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Epitope mimics and determinant spreading: pathways to autoimmunity

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Abstract. Infectious microorganisms have evolved molecules which mimic the host in order to aid in their undetected propagation. In response, mammalian hosts have evolved a highly diverse immune repertoire designed to eradicate rapidly changing pathogens. The generation of diversity in the immune repertoire results in potentially damaging self cross-reactivities which require multiple regulatory controls to keep autoreactive lymphocytes in check. Here, we review how molecular mimicry at the T cell level might be important in the development of systemic autoimmunity.

Key words. Determinant spreading; T cell; mimicry; autoimmunity; tolerance.

Introduction

The term 'molecular mimicry' was initially proposed by Damien to describe antigen sharing between a host and parasite [1, 2]. Host mimicry is presumably selected for in most microorganisms (particularly pathogens) in order to aid microbial attachment, cell entry, or pathogenesis, and new examples of mimicry are constantly being described in the literature [3]. Molecular mimicry is widely hypothesized to be detrimental to the host not only as a result of increased vulnerability to infection, but also due to increased risk of developing autoimmunity through the sharing of antigenic determinants between the foreign stimulus and self. Since autoimmune disease occurs primarily in adulthood, natural selection against deleterious cross-reactions between foreign antigens and self may not be very effective, and to some degree, autoimmunity can be viewed as a cost of adaptive immune responses. The continual and relatively rapid evolution of new mimics by microorganisms is likely to outpace counter-evolution in the host. Consequently, it is important that we understand the identities of common cross-reactive triggers of autoimmunity and, perhaps more important, the pathways by which these shared determinants might lead to disease.

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Tolerance and determinant spreading

Several areas of investigation currently shape our understanding of autoimmunity: immune tolerance, genetics of the immune response, and factors controlling determinant spreading. The level of immune tolerance to particular antigens depends upon their distribution (tissue specific vs systemic), form (intracellular, secreted, or membrane), abundance, and the affinity with which they are recognized. B cells emerging from the bone marrow which recognize antigens with high avidity (such as membrane-bound forms) or in high concentrations are deleted from the immune repertoire [4, 5]. In contrast, B cells encountering moderate levels of soluble antigen or recognizing antigen with lower avidity become anergic [6–8]. For many intracellular antigens, however, there appears to be little or no tolerance in the B cell compartment [7, 9–11]. This lack of B cell tolerance would seem potentially harmful in the face of numerous molecular mimics recognized by B cell surface immunoglobulin. However, B cells require T cell help to fulfill their effector function, ensuring a second

layer of protection against self-reactivity. Thus, tolerance to intracellular antigens is thought to be maintained at the T cell level [12]. According to the 'affinity' model of T cell repertoire selection [13–15], autoreactive T cells with very weak MHC recognition die by neglect, whereas strongly autoreactive T cells are deleted in the thymus. Thus, only those T cells with sufficient recognition of peptide plus self MHC (positive selection) and those which are not normally capable of becoming activated by self-antigen in the periphery (negative selection) are exported to the periphery. Nevertheless, there is ample evidence that many of the T cells forming the peripheral repertoire in normal individuals are self-reactive, having escaped negative selection due to their recognition of epitopes which are not normally presented (cryptic) or are presented at subthreshold levels required for deletion in the thymus [16, 17]. We have found a hierarchy of T cell tolerance to the nuclear antigen La (SS-B) in normal mice. T cells recognizing immunodominant determinants appear to be largely tolerized, while those recognizing subdominant (presumably poorly presented) determinants exist in normal animals and can be stimulated to provide T cell help [18]. Furthermore, normal mice immunized with a single subdominant T cell determinant of La produce a complex autoimmune response which diversifies to include other protein components of the Ro(SS-A)/La(SS-B) ribonucleoprotein complex [18].

The observation that immune responses undergo determinant spreading is a major finding shaping current theories regarding autoimmunity and molecular mimicry [19]. Complex patterns of autoimmunity can be initiated in experimental animals immunized with simple antigens derived from intracellular proteins (illustrated in fig. 1) [9, 18, 20–22]. Normal inbred mice immunized with any one protein component of the Ro/La ribonucleoprotein complex (which contains Ro52, Ro60, and La) produce a delayed, lower-titer IgG antibody response to each of the other components (intermolecular spreading). Likewise, animals immunized with subfragments of the La protein produce an intramolecular diversified antibody response to include other B cell determinants on La (intramolecular spreading) before continuing to spread to other Ro/La RNP components. The sequence of spreading is predictable for individual inbred strains, but some variation is observed among various strains of mice independent of MHC type, suggesting that background genetic factors influence the spreading response. This sort of variation is reminiscent of the variable antibody patterns to the La/Ro ribonucleoprotein complex observed in patients with Sjögren's syndrome and systemic lupus erythematosus (SLE).

While immune spreading to multiple ubiquitous intracellular antigens is likely to be of primary importance in the pathogenesis of systemic autoimmune disease, this phenomenon is not confined to systemic autoimmunity (see table 1). Indeed, immune diversification in relation to autoimmunity was first demonstrated in murine models of the organ-specific diseases multiple sclerosis and insulin-dependent diabetes mellitus (IDDM), and has recently been observed in human organ-specific autoimmune disease [23].

Proposed mechanisms by which immune spreading occurs are reviewed in detail elsewhere [19] but are be-

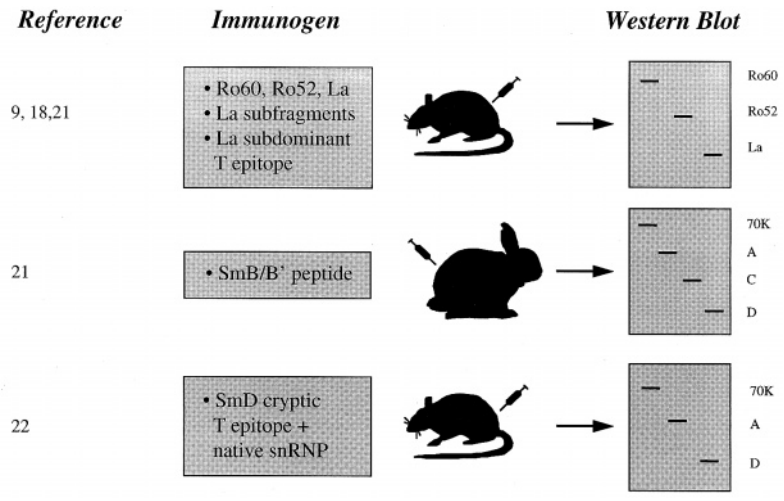

Figure 1. Serologic epitope spreading in experimental autoimmunity. Immunization of mice or rabbits with a single peptide or polypeptide derived from an intracellular antigen results in the production of autoantibodies not only to the immunogen but also to other peptides or polypeptides that are physically associated with the homologous intracellular antigen within the host.

Table 1. Selected examples of determinant spreading in animal models of autoimmunity.

System	Disease	Antigens	References
Systemic models			
Ro/La	SS, SLE	Ro52, Ro60, La	9, 20, 29, 30
Sm/nRNP	SLE	Sm (B, B′, D) U1 nRNP (70K, A, C)	21, 22, 31
Organ-specific models			
Oophoritis	autoimmune infertility	ZP3	27, 28
EAE	MS	MBP, PLP	32–34
NOD	IDDM	GAD, peripherin, Hsp65 carboxypeptidase H	35, 36
EAG	autoimmune gastritis	α and β subunits of gastric H^+/K^+ ATPase	37, 38

SS, Sjögren's syndrome; SLE, systemic lupus erythematosus; EAE, experimental autoimmune encephalomyelitis; NOD, non-obese diabetic mouse; EAG, experimental autoimmune gastritis; MS, multiple sclerosis; IDDM, insulin-dependent diabetes mellitus; nRNP, nuclear ribonucleoprotein; ZP, zona pellucida; MBP, myelin basic protein; PLP, proteolipid protein; GAD, glutamic acid decarboxylase; Hsp, heat shock protein.

lieved to involve two broad pathways: (i) the exposure of cryptic epitopes subsequent to tissue destruction or (ii) presentation of novel determinants following uptake and processing of complex antigens by B cells via their surface immunoglobulin. The latter pathway allows particular B cells to receive help from T cells of multiple specificities through classical intermolecular help. There is also some evidence that such B cells might prime novel T cell specificities [24–26]. The first mechanism is believed to be of primary importance for immune spreading in some organ-specific models such as experimental autoimmune encephalomyelitis (EAE) and IDDM. In models without tissue destruction or where spreading precedes tissue pathology, the second mechanism is suggested. In the murine oophoritis model, for example, the immune response spreads to include multiple epitopes on the ZP3 protein following peptide immunization. This spreading appears to be independent of tissue destruction, in that it still develops in animals which have undergone ovariectomy prior to the earliest signs of ovarian pathology [27, 28]. Presumably, the response is self-antigen driven without extensive tissue damage. Regardless of the mechanistic details of its occurrence, immune diversification provides a pathway for the generation of highly complex autoimmune responses potentially originating from only a single autoreactive determinant. This has obvious implications for theories of molecular mimicry and their importance in the field of autoimmunity.

The theoretical probability of molecular mimicry

Microorganisms can potentially mimic either conformational structures recognized by B cells or linear peptides recognized by T cells in the context of MHC molecules. The consequence of either type of mimicry is possible autoimmunity. Any quantitative estimation of the probability of molecular mimicry by conformational determinants is likely to be very imprecise since there are too many contingencies involved in antibody recognition. However, the recognition of T cell determinants can be broken down into the steps of MHC-peptide binding and T cell recognition of MHC-peptide complexes. There are rough rules which apply to both steps allowing us to estimate whether or not mimicry is likely. This exercise has recently been conducted by Mason [39] who argues persuasively that a high level of T cell cross-reactivity is an essential feature of T cell recognition of antigen. Mason argues that the paradigm of one T cell, one specificity would require more T cells than are feasible in a small mammal and even in humans. Therefore, T cells are destined to be polyspecific. The estimate is based on a few principles and assumptions. For example, the stringency of specificity for MHC binding and subsequent recognition by the T cell receptor does not involve every residue within the 8–18 amino acids of an average MHC ligand [13, 40, 41]. Thus, most peptides presented by MHC class II molecules require an average of two to three dominant anchor residues which control MHC-peptide binding [42–44]. Similarly, only two to three peptide residues supply the critical side chains which control interaction with the T cell receptor [45].

Accordingly, based upon (i) the level of degeneracy in MHC binding and in T cell receptor recognition, (ii) the universe of foreign peptides which might confront T cells (estimated at 10^{10}), and (iii) the physical limitation in the number of T cells we can generate, Mason [39] has made a number of estimates relating to molecular mimicry. He calculates that a single T cell has the predetermined potential to react with anywhere between 10^4 and 10^8 different peptides. Despite this remarkable flexibility in T cell recognition, T cells show exquisite

fine specificity, and the hallmark of the T cell response is a high degree of antigen specificity. One explanation for this apparent paradox is that despite the high degree of flexibility in peptide specificity of the T cell receptor (say 10^6 possible peptide ligands for a given MHC molecule), the existence of $>10^{10}$ foreign peptides to chose from means that the probability of a single T cell reacting with a random peptide is around 10^{-4}. Extensive specificity analysis of T cell clones would be required to unearth even one of the thousands of predicted cross-reactive ligands recognized by any one T cell.

Tolerance and cross-reactivity of the T cell repertoire

Given the theoretical imperative that T cells are intrinsically cross-reactive, a major task for the immune system is to cull or silence these cross-reactive specificities directed towards self-antigen. One mechanism by which this is achieved is through the tuning of T cells so that they are 30–100 times more sensitive to self-antigen during thymic selection than mature cells in the periphery [46]. This means that much lower concentrations of self-antigen are required to tolerize the developing repertoire compared with the antigen concentrations required to activate naive peripheral T cells. This concept is particularly important given that the presentation of self-antigen by antigen-presenting cells (APCs) may be skewed to high-abundance proteins, particularly membrane and secreted antigens in the case of class II molecules.

Thus, the origin of peptides eluted from class II MHC molecules, where recognizable, were derived from membrane or exogenous proteins, including fetal calf serum. Depending on the allele studied, however, these abundant peptides may account for as little as 15% of constitutively presented peptides. At one end of the spectrum, Rudensky et al. [47] found that 51–71% of peptides eluted from B lymphomas bearing I-A^b and I-E^b, respectively, were accounted for by peptides derived from six proteins, five of which were membrane or exogenous in origin. In contrast, Hunt and colleagues [41] found that the peptide spectra eluted from I-A^d was two orders of magnitude more complicated than that of I-A^b or I-E^b. Similarly, Marrack and coworkers [13] could only account for 15–35% of peptides eluted from I-A^k and I-E^k, respectively. Thus, a vast number of lower-abundance peptides (possibly up to 2000) constitutively presented by self-APCs remain to be identified and might well be derived from non-membrane intracellular proteins either by exogenous uptake of cell debris or unconventional intracellular MHC class II loading. Indeed, cytosolic proteins have been eluted from class II molecules under certain conditions [48], and pathways for endogenous intracellular antigen presentation onto MHC class II have been described [48, 49]. Efficiently presented abundant peptides derived from membrane proteins are less likely to induce autoimmunity since these will be expected to engender high levels of tolerance. In contrast, however, lower-abundance peptides, as might be derived from intracellular proteins, would be expected to be poorly tolerized and thus might be more relevant to autoimmunity in terms of molecular mimicry.

Given that a number of poorly tolerized self-peptides are likely to be presented in association with MHC molecules, is there solid evidence for cross-reactivity between foreign and self T cell determinants? Using an exquisitely sensitive assay for T cell activation, Evavold and colleagues [44] have demonstrated the existence of multiple endogenous ligands for foreign T cells. Hemmer and co-workers [42] have identified multiple cross-reactive ligands for an autoreactive T cell clone specific for myelin basic protein using a random combinatorial library approach. Other studies have documented functional cross-reactivities between foreign T cells and self ligands [43, 50], highlighting the degeneracy that exists among peptides for both MHC class II binding and T cell receptor recognition [51–55].

In summary, the current data suggest that in the context of the immune repertoire, molecular mimicry is not a rare event and in fact may be intrinsic to how the immune system functions normally. This property renders the immune system quite vulnerable to the triggering of self-reactive immune responses. Furthermore, the recently appreciated degeneracy in the recognition of peptides by T cells in the context of MHC class II leaves open the possibility that particular autoimmune disorders might have more than one trigger. While determinant spreading from a single determinant could explain simple HLA associations for complex diseases, the existence of more than one molecular trigger for a single disease might explain some cases of multiple HLA associations. In the same way, the existence of clinical subsets of patients suffering from heterogeneous diseases such as SLE may represent a triggering of this disease by different cross-reactive mimics.

Events leading to chronic recognition of self

Since naive T cells do not enter peripheral tissues, a major form of tolerance for tissue-specific antigens which do not induce thymic tolerance is their sequestration away from potentially autoreactive cells [56]. This is a form of immunological ignorance. Thus, for tissue-specific antigens such as those present in the central nervous system involved in the initiation of multiple sclerosis, activation of a T cell cross-reactive with se-

questered central nervous system antigen might be sufficient to initiate disease. In contrast, for cryptic determinants to participate in autoimmune disease induction or disease perpetuation, they must first be revealed by some perturbation of normal antigen processing and/or presentation [16, 17]. Somewhere in the middle of these two extremes lies the fate of T cells recognizing subdominant determinants, which are generated naturally but less efficiently and which therefore induce poor levels of tolerance. T cells activated by foreign cross-reactive epitopes might be able to recognize subdominant self-determinants to produce ephemeral responses leading to the induction of transient autoantibodies, an event which is known to be associated with some infections [57, 58]. The perpetuation of these responses to produce pathological conditions is likely to require some alteration in signalling between self-reactive T cells and APCs quantitatively and/or qualitatively distinct from the signalling during thymic education. Such enhanced signalling could be produced by upregulation of subdominant determinant presentation, by increased expression of HLA or adhesion molecules, by enhanced co-stimulation, by exaggerated intracellular signalling, or by some combination of any these events.

Some of the mechanisms by which antigen processing and presentation may become perturbed following infection have been reviewed [59–61]. One important pathway involves inflammatory cytokines such as interferon-γ and tumor necrosis factor-α which upregulate MHC class II expression and induce proteases in APCs that are believed to alter antigen processing [62, 63]. A second mechanism which could increase the presentation of subdominant determinants is upregulation of self-antigens by invading viruses. This has been observed for HLA class I following upregulation of viniculin expression in HIV-infected cells and might also be expected to occur in the class II compartment [64]. Another pathway perturbing antigen processing and presentation is downmodulation of membrane receptors as occurs when microorganisms use mimicry to gain cell entry by receptor-mediated endocytosis. This increase in receptor internalization may shunt some recycling receptors to degradative endosomal compartments intersecting the MHC class II pathway, while the presentation of determinants from non-recycling receptors may be increased or changed [59, 65].

Other pathways which may expose cryptic epitopes include inappropriate expression of MHC class II on certain tissues [66], antibody-mediated alterations in antigen presentation [59, 67, 68], and modification of self-antigen by viral proteins [2, 69]. B lymphocytes are likely to play a key role in the presentation of autoantigen to T cells as discussed by Liang and Mamula [70] in this volume. Therefore, differences between constitutive endogenous antigen presentation pathways and exogenous antigen uptake pathways could contribute to the induction of autoimmunity [71].

Pathways regulating autoimmunity

In the face of numerous factors capable of altering the sensitivity and outcomes of antigen recognition, and in the face of multiple foreign cross-reactive triggers, why is autoimmune disease relatively infrequent? Mechanisms regulating the activities of autoreactive T cells and self-antigen exposure must be in place to protect the majority of people from autoimmune disease. In the autoimmune-susceptible individual, the combined regulatory effect of these mechanisms is likely defective, due to polygenic influences upon multiple regulatory genes controlling immune responses and self-tolerance. Indeed, that the inherited risk of susceptibility to autoimmunity is complex and maps to multiple chromosomal loci in both mouse and humans is well established [72–77]. There are indications that some of these loci contribute independent, additive effects to risk, while others may interact in an epistatic fashion. Current models of complex inheritance must and do incorporate non-genetically encoded components to disease risk, which may be derived from environmental triggers such as molecular mimicry, or which could come from non-environmental factors such as stochastic events in lymphocyte ontogeny. While the identities of most of the genes located within implicated loci are still unknown, some of them are probably involved in immune regulation.

Not surprisingly, HLA loci are consistently linked to the probability of inheriting autoimmune phenotypes [78]. The association of particular HLA haplotypes with the production of particular autoantibodies in SLE strongly suggests that particular HLA class II alleles are directly responsible for some of this effect. This is consistent with the notion that class-II-restricted CD4 + T cells are critical for disease induction [79–83]. Similarly, HLA DR3 and DR4 are estimated to confer 35% of the total risk for developing IDDM [74]. Other HLA-linked genes influencing immune responses are likely to be involved in susceptibility to autoimmunity, but strong linkage disequilibrium between HLA class II and non-class II candidate genes has made it difficult to implicate or rule out individual gene contributions [84, 85]. Particularly strong candidate genes include those of the classical complement pathway, some of which confer definitive risk when present as total deficiencies [86]. These almost certainly influence immune complex handling but may also delay clearance of foreign antigens and alter B cell receptor signalling [75]. Other candidate genes which have been linked or strongly implicated in

autoimmunity and lie outside the HLA region are FcγRIIA, FcγRIIIB, and FcγRIIIA (CD16) [87–89].

A number of phenotypic components associated with particular genes linked to murine autoimmune disease are being dissected through the generation of congenic mice and by genetic crossing [75, 76]. Although only a few loci linked to diabetes in non-obese diabetic (NOD) mice have also been implicated in human IDDM (by mapping syntenic chromosomal regions in humans) [90], the phenotypes revealed in autoimmune mice will almost certainly uncover new checkpoints in pathways to autoimmunity which can be explored in humans. Identification of the genes in these models will also provide paradigms for understanding the complex interactions which ultimately predispose to a breakdown in immune tolerance. Some of the phenotypes associated with particular murine SLE disease genes include general lymphocyte hyper-reactivity, spontaneous loss of tolerance to particular antigens, and spontaneous expansion of peripheral CD4 + T cells [76]. Interestingly, the locus controlling spontaneous loss of tolerance resulted in the production of a specific humoral response to subnucleosomes but did not result in determinant spreading of the immune response. Thus, it is reasonable to assume that other independent genes influencing immune diversification are involved in autoimmunity. Indeed, epitope spreading in a mouse model of peptide-induced lupus was found to be genetically influenced by non-H-2 genes [31]. Additional phenotypes in murine lupus are enhanced immunoglobulin class switching and acceleration of nephritis. Many other lupus-linked loci in mice coincide with regions shown to confer enhanced responses to foreign antigens.

Several murine gene knockout, transgenic, and natural mutant models have demonstrated that perturbation of genes influencing immune regulation can induce or enhance autoimmunity. Some of these, which could represent major checkpoints in human disease, are listed in table 2. Three of the genetic mutants mentioned in table 2 cause or accelerate autoimmune disease by affecting a pathway of normal peripheral T cell selection known as activation-induced cell death (AICD). This pathway is required for reducing the number of T cells of particular clonal specificity following an immune response in order to maintain T cell homeostasis. Fas (CD95) (*lpr* in table 2) and Fas ligand (*gld* in table 2) are the primary signalling receptors involved in AICD, while signalling through the interleukin-2 receptor primes T cells for AICD by upregulating Fas ligand and downregulating FLIP, an intracellular inhibitor of apoptosis [91]. Tumor necrosis factor receptor I (TNFRI, p55; *Tnfr1* in table 2) can also signal for AICD through its intracellular death domain, which is conserved with Fas ligand. However, tumor necrosis factor receptor does not normally perform the bulk of this biological function since mice deficient in either p55 (TNFRI) or p75 (TNFRII) forms of TNFR do not show signs of disease [92–94]. Nevertheless, when p55 is deleted in mice that are also deficient in Fas, autoimmune disease is accelerated, suggesting that TNFRI can partially compensate for the loss of the Fas ligand in *lpr*/*lpr* mice [95]. Thus, although direct mutations in Fas or Fas ligand do not generally occur in human lupus [96] other genes influencing AICD are possibly important in human SLE. Overexpression of an intracellular inhibitor of apoptosis (Bcl-2) can also cause an autoimmune syndrome in mice, but does not seem to affect the AICD pathway. Rather, Bcl-2 inhibits programmed cell death (PCD), which is the result of inadequate stimulation and can be simulated by the withdrawal of growth factors in vitro [97].

Fas, TNFRI, and TNFRII all have T cell regulatory functions and are all members of the same protein family known as the TNFR family. While other members of this family have stimulatory rather than regulatory functions (CD40, OX40), another family member known as CD30 has recently been shown to fulfill a regulatory role in T cells. In an adoptive transfer model of murine diabetes, islet-specific CD8 + T cells became 6000 times more autoaggressive when derived from certain genetic backgrounds associated with CD30 knockout mice [98]. A regulatory role for CD30 has been suggested for B cells [99]. Another regulatory receptor on T cells that is critical for down-regulation of T cell activation and maintenance of T cell homeostasis is CTLA-4. Mice deficient in this gene develop severe lymphoproliferation, and death follows multi-organ lymphocytic infiltration [100–102].

Table 2. Mutant mouse, transgenic, and knockout models influencing autoimmunity

Gene	Mutant type	Checkpoint	Reference
lpr, *gld*	spontaneous	AICD	96, 104, 105
IL-2, *IL-2rb*	knockout	AICD	91, 106, 107
Tnfr1	knockout	AICD	95
bcl-2	transgenic	protection from PCD	97, 108
CD30	knockout	T cell regulation	98
CTLA-4	knockout	T cell regulation	100–102
Tgfb1	knockout	cytokine dysregulation	109–111
Tgfb1	transgenic	cytokine dysregulation	112
IFN-γ	transgenic	cytokine dysregulation	113
me/*me* *me*^{v}/*me*^{v}	spontaneous	BCR signalling	114–116
lyn	knockout	BCR signalling	117, 118

AICD, activation-induced cell death; PCD, programmed cell death; BCR, B cell receptor.

Other important known checkpoints in addition to AICD, PCD, and other forms of T cell regulation include immune regulation mediated by cytokines and B cell receptor signalling. The list of immunologic checkpoints controlling autoimmunity will likely continue to expand rapidly and some of these will be found to impact upon human disease. In addition to the possible checkpoints referred to above, evidence is mounting that the type of autoimmunity induced can determine whether it will culminate in disease. For example, the induction of a Th2-type T and B cell epitope spreading cascade to involve several pancreatic antigens protected mice from diabetes [103], whereas a Th1-type spreading cascade involving the same antigens induces diabetes [35, 36].

Are foreign molecular mimics required to trigger autoimmunity?

The events initiating autoimmunity remain undefined, and the presence of circulating autoreactive T and/or B cells in a genetically predisposed individual may inevitably lead to autoimmune disease regardless of triggering events. Indeed, for some spontaneous models of autoimmunity, environmental triggering events have not been defined (e.g. NOD mice). However, many autoimmune diseases are believed to be triggered by an infectious disease. If autoimmunity is generally triggered by molecular mimicry of a component of an infectious agent, elimination of the trigger should eliminate disease. This has been shown in some animal models such as experimental autoimmune thyroiditis [119, 120] and pristane-induced arthritis [121]. However, in other models, transfer of susceptible animals to germ-free or specific-pathogen-free facilities actually enhances disease [122, 123]. In the same way that certain cross-reactive epitopes trigger autoimmunity, others may actually have regulatory or suppressive effects. This has been demonstrated by protecting mice from adjuvant-induced arthritis by immunization with HSP60, though adoptive transfer of an HSP60-specific T cell clone induced disease [124]. Thus, the occurrence of some human autoimmune diseases might be predicted to require exogenous triggers such as cross-reactive responses with infectious agents, while the emergence of others may only be controlled by such interactions. The outcome of disease or disease regulation could depend upon the cross-reactive epitopes themselves, where the determinant could have agonist, partial agonist, or antagonistic activities [125, 126], or upon non-specific effects such as the type of cytokine environment induced during infection.

Conclusions

The generation of a highly diverse T cell repertoire has evolved in the mammalian host to fight life-threatening infections. At the same time, a number of regulatory mechanisms have evolved to prevent autoimmunity arising from the attendant and inevitable cross-reactivities of foreign determinants and self-antigen. Experimental documentation that T cell cross-reactivity is commonplace and may be an intrinsic feature of the immune system is currently emerging. While cross-reactivities at the T cell level have only recently been fully appreciated and occur more often than was originally predicted, cross-reactivites at the B cell level have long been recognized. However, cross-reactive B cells, even in the presence of a foreign trigger, require T cell help for differentiation, expansion, and autoantibody secretion. Thus, control of autoimmune T helper cell responses is probably a major checkpoint in humoral autoimmunity. The identification of common foreign ligands triggering autoimmunity may offer opportunities for therapeutic intervention. This goal, however, remains a major challenge, since these cross-reactive triggers may not possess any obvious homology with self-peptides or determinants and because multiple triggers may be responsible for initiating particular autoimmune syndromes.

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