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Molecular mimicry and the role of B lymphocytes in the processing of autoantigens

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Abstract. The immune system has evolved several mechanisms that provide lymphocytes with the intelligence to ignore self proteins while attacking foreign pathogenic agents. Notably, B and T lymphocytes that encounter self antigen at either the inappropriate levels or affinity are usually instructed to perish or become anergized. However, the presence of autoimmune disease suggests that the induction of self tolerance is not foolproof. In fact, autoreactive cells are now found to be normal inhabitants of the B and T lymphocyte repertoire. This review examines how foreign peptides which resemble self proteins can elicit autoimmunity that is amplified to many sites on a target autoantigen. In particular, B lymphocytes initiated by foreign molecular mimics can process and present self peptides in the shaping of autoimmune T cell responses.

Key words. Molecular mimicry; autoimmunity; tolerance; autoantigen; immune tolerance; epitope spreading.

Introduction

The immune system has evolved for the protection of the host from foreign pathogens. In doing so, cells of the immune system are educated to ignore the vast array of self peptides in picking out the small numbers of foreign antigens that intermittently invade the host. B and T lymphocytes, in concert with a variety of cells that may present antigen, are rapidly mobilized to clear the foreign antigen. These more obvious functions of the immune system are confounded by those instances in which autoimmunity arises. In a manner similar to the clearance of foreign antigen, immunity turned toward self proteins is highly specific to individual proteins and peptides. Autoimmunity is never found to be generalized, such that random self proteins are selected for immune attack. Specific autoimmune diseases have specific targets of autoimmune response. This observation has led investigators to seek specific mechanisms that target individual peptides in autoimmune disease.

Autoimmune responses have been postulated to be the result of foreign antigens that bear proteins of similar structure or amino acid sequence to those found in self proteins, so-called molecular mimicry. We will examine the existing evidence in support of molecular mimicry and illustrate mechanisms by which an initiating immune response from mimics may be amplified to many sites on an autoantigen. The concept of molecular mimicry is based in part on the abundant epidemiological and experimental evidence of an association between infectious agents and the presence of autoimmune disease and an observed cross-reactivity of self antigens with microbial determinants. However, direct evidence that molecular mimicry is a true etiologic basis for any form of autoimmunity has been difficult to obtain.

Although we are all commonly exposed to molecular mimics throughout our lives, autoimmunity is a relatively rare event. This suggests that regulation or suppression to self-reacting immune responses occurs when most of us encounter foreign antigenic mimics. It must also be pointed out that the concept of molecular mimicry makes little teleological sense from the viewpoint of a pathogen that has evolved mechanisms for its own survival. The pathogen will not thrive if it has provoked autoimmunity and eventual death of its host. However, the pathogen can also be thought to have mimicked its host's proteins in order to be viewed as 'self' by the immune system and evade the normal clearance mechanisms.

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Molecular mimicry as a stimulus for autoimmunity

The factors that control the immunoregulatory balance between a protective, pathogen-eliminating immune reaction and damaging, self-destructive autoreactive responses are not well characterized. The long-standing paradigm in support of the molecular mimicry hypothesis is in acute rheumatic fever [1; see contribution by Rose and MacKay in this issue]. Rheumatic fever involves autoimmune-mediated myocardial pathology that can arise following infection with group A *Streptococcus*. At the molecular level, streptococcal surface M proteins share amino acid sequence with cardiac myosin [2–5]. Serum antibodies from patients with acute rheumatic fever as well as monoclonal antibodies directed against a peptide of the streptococcal M protein cross-react with high-molecular-weight cardiac and skeletal myosin. Conversely, a monoclonal antibody raised to ventricular myosin bound the streptococcal M protein [3, 4]. Help for pathogenic autoantibody development is provided by T cell determinants that are stimulated by both streptococcal M peptides and five highly related peptides of cardiac myosin [5].

Another striking example of molecular mimicry has recently been identified in a model herpes simplex virus (HSV)-type 1-mediated keratitis, a leading cause of blindness in humans [6]. A determinant displayed on the coat protein of HSV-type 1 is recognized by autoreactive T cells also specific for a corneal self antigen. T cells that respond to both HSV-type I and corneal antigen are capable of transferring disease to naïve animals. Direct evidence for HSV-type 1 in this autoimmune disease was shown by infection with mutant viral particles (lacking the molecular mimic coat protein) which failed to elicit corneal pathology.

Other autoimmune syndromes are less easily explained by theories of molecular mimicry. Recent studies showed that myelin basic protein (MBP)-specific T cells derived from patients with multiple sclerosis could recognize quite distinct but structurally related peptides from several viral and bacterial peptides [7–9]. A database comparison was performed utilizing the amino acid anchor residues required for MHC class II binding and residues critical for T cell receptor (TCR) recognition of the MBP peptide [7]. A panel of 129 peptides of viral and bacterial sources that resembled the molecular mimicry motif were tested on seven MBP-specific T cell clones from multiple sclerosis patients. Seven viral and one bacterial peptide efficiently activated three of these clones. Remarkably, only one peptide would have been identified as a molecular mimic by sequence alignment alone. These observations modify our present understanding: foreign antigen may not necessarily share identical amino acid sequences with self protein to drive autoreactive T cell responses. This property is due to the promiscuity of the TCR to a number of unrelated peptides.

Systemic lupus erythematosus (SLE) is an autoimmune disease in which a number of intracellular macromolecules are targets of high-titer autoantibody responses. Autoimmunity to nuclear constituents including double-stranded DNA, chromatin (nucleosomes), and ribonucleoprotein particles, U1/Sm snRNPs, Ro/SSA, and La/SSB are diagnostic of SLE. The snRNP complex is composed of RNA linked to a number of proteins designated 70K and at least seven other proteins termed A through G. While the snRNP complex has an important intracellular function in the splicing of pre-mRNA, it has also served as a model autoantigen to study the progression of autoimmunity in SLE [see contribution by Farris et al. in this issue].

A role for molecular mimicry of Epstein-Barr virus (EBV) has been implicated in the induction of autoimmunity in SLE. A recurring proline-rich sequence, PPPGMRPP, is among the earliest antigenic sites to provoke a humoral autoimmune response against the B protein of the snRNP autoantigen [10]. Immunization of animal models with this peptide induces lupus-like autoimmunity, as does immunization with the closely related sequence PPPGRRP found in the Epstein-Barr nuclear antigen-1 (EBNA-1) [11–13]. Over time, epitope spreading occurred from the single octapeptide to autoantibodies that bind other snRNP proteins including D, 70K, A, and C. In support of this model, 99% of young SLE patients had seroconverted against EBV compared with only 70% of normal, non-SLE control subjects.

Epitope spreading in autoimmunity

The term epitope spreading describes the ability of immune responses to diversify to many sites on a foreign pathogen or autoantigen. Epitope spreading is commonly described in the context of autoimmune responses [14, 15]. However, epitope spreading is a basic mechanism of the immune system that has evolved for the survival of organisms, not for the development of autoimmunity. The most effective way to clear a pathogen is to attack as many different sites as possible. Moreover, it would be difficult to find immune responses to any antigen, foreign or self, directed toward only a single determinant or in which epitope spreading *does not* occur in an intramolecular fashion.

The success of our immune responses against viral, bacterial, and tumor challenges requires that multiple target sites are attacked on the offending antigen. Specific immune responses that are now revisited in the context of epitope spreading demonstrate that the B and T cell immune responses continue to evolve

throughout the course of antigenic exposure. For example, immune responses to lymphocytic choriomeningitis virus (LCMV) continuously diversify to multiple epitopes when acute versus chronic T cell responses are examined [16]. Acute T cell responses are primarily restricted to an immunodominant nucleoprotein peptide that has high affinity for class I MHC antigen. As infection persists, chronic T cell responses are directed at subdominant determinants with lower affinity for MHC. Epitopes that are selected in chronic immunity confer protection against subsequent challenge with virus. In a similar manner, acute and chronic T cell immunity diversifies in an ordered progression to epitopes on HIV and influenza [17].

With relevance to autoimmunity, recent studies indicate that the highly diverse autoimmune response in SLE can originate from a single protein or even a single cryptic self peptide without the need for foreign pathogens or molecular mimics [18–21]. Similar observations of epitope spreading have been made in murine models of multiple sclerosis and diabetes [22–24]. The explanation may be that the response originates with a single epitope and spreads in an intramolecular fashion to multiple epitopes. Although the mechanisms of epitope spreading have evolved to enhance the survival of species, the same mechanisms that generate protective diversity may also amplify autoimmune pathology when the focus of the immune response is a self antigen or self tissue. This autoimmune response is thus not a random collection of independent responses to the various snRNP component proteins but is instead a highly organized development to successive determinants on the target self antigen.

Cryptic self peptides elicit autoimmunity

The implications of molecular mimicry suggest that tolerance to self peptides is not absolute, since B and T cell subsets that recognize the mimic have never been deleted or anergized. It is logical that the immune system does not purge self-reactive lymphocytes to all possible combinations of self peptides. Indeed, this hypothesis has been examined by many studies in which synthetic self peptides used as immunogens can elicit strong 'autoimmunity'.

The term 'cryptic' peptide was first coined by the laboratory of Eli Sercarz [15] in describing immunity to a model foreign antigen, hen egg lysozyme (HEL). Simply described, immunization with selected peptides of HEL elicited T cell responses that could be stimulated by the peptide itself but not by the intact HEL protein. As an explanation, the intact HEL protein could not be processed by antigen-presenting cells (APCs) to present the appropriate stimulatory peptide to T cells. A similar explanation can be made for the induction of tolerance to self peptides. The ability of T cells to be deleted or tolerized is based on the antigen-processing functions of the APCs in the thymus or the periphery. Self peptides that are never generated in APCs never get the opportunity to delete or anergize autoreactive T cells. It is now clear that APCs cannot generate all possible self peptides from self tissues in order to purge the immune system of all autoreactive T cells [25–27].

Studies from our laboratory have exploited the concept of crypticity with respect to *self* antigens and T cell tolerance by performing 'antigen processing' at the laboratory bench with the synthesis of self peptides. These studies demonstrated that fulminant lupus autoimmunity can originate from a single molecular mimic protein or even a single cryptic self peptide [18, 27, 28]. Normal mice are unresponsive at both the B and T cell level to immunization with intact self snRNP proteins. We synthesized a panel of 25 peptides of the murine snRNP D protein which were used as immunogens in mice. We found that mice immunized with either of two cryptic self peptides (residues 26–40 or 56–70) elicited strong autoreactive T cells and autoantibodies to the D protein. This observation suggested that tolerance to the snRNP D protein is not complete and that the two immunogenic peptides are cryptic since they cannot be processed from intact autoantigen by APCs.

In similar experiments, if the immune system were then exposed to the self snRNP particle after tolerance is broken by the cryptic snRNP peptides, autoantibody responses spread to the 70K and A proteins [18]. Normal (non-autoimmune prone) mice immunized with the peptide and intact snRNP complex generated speckled immunofluorescent patterns (ANAs) resembling patterns found in spontaneous human and murine (MRL) lupus. Similarly, upon priming the immune system of normal mice with a foreign molecular mimic, the A protein of human snRNPs, the autoantibody response could then diversify to multiple protein determinants on the self snRNP particle [28]. These studies indicated that either foreign molecular mimics or cryptic peptides of self antigens could initiate autoimmunity that diversifies to many sites on the native autoantigen. Epitope spreading may arise in an 'intramolecular' or 'intermolecular' manner in which new determinants are selected either to individual sites within a single protein or to different proteins within a macromolecular complex. The latter form of spreading to proteins within a complex may be important in lupus autoimmunity where the target autoantigen is often multiprotein complexes such as the nucleosome or snRNP ribonucleoproteins.

T cell immune responses to cryptic peptides have now been implicated in the pathology of several animal models of autoimmune disease [22, 23, 29, 30]. The target of autoimmunity in experimental autoimmune

uveitis is a glycoprotein located in the retina termed interphotoreceptor retinoid-binding protein (IRBP). Immunization of rats with a foreign (bovine) cryptic peptide of IRBP leads to clinical autoimmune uveitis [29]. This study suggested that enzymes unique to the retina were capable of processing self IRBP to reveal cryptic peptides involved in the perpetuation of autoimmune uveitis. The authors surmised that normal APCs cannot enzymatically process and present the cryptic IRBP peptides.

Cryptic self peptides have also been implicated in the progression of experimental allergic encephalomyelitis (EAE), a murine model of human multiple sclerosis [22]. Many investigators have established that immunization of mice with the amino-terminal 11 amino acids (Ac1-11) of MBP (itself, not a cryptic peptide) will elicit the murine equivalent of clinical multiple sclerosis. Not surprisingly, immunization with the Ac1-11 peptide demonstrated that the early T cell responses in mice were directed at the peptide immunogen. However, as the disease progressed, T cell specificities diversified to include other cryptic peptide epitopes within the murine MBP (peptides 35–47, 81–100, and 121–140). The epitope spreading of the T cell responses correlated closely with the severity of the disease. The study suggested that after an initial priming event with the immunogenic peptide, the mouse's own MBP had entered into the progression of the autoimmune response.

Similar studies have been performed in murine models of spontaneous diabetes. Early T cell autoimmune responses in the non-obese diabetic (NOD) mouse are limited to a few immunodominant sites on the target autoantigen, glutamic acid decarboxylase (GAD) concurrent with the first expression of disease [23]. As the clinical expression of diabetes progressed over time, T cell specificity diversified to multiple sites of the GAD protein and to other β cell antigens as well.

There are several possible explanations for the development of diverse determinant targets in models of autoimmunity. SLE, diabetes, and multiple sclerosis are unlikely to be a collection of independent autoimmune responses to individual proteins of the snRNP particle or individual peptides of GAD or MBP. A second possibility is that the response originates with a single epitope and spreads in an intramolecular fashion (or within a particular tissue target) to multiple related epitopes. The latter possibility is supported by Kaufman et al. [23], who showed that T cell tolerization to GAD induced in young NOD mice inhibited the progression of autoimmunity to other β cell antigens and prevented the clinical expression of diabetes.

B lymphocytes in driving epitope spreading

Autoantibodies of SLE are clearly highly cross-reactive and promiscuous in their ability to bind proteins across many species, even related proteins down the evolutionary ladder to yeast and *Escherichia coli* [31–33]. Conversely, B cells and antibody that arises by stimulation with foreign molecular mimics have the ability to bind, process, and present the corresponding self protein. For this reason, we suspected that B cells, as autoantigen-presenting cells, may be a central feature in the generation of autoimmune diversity or epitope spreading.

In support of this notion, antigen-specific B cells elicited with either cryptic self peptides or with molecular mimics can present snRNP autoantigens in a manner that breaks T cell tolerance in normal mice [18–20, 33]. The overall mechanism of this immune response is illustrated in figure 1. In the initial phase of the immune response, professional APCs (dendritic cells or macrophages) present either foreign, molecular mimic antigens or perhaps cryptic self determinants, since either form of antigen is perceived as foreign by the immune system.

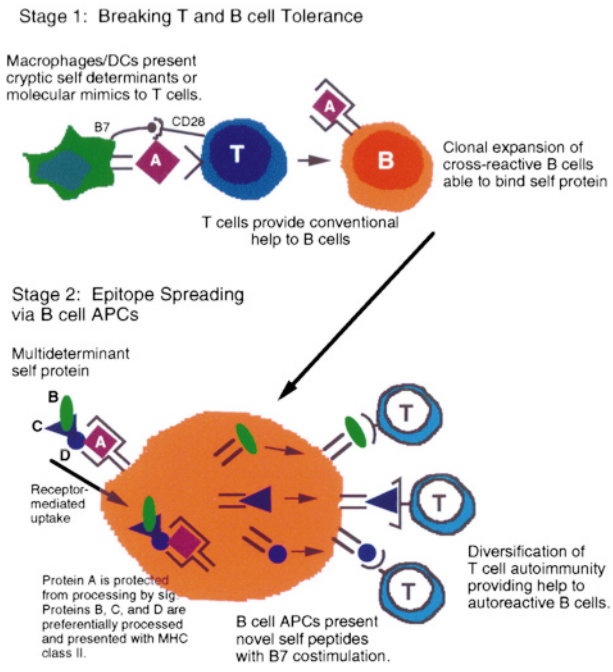

Figure 1.

It is likely that costimulation is required for this first step of T cell activation which, in turn, provides conventional cognate helper functions to B cells. This first step causes the proliferation of B cells with surface Ig receptors capable of binding and processing the native autoantigen. In the second phase of the response, the B cells present novel self determinants (or perhaps cryptic self peptides, as in diabetes or multiple sclerosis) for a second generation of T cell priming. Our studies indicate that B cells require the presence of at least the B7-2 costimulatory molecule in order to successfully activate autoreactive T cells [19]. The unfortunate product of this mechanism is a diverse and clonally expanded repertoire of autoreactive T cells. What was initially a restricted immune response has evolved to incorporate multiple determinants of the autoantigen.

Of course this mechanism is dependent on the presence and/or availability of the autoantigen to the B cell as an APC. In the absence of a source of autoantigen or if T cell tolerance (or artificially elicited neonatal tolerance) exists, epitope spreading to its diverse endpoint will not occur.

The mechanism described above was built upon the vast information that B cells are highly efficient APCs for the target antigen. Antigen-specific B cells can present peptide to T cells at up to 10,000-fold lower antigen concentrations compared to non-antigen-specific B cells [34, 35]. Moreover, receptor-mediated uptake of antigen (or self antigen) can induce B7-2 costimulators, as shown with Ig transgenic mice. The surface Ig can bind and concentrate antigen from a complex sea of self antigens, a property that may be relevant in presenting autoantigens that may be at low concentration outside cells in vivo. While small resting B cells can process and present antigen to previously primed T cells, this subclass of B cell lacks the appropriate cell surface costimulatory molecules necessary for priming naive T cells. The isotype of surface Ig (μ, δ, or γ) does not affect the ability or efficiency of the antigen-presenting function of APCs [34]. However, the cytoplasmic domain of the Ig receptor is critical for internalization of captured antigens and for directing them to the intracellular lysosomal processing compartments where peptides are generated [36, 37]. The avidity of surface Ig for its antigen is likely directly proportional to the efficiency of antigen presentation. In addition, the B cell must undergo activation from sIg as well as engagement of another surface molecule, CD40, whose ligand (CD40L) is found on the surface of CD4 T cells [38]. Antigen activation of B cells enhances the surface expression of costimulatory molecules, principally B7-2, required for the ability of B cells to break T cell tolerance [39, 40].

The fine specificity of surface Ig for its antigenic ligand can directly influence the particular peptide that is processed and transported to the B cell surface [41–43]. Antibodies have been found to confer strong effects on the stability and conformation of proteins that are bound in their cleft. In general, epitopes bound deep in the antibody cleft are protected from proteolytic degradation. Several studies by, Davidson, Watts, and colleagues have demonstrated that the specificity of surface Ig that captures antigen controls the pattern of peptide fragmentation and the subsequent specificity of T cell responses elicited [41–43]. With relevance to the diversification of autoimmune responses described above, the determinant bound by surface Ig likely is protected from (or even selected against) presentation at the B cell surface (fig. 1). For example, a determinant that is bound by the sIg of an antigen-presenting B cell will likely be protected from processing and fail to be presented with class II MHC at the B cell surface. Sites located elsewhere on the protein (or ribonucleoprotein particle) will be preferentially presented leading to a diversified T cell response. Such a mechanism could potentially account for the intramolecular diversification of T cell responses over time in the murine model of multiple sclerosis, in diabetes, or in the spreading of autoantibody specificity to multiple snRNP determinants in lupus autoimmunity.

Evidence for the importance of B cells as autoantigen-presenting cells has been found in studies of autoantibody-transgenic mice [44]. In this mouse model, all B lymphocytes bear surface Ig that originated from an anti-snRNP Ig heavy chain [45]. More than half the splenic B cells can bind and take up the snRNP autoantigen and can be provoked to secrete autoantibody. In an autoantibody transgenic mouse, would self-reactive B cells be expected to tolerize or activate autoimmune T cells? Moreover, can the specificity of T cell responses be predicted based on the specificity of autoantigen-presenting B cells? Many snRNP-reactive T cells are not deleted or anergized by transgenic B cells and their specificity is restricted to a select group of snRNP peptides, vastly different from that found in non-transgenic mice [44]. The implications of this work are that B cells presenting autoantigenic peptides can shape or dictate the subsequent specificity of T cell responses in vivo.

A unique strain of B-cell-deficient mouse has become available to examine both the progression of autoimmune diseases and pathology in the absence of B lymphocytes. Experimental murine multiple sclerosis (EAE) is still capable of arising in B-cell-deficient animals, suggesting that B cell antigen presentation functions may not be critical in the disease progression [46]. This observation is not entirely surprising since multiple sclerosis is a disease whose pathology can be induced by T cells of single specificity. Epitope spreading may not be important in the initiation of disease. However, B cells may be important in the remitting-relapsing au-

toimmune cycles that exist in the EAE murine model [46].

In contrast, murine models of diabetes and SLE fail to present most of their characteristic pathologies in the absence of B lymphocytes [47, 48]. These latter autoimmune syndromes are likely to require epitope spreading to enhance pathology. MRL-*lpr*/*lpr* mice spontaneously develop a disease that resembles SLE in humans, including immune-complex glomerulonephritis. These mice produce affinity-matured autoantibodies to snRNPs and to chromatin (DNA and histones), specificities that are disease-associated markers of human lupus. The autoantibodies generated in this mouse are of titers and isotypes (IgG1, IgG2a, IgG2b) that suggest T cell help is required for their production. MRL-*lpr*/*lpr* mice with a mutation that prevents development of mature B cells (JhD) do not develop the typical pathology of murine SLE, glomerulonephritis, vasculitis, or interstitial nephritis [48]. In contrast, wild-type MRL-*lpr*/*lpr* mice with a normal repertoire of autoimmune B cells develop severe nephritis and autoantibodies. A second feature of the MRL model of SLE is the spontaneous appearance of activated and memory T cell subsets ($CD44^{hi}$, $CD62L^{lo}$) that increase in number with the age of the animal and with the progression of disease pathology. By contrast, B-cell-deficient MRL-*lpr*/*lpr* mice fail to generate activated T cell populations that are observed in age-matched wild-type mice [48]. These results indicate that B cells and/or autoantibodies play a primary role in the activation of autoreactive T cells and in the development of the lupus nephritis and vasculitis.

Great controversy still exists over the ability of B lymphocytes to act as APCs in the induction of T cell tolerance [49–51] versus the priming of naive T lymphocytes [19, 20, 33, 44, 52–54]. Some studies have demonstrated that B lymphocytes may be important APCs in the induction of peripheral T cell tolerance to self antigens. While we will not detail all the differences between these studies, we will simply emphasize that the role of B lymphocytes as 'professional' APCs, in comparison with dendritic cells and/or macrophages, has yet to be clearly established.

Costimulation in lupus autoimmunity

The optimal activation of T lymphocytes requires the binding of accessory, or costimulatory molecules on its surface as well as the binding of the TCR to its appropriate peptide/MHC complex [55–57]. T cell anergy usually results when TCRs find their cognate peptide/MHC in the absence of costimulatory signals, a mechanism that may be important in tolerance to self antigens in the peripheral tissues.

The best characterized costimulatory molecules in this process are B7-1 and B7-2 [CD80 and CD86, respectively; reviewed in ref. 57]. Although both B7 molecules are members of the Ig supergene family, they share only 25% amino acid sequence homology. B7-1 and B7-2 are independently regulated on the surface of APCs, suggesting distinct functional roles for each in the costimulation of T cells. B7-1 is found primarily on dendritic APCs and at low or marginally detectable levels on B lymphocytes. B7-2 is constituitively expressed on dendritic cells and at low levels on B and T cells, and natural killer cells. B7-2 is rapidly up-regulated within 24 h on activated B cells while B7-1 levels increase much later in time (after 48 h) and decline rapidly thereafter. Several modes of B cell activation including surface Ig cross-linking (either by anti-Ig antibody or by antigen), lipopolysaccharide mitogen stimulation, and CD40-CD40L interactions all upregulate B7 surface expression which is a critical component in the role of B cells as autoantigen-presenting cells [19, 33]. The rapid and early upregulation of B7-2 suggests that this molecule may first influence the decision that a T cell makes in whether to become anergic or activated.

The natural ligands for B7 molecules are termed CD28 and CTLA4 [57]. CD28 is constituitively expressed on both resting and activated T cells while CTLA4 is found exclusively on activated T cells. Both CD28 and CTLA4 can bind either B7-1 or B7-2 costimulatory molecules. While the complete functions of B7-CD28 interactions are still under investigation, it is generally accepted that positive effector signals are transmitted to the T cell including the induction of cytokines (interleukin-2), apoptosis-inhibiting proteins such as bcl-xL, and CD40L. By contrast, CTLA4-B7 interactions serve as negative regulatory signalling thought to turn off T cell activation.

Since costimulation is critical in conventional immune responses, understanding whether spontaneous autoimmunity has similar requirements for B7-mediated signalling is important. Early work that has addressed this question utilized B7-blocking reagents, either anti-B7 antibodies or CTLA4Ig, the latter a soluble fusion protein of the natural ligand for both B7 molecules [58, 59]. Murine SLE in the NZB/NZW F1 mouse can be ameliorated by treatment with a cocktail of anti-B7-1/B7-2 antibodies, evident by a significant decrease in anti-DNA autoantibodies and diminished pathology [58]. However, autoimmunity in the MRL-*lpr*/*lpr* model of lupus may be less dependent on B7 costimulation [60]. Long-term treatment of MRL-*lpr*/*lpr* mice with either anti-B7-1 or anti B7-2 antibodies did not lower the anti-snRNP or anti-DNA responses and did not affect long-term survival or kidney pathology. However, treatment of MRL-*lpr*/*lpr* mice with both anti-B7-1 and anti-B7-2 together did slightly reduce titers of

anti-dsDNA and anti-snRNP autoantibodies. These studies are supported by the analysis of B7 knockout strains of MRL-*lpr*/*lpr* mice in our laboratory. Both B7-1 and B7-2 knockout strains of MRL-*lpr*/*lpr* mice have elevated titers of anti-DNA and anti-snRNP autoantibodies that arise with kinetics virtually identical to wild-type mice [60]. Interestingly, B7-1 knockout MRL-*lpr*/*lpr* mice have significantly more severe glomerulonephritis with crescent formation in the absence of endovasculitis, compared to control mice. We are presently investigating the specifity of antibody responses that arise in the absence of either B7 molecule. While these mechanisms await further examination, it is possible that MRL autoimmunity bypasses the conventional B7-mediated T cell activation pathway.

Previous studies from our laboratory have demonstrated an importance for the B7-2 molecule on B cells capable of activating autoreactive T cells [19]. B cells as autoantigen-presenting cells were generated by immunizing mice with human cytochrome c (cyt c), a foreign molecular mimic of the self cyt c protein. Antibodies and B cells elicited in this manner are promiscuous in their ability to bind both human and mouse cyt c protein. In adoptive-transfer studies, cyt-c-specific B cells were purified according to their expression of either B7-1, B7-2, or both B7 molecules. B cells capable of activating autoreactive T cells in vivo required the presence of B7-2 as costimulation. B cells bearing only B7-1 or no B7 molecules were unable to activate autoreactive T cells. These studies were performed in non-autoimmune strains of mice and it is as yet unclear whether T cell activation in MRL-*lpr*/*lpr* models of SLE have similar requirements for B7 costimulation as described above. The biological activity of B7 costimulation may differ between T cell subsets with different thresholds of activation through the TCR [57].

Overall, the induction and perpetuation of autoimmunity may depend on a variety of extrinsic factors, such as the presence of foreign molecular mimics, as well as intrinsic factors including the state of immune tolerance of B and T lymphocytes and the presence of costimulatory factors. Under the appropriate experimental conditions, B lymphocytes, stimulated by either foreign molecular mimics or cryptic self determinants, are capable of presenting novel self peptides in the initiation of autoimmune T cell responses. However, the immune system frequently has the ability to regulate untoward autoimmunity since individuals are exposed to molecular mimics throughout life. It will be a challenge to identify the regulatory mechanisms that allow cells of the immune system the intelligence to attack and clear foreign molecular mimics while ignoring the corresponding self proteins.

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