and T_H1 cell reactivity to the OspA(165–173) peptide. Interferon-γ (IFN-γ) produced by the T_H1 cells up-regulates expression of LFA-1 on synoviocytes and invading leukocytes and HLA-DR4 molecules on APCs. As a result, there is enhanced presentation of self-peptides derived from LFA-1α, which are either endogenously synthesized or phagocytozed, that augments and propagates the inflammatory response, even after borrelial antigens have been cleared. Support for this scenario comes from the finding that LFA-1 is, indeed, highly expressed on cells infiltrating the synovia of treatment-resistant Lyme arthritis patients, but not those with other arthritides[28].

Thus, the case for OspA–LFA-1α epitope mimicry being responsible for the initiation of antibiotic-resistant Lyme arthritis fulfills two, perhaps three, of the criteria we have proposed. First, the association between infection by *B. burgdorferi sensu stricto* and the eventual development of chronic, treatment-insensitive arthritis is well documented. Inflammation occurs once the microbe has been cleared, but the immune response to the OspA protein and the time of onset and severity of joint inflammation correlate well. Second, the culprit epitopes were defined as OspA(165–173) and hLFA-1α(L332–340); in addition, T cells that were capable of responding to both were elicited in HLA-DRB1*0401-transgenic mice immunized with OspA. Third, dual-responsive T cells were found specifically in patients with antibiotic-resistant Lyme arthritis, especially in the inflammatory lesions.

However interesting and suggestive this putative example of epitope mimicry appears to be, it cannot yet be considered definitive. A major problem has been the lack of an adequate rodent model. Thus, it has

not been feasible to evaluate the effect of engineered mutations of the OspA and LFA-1α epitopes on arthritis development; nor has it been possible to provoke arthritis in normal recipients by transferring dual OspA–LFA-1α–reactive T cells. HLA-DRB1*0401-transgenic mice injected with OspA responded primarily to the relevant OspA(165–173), but developed no signs of arthritis (or any other autoimmune disease[23]). This was probably because the corresponding region of LFA-1α differs between mice and humans[29]. Another problem is the extensive cross-reactivity that has been shown for T cells reactive to the OspA(164–173) epitope: "supertopes" have been identified *via* amino acid substitution analysis and used to screen protein databases. Many (475) supertope-matching peptides were found in human or murine proteins and 16 of these could stimulate at least one of seven OspA(164–175)-reactive T cell hybridomas[8]. Thus, one must consider the chance of finding some self-peptide epitope that cross-stimulates with OspA purely due to "multiple sampling". A similar point has been made concerning candidate T cell epitopes and epitope mimics in a chronic borrelial disease of the central nervous system[9]. A final problem worth mentioning is that certain features of the proposed epitope mimicry scenario remain unsatisfying: for example, there are no clues as to what precipitates an inflammatory response several months after the borrelial infection and no evidence for whether LFA-1α peptides are actually being presented in the joints or, if so, by which APCs.

A simplistic (almost certainly oversimplistic) alternative scenario that needs to be ruled out is as follows. An OspA(165–173)-directed immune response is made systemically (perhaps, but not necessarily, including the joint). This leads to the production of anti-OspA and overproduction of inflammatory cytokines, in particular TNF-α and IL-1. Antibodies, cytokine effectors or both provoke a self-propagating arthritis that is similar to those reported for different mouse models[30,31]. This could explain the inflammatory joint response in the absence of any evidence of the inciting microbe. In this scenario, dual reactivity of synovial T cells for OspA and LFA-1α is a chance event that merely reflects the impressive degeneracy of TCR recognition of MHC-peptide complexes.

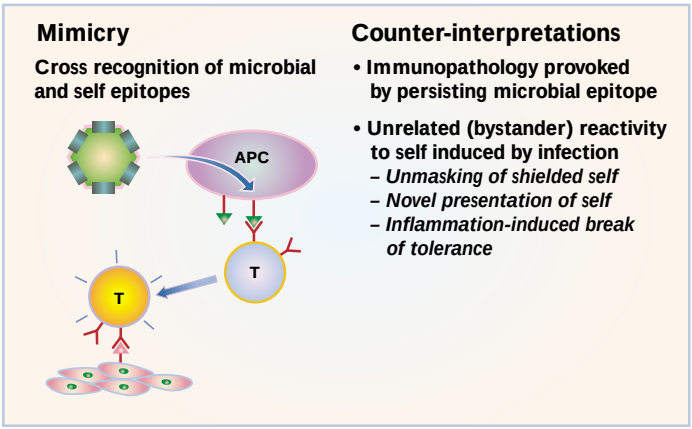

Figure 1. Alternative explanations for autoimmunity.

UL6-corneal antigen and herpetic stromal keratitis

Infection of the eye with herpes simplex virus 1 (HSV-1) can provoke a chronic inflammation of the corneal stroma that is called herpetic stromal keratitis (HSK); HSK is a leading cause of human blindness[32]. Some, though not all, strains of mice develop HSK when ocularly infected with HSV-1 isolated from infected human tissue, and these strains provide a very useful animal model[33]. In mice, the disorder is thought to be mediated primarily by $CD4^+$ T_H1 cells, as they will transfer the disease into ocularly infected immunodeficient recipients. However, roles for $CD8^+$ T cells, $CD4^+$ T_H2 cells and antibodies have also been proposed[32]. Somewhat paradoxically, stromal opacity in mice peaks 1–2 weeks after HSV-1 infection, when viral titers have plummeted and virus-derived transcripts are no longer detectable[34]. Therefore, it was inferred that the perpetuation of inflammation that results in HSK is the manifestation of an autoimmune response to a corneal antigen.

A more convincing, though still quite indirect, argument for autoimmunity came when the basis of murine strain variations in HSK susceptibility was determined. Development of HSK after HSV-1 infection is controlled in a monogenic dominant manner by genes linked to the *Igh* locus[35], in particular by the genetic segment encoding the Ig heavy chain constant region[36]. Inbred strains carrying the Igh^a, Igh^d or Igh^e alleles are susceptible to HSK, whereas those harboring the Igh^b allele are resistant[35,37,38]. When injected in a tolerogenic mode into Igh^d animals shortly before corneal HSV-1 infection, purified Igs from resistant Igh^b, but not susceptible Igh^e, mice protected Igh^d animals from HSK[39]. Because transfer of T cells from HSV-1–infected Igh^b mice that had been injected with purified Igs did not provoke HSK in ocularly infected immunodeficient recipients, whereas transfer of cells from uninjected infected animals did, it was suggested that T cell tolerance had been affected.

This apparent tolerization led to the hypothesis that HSK is mediated by T cells that recognize Igh^b-derived peptides. In concordance with this theory, injection of Igh^d mice with Igh^b, but not Igh^e, antibodies in an immunization mode elicited T cells capable of provoking HSK in cornealy infected immunodeficient recipients. Immunization with Igh^b antibodies, specifically of the IgG2a isotype, was as effective; indeed, two T_H1 clones specific for $IgG2a^b$, but not T_H1 clones of other specificities, could induce HSK under these conditions. In addition, the two $IgG2a^b$-specific clones responded to murine corneal extract *in vitro*, but not to extracts from other tissues. The $IgG2a^b$ peptide responsible for stimulating the two clones encompassed aa 292–308. This peptide could block HSV-1–induced HSK when pre-injected under tolerizing conditions, and immunization with this peptide also elicited T cells capable of provoking HSK in ocularly infected immunodeficient hosts. On the basis of these results, it was argued that HSK is an autoimmune disease induced by $CD4^+$ T_H1 cells that are elicited by HSV-1 infection and reactive to both a corneal antigen and $IgG2a^b$.

The critical next step was to more directly link the dual T cell reactivity to $IgG2a^b$ and a corneal protein with reactivity to an HSV-1–encoded protein[40]. The two HSK-inducing T_H1 clones mentioned above, C1-6 and C1-15, responded to extracts of HSV-1–infected, but not uninfected, Vero cells. A search of the Genbank Database for HSV-1 proteins with sequence homology to the peptide $IgG2a^b$(292–308) revealed the best match with UL6(299–314), which had identical or chemically similar amino acids at seven of eight sequential positions. A 15 residue peptide that includes this sequence specifically stimulated both clones and also prevented HSK when pre-injected under tolerizing conditions into HSV-1–infected mice. In addition, when injected into animals under immunizing conditions, it elicited T cells that could provoke HSK in

cornealy infected immunodeficient recipients. Strikingly, HSV-1 variants that lacked UL6, and which were also replication-defective, did not make proteins that stimulated the two keratogenic T_H1 clones. In addition, they did not provoke HSK in susceptible strains, whereas another replication-defective isolate still could. These results led to the proposition that HSV-1 infection elicits T_H1 reactivity to the UL6(299–314) peptide and cross-reactivity to an as yet unidentified corneal antigen; the latter precipitates a corneal inflammation that culminates in HSK. A second cross-reactivity to the IgG2a^b(292–308) peptide results in tolerization of UL6(299–314)-reactive T cells in *Igh*^{b} strains and resistance to HSK.

This body of data seems to add up to a strong case for T cell epitope mimicry: it is arguably the strongest to date. There is at least partial satisfaction of four of the five criteria listed above. First, there is a clear association between HSV-1 infection and HSK, although it must be said that the correlation has not yet been extended to the response to a particular HSV-1 protein. Second, the inciting microbial epitope has been identified as UL6(299–314); the culprit corneal self-epitope has not yet been defined, in fact, direct evidence of cross-reactivity to a corneal antigen is limited to two T cell clones. Third, the requisite microbial epitope deletion experiment has been done but, obviously, not the corresponding self-epitope deletion analysis. Fourth, the two UL6(299–314)-reactive T cell clones could provoke HSK in cornealy infected immunodeficient hosts, as could T cells from mice immunized with the UL6 peptide, although ocular insult was always required.

Given this impressive body of supporting data, and the elegance of certain of the experiments, reports that question a role for epitope mimicry in this context—at least mimicry involving the UL6 sequence—have been provocative. Two ovalbumin-specific TCR-transgenic mouse lines on a recombination-activating gene–deficient background developed severe HSK upon HSV-1 infection. This was despite the fact that their monoclonal TCRs were not reactive to an HSV-1–encoded protein and they did not develop anti–HSV-1 T cell reactivity[41,42]. In addition, no cross-reactivity in the responses of *Igh*^{d} mice to injection of the UL6(299–314) and IgG2a^b(292–308) peptides could be detected. Surprisingly, the anti-UL6(299–314) response did not even cross-react with extracts of HSV-1–infected cells[42]. In addition, when B cell–deficient *Igh*^{b} mice—which were now capable of responding to IgG2a^b(292–308)—were infected with HSV-1, they developed HSK, but no IgG2a^b(292–308)-responsive T cells could be found, nor even any UL6(299–314)-reactive cells.

These findings clearly bring into question a role for molecular mimicry that involves the UL6 and IgG2^b peptides. They suggest alternative hypotheses (**Fig. 1**) that invoke bystander activation and note that HSK in the animal model always requires corneal insult. According to one scenario, ocular HSV-1 infection results in local injury. This promotes a proinflammatory environment in the cornea, permits CD4$^+$ T cells of any specificity to enter when they normally could not and provokes their activation and further differentiation in an antigen-nonspecific manner that is probably mediated by cytokines. Although it fits the data nicely, this scenario is not entirely satisfying because the supporting data rely too heavily on systems—both in the TCR-transgenic and B cell–deficient mouse lines—that do not permit effective clearance of HSV-1 after the infection. Because of this they are not precisely reflective of standard infected mice. A related scenario would be that a local anti–HSV-1 response is involved, but that HSK results from intermolecular epitope spreading or simply virus-induced immunopathology.

There is currently no clear explanation for the discrepancies between these two sets of results, although they might be related to the different strains of mice or viruses employed and/or to other aspects of the analysis systems used. The further complexity of T cell precursor frequency was additionally highlighted when it was found that epitope mimicry is essential for HSK development after low-level HSV-1 infection of animals harboring a limited number of autoreactive T cells, whereas innate immune mechanisms sufficed with stronger infection and higher T cell numbers[43].

Judgment

We have weighed what we consider to be the two best-argued examples of T cell epitope mimicry between microbial and self-peptides that participate in autoimmune disease. Our conclusion is that the case is not yet convincing enough to espouse, either for these two examples or for the many others that have been reported but are based on sparser substantiating data. The increasingly more appreciated degeneracy of the T cell repertoire[8–12] implies that the potential for such a role clearly exists, and new computational and experimental screening tools make identification of candidate epitopes almost too easy. Indeed, those attracted by the concept of epitope mimicry must now be wondering less about how autoimmunity is provoked and more about why it does not happen more often. What we need at this point are new approaches for subjecting the candidates to experimental validation, in particular in the difficult human system.

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