Commentary

Absence of "Original Antigenic Sin" in Autoimmunity Provides an Unforeseen Platform for Immune Therapy

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In this issue of *The Journal of Experimental Medicine,* Tuohy et al. study the spreading of the autoimmune response to myelin antigens in experimental autoimmune encephalomyelitis (EAE) and its likely human counterpart, multiple sclerosis (MS) (1). They demonstrate that as disease develops in EAE and MS, reactivity to the initiating antigen diminishes, and an orderly and definable set of new immune reactivities arises. The data are clear and the scope of the study in humans and in experimental animals is broad. For example, the investigators elegantly look at T cells in the central nervous system (CNS) in EAE to see whether the reduction in peripheral activity is due to sequestration of such T cells in the brain and spinal cord. The answer to this question is a resounding "no." Loss of reactivity is not due to sequestration of the immune response in the CNS. The implications of this study present challenges to the doctrine of "original antigenic sin," and to the hope of developing antigen-specific therapy for autoimmune disease.

In organ-specific autoimmune diseases such as MS, rheumatoid arthritis, and insulin-dependent diabetes mellitus (IDDM), there are vigorous debates among experts on which antigen triggered the autoimmune response. Furthermore, there are arguments about which antigens dominate the diverse immune responses that can be detected at the site of disease. Thus, in MS, where an apparent autoimmune T and B cell response occurs in myelin sheath of the CNS, there are arguments whether the initial or dominant immune response might be directed at myelin basic protein (MBP; references 2–4), myelin oligodendroglial glycoprotein (MOG; references 5, 6), proteolipid protein (PLP; reference 7), or various other myelin antigens (8). For IDDM, investigators argue whether the primary response is against glutamic acid decarboxylase (9, 10), insulin (11), heat shock protein 65 (12), or other islet cell antigens.

The concept of epitope spreading described by Lehmann et al. for EAE describes how antigen-specific autoimmune responses can spread to different epitopes on one protein, termed "intramolecular epitope spreading" (13), to other epitopes on other structural proteins, termed "intermolecular epitope spreading" (14), at the site of disease (Fig. 1). Thus, in EAE induced with an injection of an epitope of PLP, the immune reactivity of populations or ensembles of T cells can spread to other epitopes on PLP, and then on to other myelin antigens such as MBP and MOG. Tuohy et al. demonstrate that during the course of EAE initiated by immunization to one epitope both intramolecular and intermolecular epitope spreading allow the autoimmune response to evolve in an orderly manner to encompass detectable T cell responses to other epitopes on the initiating antigen and to other myelin antigens. Remarkably the T cell response to the initiating epitope is lost as disease progresses.

When Tuohy et al. searched for this phenomenon in human demyelinating disease, they faced a truly complicated task. For it is difficult to know exactly when that disease is initiated. In fact, some scientists argue that autoimmune diseases, such as MS and IDDM, are due to a clinical deficit that occurs only years after the primary event. Fortunately, the investigators were able to follow, over the period of many years, the response of peripheral blood lymphocytes in patients with an isolated neurologic deficit as it evolved into clinically definite MS. As patients progressed to MS, they lost reactivity to the myelin epitopes that were recognized during the initial immune response, and developed T cell immune reactivity to other myelin epitopes. The human studies revealed smaller stimulation ratios than those that can be attained in EAE work, but were nevertheless convincing in demonstrating that the initial immune reaction certainly waned as disease progressed.

This is indeed the converse of what was described as "original antigenic sin" (15, 16). In this doctrine, the immune response to a subsequent exposure to a new strain of influenza virus boosts the response to the original strain of immunizing antigen. This doctrine pertains to both antibody and cytotoxic T cell responses to viral antigens (17, 18). It is raised as a major problem for vaccine manufacturers who would like to immunize against viral variants (19). This is a major challenge on a yearly basis for influenza vaccines, and a dramatic challenge in developing a vaccine to HIV, which is so variable. But examination of this doctrine reveals that quite the opposite seems to occur in autoimmunity. The immune response to the initiating self-antigen in autoimmunity disappears, as disease enters the stage where clinical progression and then chronicity prevail.

If intramolecular and intermolecular epitope spreading are characteristic of the immune response in autoimmune disease, would this negate the possibility of antigen-specific immune therapy? Fortunately, data from Tuohy and colleagues (20), and others (21, 22), indicate that certain dominant immune responses prevail in chronic autoimmunity, and that control of these responses can culminate in ame-

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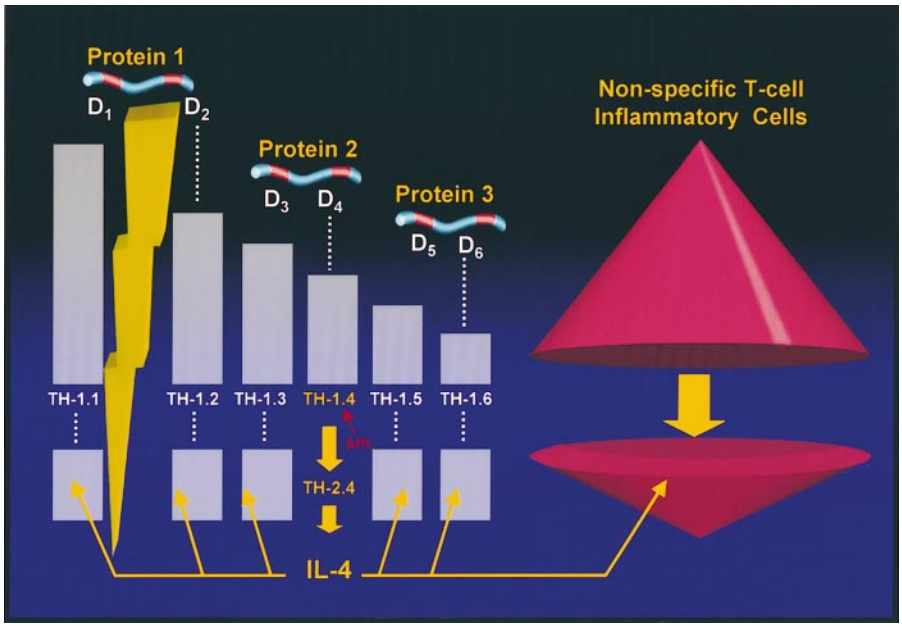

Figure 1. Mechanism for intramolecular and intermolecular epitope spreading in autoimmunity. After the initial encounter with a virus mimicking an epitope on a myelin protein, immunity to various myelin components arises. First responses often may be directed to a PLP peptide like PLPp210–244 during the initial phase of the disease. As the disease recurs or progresses, the T cell responses spread to other determinants (indicated by the letter D) on PLP, such as PLP peptide p50–59, protein 1 D_2. As intramolecular spreading occurs, the residual response to protein 1 determinant 1 wanes and becomes undetectable. The immune response spreads to other determinants on other proteins, a process called intermolecular epitope spreading. T cells can be detected that are reactive to MBP, protein 2 determinants 3 and 4, or MOG, protein 3 determinants 5 and 6. One can suppress the spreading response by giving a soluble fragment of a protein that elicits Th2 T cell responses, involving cytokines like IL-4, which subverts spreading (see APLs). The yellow arrows indicate that IL-4 is turning each Th response from a Th1 to a Th2 response (lower bars). Although the decreasing heights of the bars indicate that the sequential Th1 responses are reduced, they may be increased upon stimulation during relapses of disease. The yellow thunderbolt indicates that the initiating autoimmune response wanes, and may be undetectable as the disease progresses. In this way an entire inflammatory infiltrate can be cleared using one suppressive peptide fragment (22). The red cones on the right indicate the size of an inflammatory infiltrate, comprised largely of bystander T cells, at the site of disease. Treatment with APLs can reduce the size of these inflammatory infiltrates (22).

lioration of ongoing disease (14, 21–23). For instance, at autopsy in MS brain, T and B cells reactive to an epitope on MBP, p87–99, can be detected (3, 4). Three years ago, in the pages of this journal, Tuohy and colleagues revealed that they could block relapses of EAE, after disease was initially induced with PLPp139–151, by administering MBPp87–99 (20). They induced EAE by immunizing mice with PLP. The immune response spread intramolecularly to other PLP epitopes, and then intermolecularly to other myelin antigens, including MBP. Epitope spreading was manifest clinically as relapsing paralysis. One of the antigens targeted by the immune response after intermolecular epitope spreading was MBPp87–99. Administration of this MBP fragment suppressed further episodes of paralysis. This transacting suppression is mediated by cytokines such as IL-4 (14, 22), which are released after T cells encounter low affinity MBP peptides or altered peptide ligands (APLs; reference 14). These results implied that if one can suppress an immune response to a critical immunogenic epitope that can be detected during chronic disease, it may be possible to intervene and treat autoimmunity, despite the possibility that an alternate antigen or microbial mimic may have initially triggered the disease. An APL of MBPp87–99 is now in phase II trials of MS, based on the finding that a major T and B cell response is detectable in an MS brain at autopsy. Indeed, antibodies to MBPp87–99 can be seen in MS at the site of disease, where vesiculated myelin is demonstrable by electron microscopy (23).

There are stark differences between immunity to viral antigens, where "original antigenic sin" provides a reasonable explanation for the persistence of responses to the first encounter with virus, and autoimmunity to self-antigens, where the initial immune response wanes over time. It is also important to recognize some essential differences between autoimmunity and immunity to microbes. In autoimmunity, the antigen persists, although ancillary signals surrounding the self-constituent, such as cytokines, costimulatory molecules, and MHC, may be varied over time, thus changing the "antigenicity" of self. In immunity to microbes, the pathogen is either removed by the immune reaction or immunity is subverted, resulting in persistence of the microbe if the host survives. Elaborate microbial escape mechanisms include mutation of microbial genes and variations in microbial antigenicity, as well as the production of mediators, with the properties of cytokines and chemokines, that suppress immune attack. Often persistence involves microbial genes turning off critical genes in the host. Thus, original antigenic sin may describe how certain initial immune responses to microbes remain dominant over time. However, in autoimmunity, the response to the inciting antigen fades, whereas in microbial immunity the initial response may dominate.

There are some situations where microbial immunity and autoimmunity do share some similarities, and the concept of original antigenic sin is violated, even for viral immunity. Using MHC class I tetramers complexed with a peptide from lymphocytic choriomeningitis virus (LCMV), Gallimore et al. demonstrated that the fate of $CD8^+$ virus-specific T cells is determined in part by antigen load (24). After exposure to high doses of virus, these anti-LCMV $CD8^+$ T cells were present in the spleen during acute infection, but disappeared 2 mo later. These cells may have died from IL

starvation or activation-induced apoptosis. The characteristics of the autoimmune response more closely resemble stimulation with high doses of virus, which may resemble the persistent and sometimes "high dose" of a self-antigen. One of the problems in directly comparing these studies in microbial immunity with work on autoimmunity is that most assays in microbial systems focus on $CD8^+$-mediated cytotoxicity, whereas most research on autoimmunity involves analysis of proliferation responses in $CD4^+$ T cells.

Understanding of these differences between autoimmunity and microbial immunity is further complicated by the imaginary boundary between the world of self and the world of microbes. For example, MBPp87–99, a dominant target of the T and B cell response in MS brain, is comprised of a motif with the peptide HFFK. This motif contains the major TCR contact lysine (2), which is also the main antibody contact (4), and the major MHC anchor in the neighboring residue, phenylalanine (2). The peptide sequence HFFK is common to a large number of microbial antigens (4), including many subtypes of human papilloma virus and other viral antigens. Some of these peptide sequences from microbes can either trigger ongoing demyelinating disease (25), or protect from paralytic disease (26). Thus, it is very puzzling how the immune system can discriminate between an epitope containing HFFK, which could be derived from either a microbe or a self-constituent. Solution of this enigma might help explain the basis of self-/non-self-recognition. At present, the explanation of the persistence and dominance of the initial immune response to a virus can be explained with the concept of original antigenic sin. Yet, it is now clear that the very opposite of original antigenic sin ensues as autoimmunity develops. What may confound immunization to viruses may be a potential blessing in the design of immune therapies to counter epitope spreading in autoimmune disease.

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