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# Epitope spreading

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Epitope (determinant) spreading is the development of immune responses to endogenous epitopes secondary to the release of self antigens during a chronic autoimmune or inflammatory response. The past year has seen considerable advances in our understanding of the contribution of epitope spreading to the chronic pathogenesis of experimental T-cell-mediated and antibody-mediated autoimmune diseases. Most significantly, conclusive functional evidence for a major role for epitope spreading in the chronic pathogenesis of murine relapsing–remitting experimental autoimmune encephalomyelitis, a CD4+ T-cell-mediated model of multiple sclerosis, was forthcoming.

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**Abbreviations**

| | |
|---|---|
| **APC** | antigen-presenting cell |
| **BCR** | B cell receptor |
| **CNS** | central nervous system |
| **DTH** | delayed-type hypersensitivity |
| **EAE** | experimental autoimmune encephalomyelitis |
| **GAD** | glutamic acid decarboxylase |
| **MBP** | myelin basic protein |
| **NOD** | nonobese diabetic |
| **PLP** | proteolipid protein |
| **R-EAE** | relapsing–remitting EAE |
| **SLE** | systemic lupus erythematosus |
| **TCR** | T cell receptor |
| **TNF** | tumor necrosis factor |

## Introduction

It has been proposed that autoimmune diseases result directly from dysregulation of the immune system or as a secondary consequence of microbial infection [1,2]. Because of the promiscuity of TCRs and B cell receptors (BCRs), cross-reactivity between infectious agents and self antigens (molecular mimicry) is not rare, although such activities are better documented at the antibody level than at the T cell level. Recent evidence from animal models of autoimmune disease indicates that disease progression may be due to the activation and recruitment of autoreactive lymphocytes, regardless of the initiating event. These autoreactive lymphocytes are specific for epitopes that are distinct from and non-cross-reactive with the disease-inducing epitope, and result from chronic tissue damage (epitope spreading). Support for this hypothesis comes primarily from autoimmune models in which disease is induced with a defined autoepitope and responses to non-cross-reactive T- and/or B-cell epitopes on the same or different self proteins are assessed for pathological potential during disease progression. Induction of chronic tissue pathology by viruses also leads to epitope spreading. Epitope spreading has been demonstrated at the T cell level, particularly in relapsing–remitting experimental autoimmune encephalomyelitis (R–EAE), in antibody-mediated disease models such as systemic lupus erythematosus (SLE), and in viral diseases including Theiler's murine encephalomyelitis virus-induced demyelineating disease.

## Epitope spreading in T-cell-mediated immune responses

### Murine experimental autoimmune encephalomyelitis

Murine R–EAE currently constitutes the best characterized chronic CD4+ T-cell-initiated experimental autoimmune model and has provided much of the initial evidence in support of a major pathological role for epitope spreading in chronic disease due primarily to the precise knowledge of disease-related epitopes on multiple myelin proteins [3,4•]. Early evidence for epitope spreading in murine R–EAE models showed diversification in the number and MHC restriction of myelin epitopes that are recognized following recovery from acute clinical disease [5–9]. These reports provided intriguing evidence that the T cell repertoire is dynamic, and that recruitment of T cell reactivity to additional specificities occurs during the course of R–EAE.

#### *Recent evidence in R–EAE*

Our laboratory has examined intramolecular and intermolecular epitope spreading in the SJL/J mouse in R–EAE that has been induced with the highly immunodominant proteolipid protein (PLP)139–151 epitope or with the weakly encephalitogenic myelin basic protein (MBP)84–104 epitope [10••]. T cell proliferative and delayed-type hypersensitivity (DTH) responses to the secondary (PLP178–191) epitope, but not to the immunodominant (MBP84–104) epitope, are induced in SJL/J mice following the acute phase of both active and adoptive PLP139–151-induced R–EAE (intramolecular epitope spreading). Central nervous system (CNS) myelin damage is necessary for the initiation of epitope spreading. When induced following disease initiation but prior to the acute clinical episode, tolerance to the disease-inducing PLP139–151 epitope prevented the development of T cell reactivity to the PLP178–191 epitope, and the magnitude of PLP178–191-specific DTH responses correlated with the severity of CNS damage during acute disease [10••]. In addition, PLP139–151-specific T cell responses were activated in mice following acute tissue damage in MBP84–104-induced R–EAE (intermolecular epitope spreading). Intramolecular and intermolecular T

cell epitope spreading has also been reported in SJL/J mice in which R–EAE was induced with a T cell line specific for an MBP exon-2 encoded peptide [11•], and in B10.RIII mice primed with MBP89–101 [12•]. More recently, Yu *et al.* [13••] reported a predictable sequential epitope spreading cascade in (SWR×SJL)$F_1$ mice with R–EAE induced by the immunodominant PLP139–151 epitope. During disease progression, responses to PLP249–273 appeared first, followed by proliferation to MBP87–99, and then to PLP173–198.

*Functional evidence for epitope spreading in R–EAE*

The pathological contribution of epitope spreading to chronic R–EAE has been verified through the employment of several experimental approaches. Firstly, serial transfer studies have proven the encephalitogenic potential of responses to endogenous myelin epitopes. Splenocytes from mice in remission from PLP139–151-induced active or adoptive R–EAE that are activated *in vitro* with the relapse-associated PLP178–191 epitope transfer R–EAE into naive recipients [10••]. Similar success in the serial transfer of R–EAE by T cells activated with relapse-associated epitopes has been reported in SJL/J mice in disease that was initiated by T cell lines specific for intact MBP [8] or for an MBP exon-2 encoded peptide [11•] and in (SWR×SJL)$F_1$ mice in disease that was initiated by PLP139–151 [13••]. Secondly, PLP178–191-specific T cells are demonstrable in the CNS of mice that are in remission from PLP139–151-induced R–EAE (CJ Vanderlugt, SD Miller, unpublished data). Most importantly, induction of tolerance to the intact PLP [10••] or to the relapse-associated PLP178–191 epitope, but not to the disease-inducing PLP139–151 epitope (Table 1), protects mice that are in remission from acute PLP139–151-induced R–EAE from renewed disease progression. Similar results have been reported by Yu *et al.* [13••] in (SWR x SJL)$F_1$ mice with PLP139–151-induced R–EAE in which disease progression is blocked by tolerance to MBP87–99. These reports verify our earlier report concerning adoptive MBP-induced R–EAE [14], wherein during disease remission induction of tolerance to mouse spinal cord homogenate (a crude mixture of myelin neuroantigens), but not to the disease-inducing MBP, ameliorated disease relapses. Lastly, we have shown that during remission [15••], blockade of the CD28/B7 costimulatory pathway by treatment of SJL/J mice with anti-B7-1 Fab fragments blocked the development of PLP178–191-specific DTH responses and disease progression in PLP139–151-induced R–EAE. Collectively, these studies provide conclusive support for a dominant role of responses to endogenous myelin epitopes in mediating disease relapses.

Samson and Smilek [16] showed, in MBP-induced R–EAE in (PLJ×SJL)$F_1$ mice, that tolerance induced during remission with MBP Ac1-11[Y] protected the mice from relapse. This is in contrast to the preceding data and to the reports by others of epitope spreading in this model [5–7]. MBP Ac1-11 is the dominant encephalitogenic epitope in this system, and MBP Ac1-11[Y] is an altered peptide which tolerizes more efficiently than the native epitope. It is possible that new epitopes are not primarily responsible for the first relapse in this model or that the tolerance induced by the altered peptide works primarily via an antigen nonspecific bystander mechanism.

## Diabetes in the nonobese diabetic mouse

The nonobese diabetic (NOD) mouse serves as a spontaneous murine model of insulin-dependent diabetes mellitus, in which insulitis leads to the destruction of pancreatic β cells and consequently to clinical diabetes. T cell and B cell responses to β cell antigens arise spontaneously in NOD mice. It is generally believed that islet cell destruction is initiated by a Th1 response against the 65 kDa isoform of glutamic acid decarboxylase (GAD)65, which arises within four weeks of age, and, as the animals progress to overt diabetes, that T cell reactivity subsequently spreads to other pancreatic β cell antigens such as carboxypeptidase H, insulin, and heat shock protein 65 [17,18]. This hypothesis is supported by reports that induction of neonatal tolerance to GAD65 via intrathymic [18] or intravenous [17] peptide injections blocked the activation of responses to other β cell epitopes and the subsequent development of insulitis and diabetes.

**Table 1**

**PLP178–191 is primarily responsible for relapses in SJL/J mice primed with PLP139–151.**

| Tolerogenic treatment* | Number of relapses per mouse | Relapse frequency | Mean peak clinical score | Mean day of onset of relapse |
|---|---|---|---|---|
| Sham-SP | 8/10 | 0.80 | 2.9 | 33 |
| PLP139–151-SP | 5/10 | 0.50 | 2.8 | 37 |
| PLP178–191-SP | **2/10†** | **0.2†** | 2.7 | 38 |
| PLP139–151-SP + PLP178–191-SP | **2/10†** | **0.2†** | 2.5 | 42 |

*Mice were tolerized with $5\times10^7$ ECDI (1-ethyl-3-[3-dimethylaminopropyl]-carbodiimide HCl)-fixed syngeneic splenocyte coupled with the indicated PLP peptides following recovery from the acute phase of active PLP139–151-induced R–EAE (at approximately day 24) and observed for development of clinical relapses. †Boldfaced values are significantly different to those of mice tolerized with Sham-SP ($P<0.05$).

More recently, Kaufman and co-workers [19••] have shown that intranasal administration of GAD65 induced a Th2 response characterized by an interleukin-5 dominant T cell response and the production of large amounts of GAD65-specific $IgG_1$. More importantly, CD4+ splenic T cells from GAD65-treated mice protected NOD–severe combined immunodeficient mice from diabetes induced by the transfer of NOD T cells (40% late onset compared to 90% incidence in the controls) and also blocked the induction of proliferative responses to heat shock protein and insulin.

## Epitope spreading in antibody-mediated immune responses

SLE is a systemic rheumatic disease characterized by anti-DNA and antispliceosomal complex antibodies (anti-SM and anti-nribonucleoprotein). James *et al.* [20••] used SmB peptide epitopes, immunodominant in human SLE, to induce an SLE-like syndrome including the development of antinuclear antibodies anti-DNA antibodies, thrombocytopenia, seizures and proteinuria in mice. These animals also developed autoantibodies that bound to other non-cross-reactive spliceosomal proteins. The authors hypothesize a role for B cell epitope spreading in which B cells directed against disease-initiating epitopes mediate antigen-specific uptake of large complexes leading to the efficient presentation of self epitopes from distinct proteins that make up the complexes. Autoantibodies to both components of the La/Ro ribonucleoprotein complex are seen in SLE and are a prominent feature of Sjögrens syndrome. Intramolecular epitope spreading was demonstrated by the induction of autoantibodies to multiple nonoverlapping regions of La after immunization with the La A subfragment and intermolecular spreading was demonstrated by the appearance of anti-60 kDa Ro IgG antibodies in mice immunized with mouse or human La [21••]. Thus, the development of autoantibodies to multiple components of the La/Ro ribonucleoprotein complex follows the initiation of an immune response to a single component and epitope spreading is likely to account for the appearance of mixed autoantibody patterns in systemic autoimmune diseases.

## Epitope spreading to self determinants in viral disease

Transient production of autoantibodies commonly occurs in acute and chronic viral infections in animals and man. Most of these responses are probably not pathological and may even be immunoregulatory. Self-specific T cell responses during viral infection are less well documented. In genetically susceptible individuals, infection-induced autoimmunity has been postulated to ensue from the activation of autoreactive T cells secondary to an encounter with a pathogen by molecular mimicry [22], by the release of sequestered myelin antigens secondary to virus-specific T-cell-initiated myelin damage, that is, epitope spreading [3,4•,10••], and/or by the nonspecific stimulation of autoreactive T cells by microbial-encoded superantigens [23].

Epitope spreading has been reported in animal models of virus-induced demyelination. Splenic T cells from Lewis rats infected with measles virus or murine coronavirus, strain JHM, have been reported to proliferate in response to MBP and to transfer R–EAE to naive syngeneic rats when activated *in vitro* with MBP. No cross-reactivity between MBP and measles virus was demonstrable, however, [24–26]. Measles virus infection also enhanced the susceptibility of Lewis rats to a normally nonencephalitogenic MBP. Proliferation and Th1-type cytokine production in response to MBP has also been reported in SJL/J and B6 mice infected with Semliki Forest virus [27] and in SJL/J mice infected with Sindbis virus [28].

Infection of SJL/J mice with Theiler's murine encephalomyelitis virus induces a chronic progressive CD4+ T-cell-mediated demyelinating disease initiated by virus-specific Th1 cells targeting virus that is persisting in the CNS [29]. T cell responses to virus epitopes arise within 7–10 days postinfection, preceding the development of clinical disease which begins 25–35 days postinfection. T cell proliferative and DTH responses to the immunodominant PLP139–151 epitope are demonstrable 3–4 weeks after disease onset [4•] and DTH responses to additional encephalitogenic myelin peptides (PLP178–191, PLP56–70 and MOG92-106) are apparent 157–207 days postinfection (SD Miller *et al.*, unpublished data). Significantly, no cross-reactivity between these autoepitopes and Theiler's murine encephalomyelitis virus epitopes has been found.

Patients with infectious mononucleosis develop IgM autoantibodies to hematopoietic cell antigens p542 and p554. Anti-p542 antibodies cross-react with a shared region of Epstein–Barr virus nuclear antigen-1. Anti-P554 antibodies do not cross-react with Epstein–Barr virus peptides, however, and appear to arise via epitope spreading. Significantly, patients with progressive systemic sclerosis, SLE, ulcerative colitis, Sjögrens syndrome, rheumatoid arthritis, ankylosing spondylitis, and Crohn's disease develop high titers of IgG anti-p542 specific for non-cross-reactive determinants [30,31].

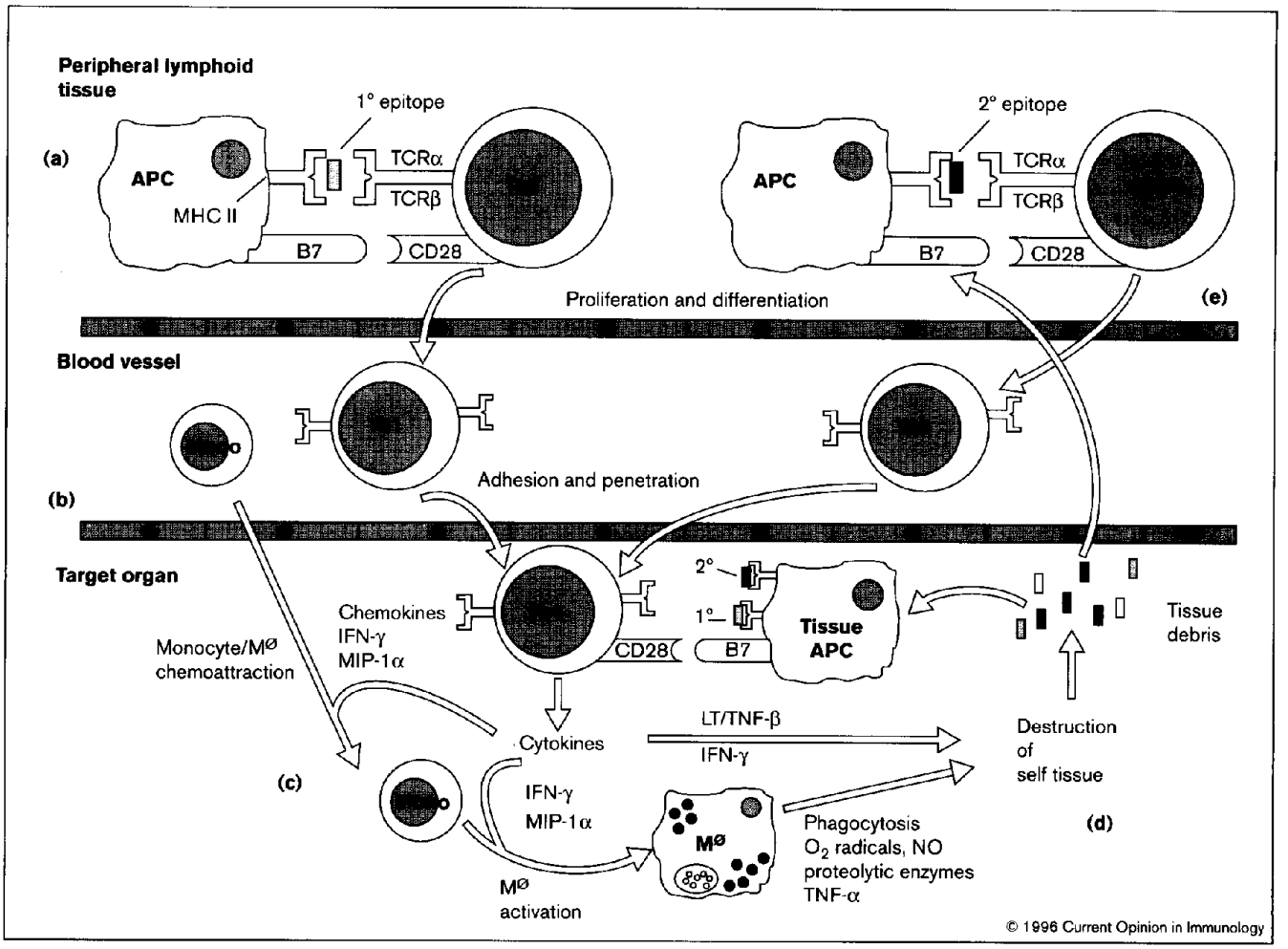
## Hypotheses and models

Sercarz and co-workers [32,33] have proposed a comprehensive model in which dominant epitopes are defined as those epitopes to which an animal initially responds when primed to a protein or an infectious agent. Responses to other epitopes on that molecule, which arise later or upon hyperimmunization, are termed secondary or cryptic. According to this hypothesis, an immune response targeting one or two dominant epitopes on a infectious agent is not sufficient. The immune system has evolved a mechanism, therefore, for increasing the number of epitopes targeted during an infection. This results in the

appearance of a response against cryptic epitopes, but can also lead to autoimmunity via the activation of autoreactive T and/or B cells which would not have undergone central or peripheral tolerance. This hypothesis has concentrated mainly on the diversification of the immune response after priming with intact proteins, for example, MBP in R-EAE, wherein responses to the cryptic epitopes arise only following initial tissue damage.

Our model for epitope spreading in chronic CD4+ T-cell-mediated autoimmune disease is shown in Figure 1 [3]. In brief, T cells specific for the initiating self or viral epitope induce the inflammatory cascade in the target organ, resulting in tissue damage. Tissue debris is taken up by macrophages and/or antigen-specific B cells and presented to naive tissue-specific T cells which, once activated, perpetuate the inflammatory response. This hypothesis is consistent with that of Elson *et al.* [34], who propose that epitope spreading is a Th1-linked phenomenon linked to altered processing of self epitopes and with the hypothesis of Mamula and Janeway [35], who suggest that antigen-specific B cells (10 000-fold more efficient than other APCs) may be responsible for the diversification of autoimmune responses.

**Figure 1**




Model of epitope spreading in chronic T-cell-mediated autoimmune disease. **(a)** Upon priming with the initiating self (1°) epitope in an appropriate adjuvant, Th1 cells are activated in the peripheral lymphoid tissue. These Th1 cells proliferate, upregulate appropriate homing receptors, traffic via the bloodstream to the blood–tissue barrier, and transmigrate (adhere and penetrate) into the target organ **(b)**. The autoreactive Th1 cells encounter antigen presented in the context of MHC class II by tissue-specific APCs triggering local secretion of chemokines and cytokines **(c)**. These soluble mediators attract and activate peripheral monocytes (Mono) and macrophages (Mø) and tissue-resident mononuclear inflammatory cells. The phagocytic activity of these activated macrophages along with the secretion of cytotoxic and proinflammatory molecules like TNF-α, nitric oxide (NO), and $O_2$ radicals cause self-tissue destruction **(d)** resulting in the expression of clinical symptoms. Tissue debris phagocytized by macrophages and/or B cells could be presented to naive T cells, which can traverse the compromised blood–tissue barrier, in the target organ and/or in the peripheral lymphoid tissue **(e)**, leading to the activation and expansion of pathological T and/or B cells specific for self epitopes (2°) other than the initial disease-inducing (1°) epitope which mediate a second wave of tissue destruction. LT, leukotriene; MIP, macrophage inflammatry protein; TNF, tumor necrosis factor.

## Conclusions

Evidence that autoimmune responses are dynamic, with specificities evolving over time, has been demonstrated in a variety of experimentally induced, virally induced, and spontaneous animal models of autoimmunity at both the T cell and B cell levels. Most significantly, evidence supporting a major functional role for epitope spreading in chronic autoimmune disease has emerged from the study of murine R-EAE models wherein disease progression can be ameliorated using either antigen-specific tolerance to the relapse-associated epitopes or blockade of the CD28/B7 costimulatory pathway. Future areas of interest include: elucidation of the factors which govern epitope dominance and the sequential pattern of epitope spreading; determination of the site of priming of T cells specific for endogenous self epitopes and study of the role of B cells and tissue-resident APCs and costimulatory requirements involved in this process; and determination of the relative efficiencies of and mechanisms by which various antigen-specific and nonspecific immunoregulatory strategies control the epitope spreading process.

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