

The Mechanisms of Autoimmune Response : Insights into an Enigmatic Repertoire

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Abstrak

Makalah ini mendiskusikan penelitian-penelitian tentang mekanisme respon autoimunitas yang menyebabkan terjadinya penyakit autoimun. Kegagalan toleransi sel B dan T autoreaktif, kurang berfungsinya sel T supresor, kerusakan mekanisme apoptosis, peningkatan ekspresi superantigen, efek samping sitokin, dan kemungkinan infeksi mikrobial dianggap sebagai mekanisme yang bertanggung jawab terhadap terjadinya respon autoimunitas. Namun, terlihat bahwa sulit menerapkan satu mekanisme autoimunitas untuk menerangkan terjadinya satu macam penyakit tersebut; dengan kata lain, satu penyakit autoimun mungkin akibat dari kombinasi mekanisme tersebut. Perlu pula diteliti lebih lanjut untuk menggunakan hasil penelitian yang memakai model binatang percobaan pada manusia.

Abstract

Several possible mechanisms of autoimmune response leading to the development of autoimmune diseases are discussed briefly herein. Failure of both B and T cell tolerance, lack of suppressor T cell functions, an apoptosis defect, increased expression of superantigens, adverse effects of cytokines and possible microbial infections have all been proposed as the mechanisms of autoimmune response. Yet, none of the proposed mechanisms seems to explain satisfactorily and exclusively the development of a single autoimmune disease, suggesting that the diseases may involve complex mechanisms rather than due to a single pathway. Whether findings based upon the animal models can be extrapolated in humans remains also to be investigated further, since it would provide a direction for future bimodal therapy.

Keywords : Immunoregulation, autoimmunity, autoimmune diseases

The induction of the immune system following an antigen recognition involves highly complex interaction of all immunocompetent cells and molecules. It is in this respect that the ability to recognize both self- and non self antigens is a key feature of the immune system. Thus, failure to suppress the immune response against self antigens would result in the induction of autoimmune response;¹ however, the exact mechanism by which the autoimmune response occurs remains questionable. Distinct mechanisms such as failure of deletion of autoreactive T and B cells have been reported. Yet, whether these proposed mechanisms can explain the immunopathogenesis of all known autoimmune diseases is unclear, since each of these diseases is characteristically distinct in terms of the autoan-

tigen-activated effector cells and/or molecules. The aim of this paper is to discuss several proposed mechanisms of the autoimmune response and its association with the development of certain autoimmune diseases.

Failure of self-T cell tolerance

Both intra and extrathymic development of T cells which result in the ability of the cells to discriminate between self- and non self antigens are perhaps one of the central questions among immunologist. The precise mechanism by which these phenomena occur is still far from clear; however, two debatable pathways, i.e., clonal deletion and clonal anergy, have been put forward to explain the T cell negative selection during its ontogeny in both intra thymic (central) and extrathymic (peripheral) environment.²

Clonal deletion or elimination of self-reactive T cells is considered as the main mechanism of the T cell

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negative selection intrathymically, based on the fact that lack of self-reactive T cell clones bearing V β (T cell receptor β locus) occurs.³ In this respect, the transitional development of double negative to double positive thymocytes requires the presence of T cell receptor (TcR) β locus,⁴ suggesting that lack of this locus would result in failure of deletion of self-reactive T cells. The mechanisms by which clonal deletion occurs remains obscure. It seems that major histocompatibility (MHC) molecule-bearing thymic epithelial and mesenchyme cells determine such selection. Both cells are required to develop TCR⁻CD4⁻CD8⁻ cells to TCR⁺CD4⁺CD8⁺ cells in the thymus,⁵ whereas TCR-bearing thymocytes which recognize self antigen-presenting thymic dendritic cells would be neglected.⁶ How autoreactive T cells evade the clonal deletion-mediated negative selection remains to be elucidated; it seems that, increased expression of endogenous superantigens such as MIs in mice would result selectively in deletion of V β locus-bearing T cells (see also below).⁷

However many investigators believe that it is difficult to reconcile the clonal deletion as a sole mechanism in the T cell development. In animal models of systemic lupus erythematosus (SLE), no clonal deletion occurs and normal TCR V β expression can be detected.⁸ It has also been argued a V β usage as the mere explanation of autoimmune response due to the fact that in autoimmune diseases such as multiple sclerosis (MS), sharing TCR V β -CDR3 region rather than V β alone is commonly seen.⁹ Clonal anergy rather than clonal deletion can also be seen in a study showing that peptide-hyperactivated human T cell clones failed to proliferate, following restimulation with optimal doses of peptides.¹⁰ Using an in vitro system, it appears that following recognition of self antigens, T cell anergy is mediated by lack of IL-2 production for self growth, perhaps due to antigen presentation function of non-professional antigen presenting cells (APC).^{11,12} It has, in this respect, been shown that in transgenic mice expressing MHC class II on pancreatic beta cells, T cells recognizing transgenic proteins presented by islet beta cells were functionally tolerant, suggesting that T cell anergy caused by autoantigen recognition occurs.¹³ Thus, clonal anergy can be regarded as the mechanism of autoreactive T cell tolerance in the peripheral sites. Whether failure of peripheral T cell tolerance generating the autoimmune response is due to the function of "proper" type of APC is therefore worthy to determine. Using BXSB mice (H-2^b) which spontaneously develop SLE, insertion of E α^d gene to fertilized eggs of these mice prevented mice from hypergammaglobulin, autoantibody production and

autoimmune glomerulonephritis.¹⁴ In this study, I-E α chain-derived peptides were presented by I-A^b molecules of B cells, implying that these peptides competed with autoantigens on I-A molecules of B cells. One may assume therefore that B cells indeed present autoantigens to autoreactive T cells, but this event is preventable by other unrelated peptides. It should however be noted that clonal deletion may, to some extent, occur in the peripheral or postthymic sites, due to an extremely compelling response to immunogens.¹¹ Not surprisingly, peripheral self-T cell tolerance involves a multistep event which may in turn maintain both physical and functional depletion of autoreactive T cells.¹⁵

The evidence implicating the role of T cells, particularly CD4 cells, in the development of autoimmune diseases is overwhelming. The question remains however whether activated autoreactive CD4 cells are resulted from the failure of central and/or peripheral T cell tolerance. In myasthenia gravis (MSG) muscle acetylcholine receptor (AChR)-specific CD4 cells helped B cells to produce autoantibodies if CD8 cells were removed,¹⁶ suggesting that this autoimmune response is due to failure of CD8 cells to downregulate autoantigen-activated CD4 cells rather than failure of central T cell tolerance *per se* (see also below). In fact, suppressed AChR-specific antibody production in the MSG patient-derived B and CD4 cell coculture system was mediated by suppressor macrophages, but not CD8 cells,¹⁷ supporting the above contention. Similarly, enhanced expression of myelin basic protein (MBP) in MS may be presented by local APC such as microglial cells to naive CD4 cells which are in turn activated to become autoantigen-reactive CD4 cells,¹⁸ suggesting that peripheral T cell tolerance fails to occur. Of interest, the occurrence of this diseases is strongly associated with TCR V β -CDR3 expression.⁹ Thus, whether this disease is due to failure of central and/or peripheral tolerance remains to be elucidated. Failure to delete clonally autoreactive T cells can also be seen in the development of autoimmune gastritis in which immunisation of gastric proton pump-derived α and β subunit in the presence of adjuvant induced the organ specific autoimmune disease in an animal model.¹⁹ Based upon these findings, it seems plausible, therefore, that failure of one of the clonal selection theories would only mediate specifically certain but not all types of autoimmune diseases.

Should both clonal negative T cell selection theories not be sufficient to delete the development of autoreactive T cells, it needs other explanation to determine the persisted autoimmune response in this cell repertoire.

One possible mechanism of T cell tolerance is the "ignorance" of T cells to self antigens.²⁰ In this proposed mechanism, two possible concepts, i.e., affinity binding and accessibility, have been put forward. Clonal selection-evading autoreactive T cells would normally have low affinity in binding with self antigen-bearing APC. Under certain not yet defined circumstances, increased expression of self antigens could occur and, in turn, attract the T cell-APC binding, leading to autoreactive T cell activation. This concept comes from elegant studies using three sets of transgenic mice, i.e., RIP-K^b mice expressing class I MHC gene H-2K^b on islet β cells, Des-TcR mice expressing TcR anti-K^b antibodies and RIP-IL-2 mice expressing RIP-controlled IL-2 gene.^{21,22} No cell infiltration on pancreatic islets could be seen in RIP-K^b X Des- TcR F₁ mice, even though anti-K^b T cells were numerous. However, if RIP-K^b X Des-TcR F₁ mice were matched with RIP-IL-2 mice, β cell destruction and diabetes could occur in these triply transgenic mice. These results suggest therefore that high levels of IL-2 may enhance the expression of self-antigens which are then capable of stimulating T cell-mediated autoimmune response. The accessibility-related concept is presumably associated with the structure of antigens. Sequestered self antigen is commonly inaccessible to be recognized by T cells; however, some molecules may appropriately be presented and recognized by T cells which are then being activated. The second concept can be seen from a study showing that whole murine cytochrome c failed to induce T cell activation, but peptide 81-104 derived from these proteins elicited T cell response, suggesting that self antigen-derived certain peptides which are commonly unexposed may induce autoimmune response of T cell repertoire.²³ However, the extrapolation of these studies in the development of autoimmune diseases needs to be elucidated.

Failure of self-B cell tolerance

Using transgenic mice, it appears that the fate of autoreactive B cells closely resemble that of T cells. In transgenic mice expressing hen egg lysosome, immunisation of the lysosome has resulted in suppressed specific antibody production without physical loss of B cells, suggesting that autoreactive B cells undergo clonal anergy.²⁴ In sharp contrast, transgenic mice carrying genes encoding anti-MHC antibodies become tolerant to appropriate self antigens by deleting MHC-specific B cells, suggesting that clonal deletion occurs.²⁵ Clonally deleted self-reactive B cells have also been shown by using transgenic mice carrying genes encoding anti-CD8.2 immunoglobulin mu chain.²⁶

Activated autoreactive B cells which produce autoantibodies are believed to play a crucial role in the development of certain autoimmune diseases.²⁷ However, the mechanism by which autoreactive B cells can be activated to induce the autoimmune response is not fully understood. In lysosome transgenic mice, self-reactive B cells were inactivated.²⁸ In this study, if continuous autoantigenic stimulation was removed, these putative cells would then be responsive to LPS or CD4 cells, suggesting that self-reactive B cells may be activated polyclonally. One possibility is that polyclonal B cell activation may be enhanced by high levels of IL-6 as seen in patients with SLE.^{29,30}

Studies using the lysosome transgenic mice have also provided a line of evidence that functionally silent autoreactive B cells can be activated following an intimate T-B cell interaction. Thus, autoantigen-activated CD4 cells help naive or autoreactive B cells to produce specific autoantibodies. A support can be drawn from graft-versus-host- and chemical-induced experimental systemic autoimmune diseases.³¹ In this study, IL-4-producing CD4 cells were activated by alloantigens and chemicals such as mercury and they in turn provided signals for B cell activation to produce autoantibodies such as anti-DNA antibodies. Likewise, in vivo depletion of CD4 cells with monoclonal anti-CD4 cell antibodies has resulted in inhibition of autoantibody production in an animal model of SLE and MS.³²

During the generation of antibody diversity, somatic hypermutation of rearranged immunoglobulin V-region genes is required to produce high affinity antibodies.³³ It is in this respect that anti-DNA autoantibodies from autoimmune mice show extensive hypermutation of V-region genes and appear to have high affinity to self-antigens.³⁴ Indeed, Ig-V gene usage is seen more frequently in SLE patients than in normal subjects.³⁵ Thus, it is possible that following secondary autoantigen recognition, self-reactive B cells which normally produce low affinity antibodies and do not respond to self-antigens undergo somatic hypermutation. Despite the fact that this contention remains speculative, this pathway may reflect that these putative B cells evade the clonal anergy.

The role of suppressor T (Ts) cells

The existence of suppressor T (Ts) cells as a negative regulator of both cell- and humoral-mediated immune response is well known. Recent findings on the cytokine profile of this cell population in which Ts

cells can be divided into two types, i.e., IFN- γ -producing Ts cells type 1 and IL-4-producing Ts cells type 2, have sharpened the role of this T cell subpopulation in the immune response.^{36,37}

The exact role of Ts cells in the development of autoimmune response is still debatable and appears to depend upon the nature of specific autoimmune diseases. In the case of experimental autoimmune interstitial nephritis, tubular antigen-specific CD8 cells are the effector cells capable of developing cell-mediated immune response and damaging renal tubular basement membrane.³⁸ Surprisingly, the initial activation of these cells are inhibited by CD4⁺ suppressor cells (Ts1) which in turn induce transforming growth factor (TGF)- β 1-producing CD8⁺ cells (Ts2) acting as suppressor cells for the tubular-specific effector cell activity.^{39,40} On the otherhand, observations in diseases such as uveitis, MS and SLE suggested that Ts (CD8) cells fail to suppress the induction of autoreactive CD4 effector cells.⁴¹ In experimental allergic encephalomyelitis (EAE), an animal model of human MS, lack of functionally active TS cells occurs in genetically susceptible animals, suggesting that Ts cells are protective in EAE, perhaps via the action of Ts cell-derived TGF- β .^{42,43} Thus, adoptive transfer of Ts cells isolated from spontaneously recovery EAE inhibited the induction of EAE in the recipients and proliferation of myelin basic protein (MBP) specific T cell lines in vitro.⁴⁴ Likewise, in vivo depletion of Ts (CD8) cells using a respective monoclonal antibody increased the susceptibility to develop mercury chloride-induced autoimmune response in Brown Norway rats.⁴⁵ Functionally impaired Ts cells in these diseases have also been shown by using oral administration of the respective antigens. This route of antigen administration has led to induce specific Ts cells and reduce the course of diseases such as MS, uveitis and rheumatoid arthritis (RA) in both animal models and human studies.^{46,47} Moreover, depletion of Ts (CD8) cells in vivo by injecting anti-CD8 cell monoclonal antibodies did not prevent the induction of experimental autoimmune uveitis (EAU) in Lewis rats,⁴⁸ and accumulated evidences seem to suggest that Ts (CD8) cells function to suppress S-antigen or interphotoreceptor retinoid-binding protein-specific T cell activity in EAU.⁴⁹

Whilst the above discussion reveals that Ts suppressor cells of both CD4 and CD8 cell phenotypes play a crucial role in suppressing autoantigen-specific T cell functions, not all models follow this pathway. In MSG, suppressed AChR-specific CD4 cell activation was not associated with Ts (CD8) cell functions, rather it was mediated by suppressor macrophages.¹⁷ As yet, no

clear explanation can be forwarded for this discrepancy. Presumably, the precise time at which CD8 cells function in this disorder as seen in the murine nephritis model is important in determining the role of these cells in vivo.³⁸⁻⁴⁰

The role of apoptosis (programmed cell death)

Apoptosis is a phenomenon of the cell death driven physiologically by activated genes such as *Fas* and shown by condensed cellular cytoplasm and chromatin.⁵⁰ In the immune system, along with the possible mechanisms as discussed above, clonal deletion of both thymocytes and peripheral autoreactive T cells has been demonstrated due to apoptosis.⁵¹ Yet, it has been argued that the negative selection of thymocytes may occur due to simply terminal differentiation rather than due to apoptosis.⁷ Despite the controversial evidences, apoptosis-induced B and T cell tolerance are relevant to the possibility that autoimmune response is partly due to impaired apoptosis.

Since *lpr* gene is mapped to the same area of chromosome of *Fas* gene, it has been postulated therefore that spontaneously developed SLE in murine homozygous for *lpr* is due to defect of *Fas* gene.⁵² Indeed, it is now recognized that different strains of mice which develop spontaneous autoimmune disorders have mutation in apoptosis-associated genes. For example, in *MRL-lpr/lpr* mice, defect of *Fas* gene expression is due to insertion of a retrotransposon into the second intron of the *Fas* gene.^{53,54} These phenomena may explain lymphoproliferative disorder, loss of T cell tolerance and B cell defect occurring in these mice. The apoptosis defect seems also to occur in SLE patients as seen in a study carried out by Cheng and colleagues.⁵⁵ In this study, increase of soluble form of the *Fas* molecules was accompanied by reduced apoptosis, suggesting that increased expression of these soluble molecules would result in altered clonal negative selection of autoreactive cells which would in turn lead to initiate the induction of autoimmune disease.

The apoptosis defect may not only be associated with the failure of *Fas* gene expression, but also with increased expression of *Bcl-2* gene. *Bcl-2* (B-cell lymphoma/leukemia-2) gene is frequently translocated in immunoglobulin locus of follicular B-cell lymphoma and its expression is related with cell survival; hence, this gene functions as an inhibitor for apoptosis.^{56,57} In this respect, Strasser and colleagues have shown that enhanced expression of *Bcl-2* resulted in sustained

survival of B cells and aged transgenic mice carrying this gene developed autoimmune disease.⁵⁸ In SLE patients, circulating CD4 and CD8 cells, but not B cells, expressed high level of Bcl-2 protein, whereas increased expression of Bcl-2 mRNA in mononuclear cells could be seen, suggesting that dysregulation of apoptosis in lymphocyte population may occur in these patients.⁵⁹ These findings demonstrate that altered Bcl-2 expression may result in the failure of autoreactive B and/or T cell deletion which in turn accelerates the autoimmune response. The precise mechanism by which altered Bcl-2 gene expression occurs in autoimmune disease is however uncertain, since several evidences revealed that Bcl-2 gene failed to induce the survival of self-reactive B cells.⁵⁷ Of interest, insertion of retroviral gene into the myeloid leukemia cell line (HL-60 cell line) was able to over-express this gene.⁶⁰ By analogous, one may assume that viral infections which are suspected to associate with certain autoimmune diseases such as type I diabetes mellitus⁶¹ may increase the expression of this gene, leading to induce longer life-span of both autoreactive B and T cells. The

contention remains speculative and needs to be investigated further.

The role of superantigens

Superantigens such as Staphylococcus enterotoxins B (SEB),⁶² group A streptococcal antigens⁶³ and mouse mammary tumor viruses (MMTV)⁶⁴ have been shown to activate T cells specifically and more efficiently than in the classical MHC-peptide interaction. Unlike the classical T cell recognition in which antigens must be processed and presented by APC in small peptides, superantigens can be presented as entire molecules. In fact, crosslink between MHC and TcR molecule, especially at V β region, can be mediated by superantigen at the lateral site, whereas classical antigens lie in the relatively centre site of the interaction (see Figure 1).⁶⁵ Food poisoning and toxic shock syndrome are among the diseases associated with superantigens.

The role of superantigens in the development of autoimmunity has been a focus of investigations, but

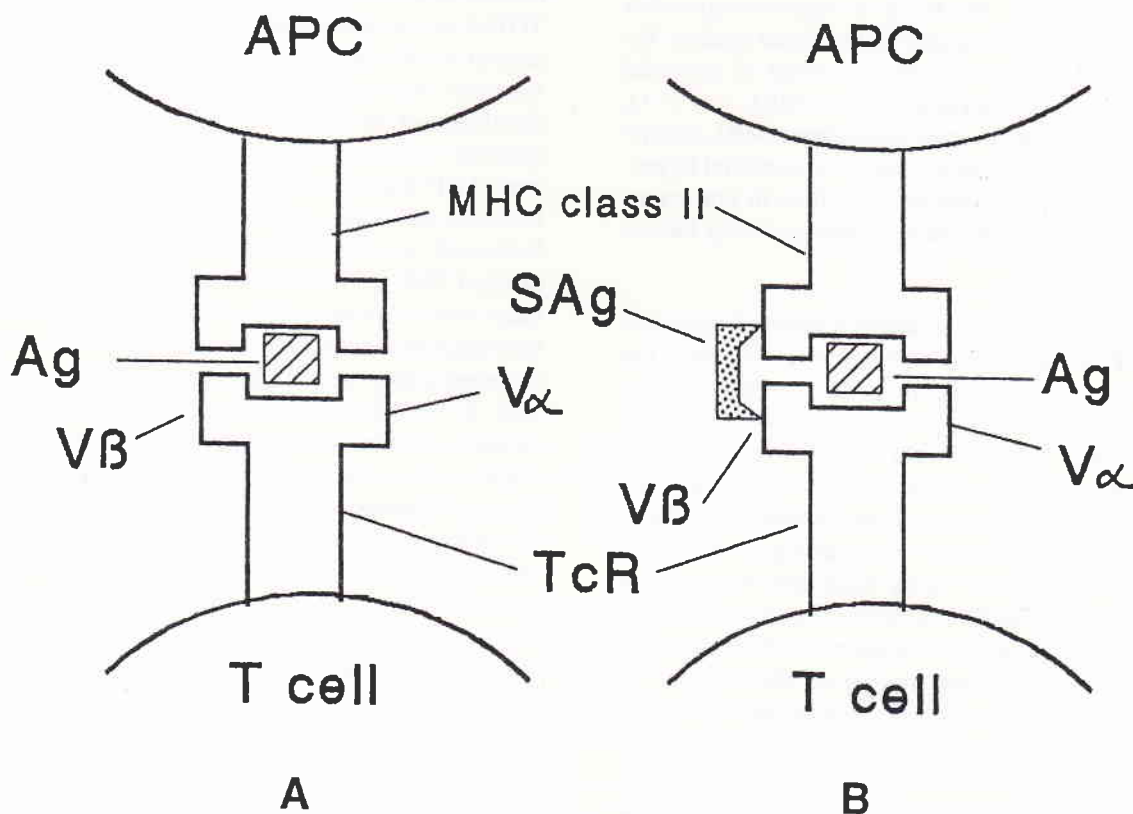


Figure 1. Antigen and superantigen recognition involving MHC and TcR molecule interaction. CD4 and CD8 molecule amplify the interaction, but are not shown herein (A). Processed antigen peptides (Ag) are presented by antigen presenting cells in association with MHC class II or class I molecule to T cells bearing T cell receptors (TcR). (B) Superantigens (SAg) crosslink the V β region of TcR and MHC class II molecule.

not yet precisely defined. Since such antigens can induce polyclonally B cell and specifically T cell activation, one or two cells in the autoreactive cell repertoire may be activated; with other words, superantigens may break the existence of self-tolerance. Rheumatoid arthritis (RA) and MS are among autoimmune diseases in which superantigens may involve.⁶⁵ In the case of MS, retroviruses have been believed to play a role, suggesting microbial infections may be involved.⁶⁶ Two separate lines of evidences may support the role of superantigens in MS. First, T cells infiltration in the central nervous system in EAE were predominated by Th1 cells.⁶⁷ Secondly, superantigens induce preferentially Th1 cell activation, at least, via the production of TGF- β .⁶⁸⁻⁷⁰ Furthermore, increased number of V β 17-positive T cells in patients with RA, compared to those in the controls could be observed, suggesting that the development of RA may be associated with superantigen infections.⁷¹ One should however be cautious in extrapolating this study into a general conclusion, since this study did not show whether increased number of this cell population was accompanied by increased expression of superantigen-derived peptides. A direct evidence showing a superantigen-RA relationship comes obviously from animal models. Injection of SEB resulted in high number of synovial cells in V β 8 TcR transgenic mice (MRL - + / +), compared to those in non transgenic MRL-*lpr/lpr* mice.⁷² In this study, higher degree of synovial hyperplasia was seen in transgenic mice than in non transgenic mice, suggesting that superantigens may induce chronic arthritis.

It seems plausible that superantigen-induced autoreactive B or T cell activation still needs to encounter the respective autoantigens, in order to develop the specific autoimmune response.⁶⁵ In EAE, superantigen-activated T cells would then be reactivated by MBP presented by microglia cells or astrocytes in the brain,^{16,73} suggesting that the secondary autoantigen challenge is required in superantigen-mediated autoimmune response. Using SEB and toxic shock syndrome toxin (TSST)-1, a superantigen produced by *Staphylococcus aureus* B, it appears that both superantigens bound to the same region of HLA-DR1.^{74,75} These studies also revealed that whilst the binding of these superantigens onto the region of DR1 molecules was dependent upon the classical antigen peptides, they did not block each other completely, suggesting that the classical antigen peptides direct the superantigen binding and that superantigen-induced T cell activation may still be dependent upon the antigen peptides. These findings imply therefore that the secondary challenge by the respective autoantigens is

indeed a prerequisite in determining the role of superantigen-associated autoimmune response; with other words, superantigens may be a predisposition in the induction of autoimmune response. Care should however be taken in extrapolating the data based upon V β expression into the possible role of superantigens in these diseases, since the idea of V β -associated autoimmune diseases still needs to be investigated further.⁹ Indeed, V α expression would also be important in determining tight MHC-TcR-superantigen interaction if the MHC-superantigen crosslink is weak.⁷⁶

The role of cytokines

During antigen-driven immune response, signals provided by cytokines to activate the immunocompetent cells and molecules are prerequisite. Indeed, cytokines are not only important in protection, but also in maintaining autoreactive B and T cell activation and inducing tissue destruction.⁷⁷ Cytokines such as IL-6 may in fact induce secretion of proteinases such as granzymes which in turn damage target cells and release autoantigens as seen in multiple sclerosis.⁷⁸ TGF- β can be protective in this disease as seen in an animal model, perhaps by inhibiting IL-1 production, whereas this cytokine has been implicated in the development of RA, by recruiting leukocytes in the synovial tissues.⁷⁹ However, injection of monoclonal anti-TGF- β antibodies reduced the severity of streptococcal cell wall-induced arthritis in a rat model.⁸⁰ Increased levels of IL-4, IFN- γ and IL-1, but suppressed TNF- α in SLE have also been reported.³⁰ The exact role of these impaired cytokine levels in SLE is still obscure; likely, high levels of IL-5 may play a role in determining the activation of CD5⁺ B cells which may in turn produce autoantibodies in SLE.⁸¹ This cytokine profile of SLE patients is in fact parallel with studies using the animal models. For example, continuous injection of anti-IL-10 antibodies in NZB/W F1 mice resulted in reducing the severity of spontaneously developed lupus-like autoimmunity and increased serum levels of TNF- α .⁸² These findings suggest therefore that TNF- α is protective in SLE. In insulin-dependent diabetes mellitus, monocyte-derived IL-1 may be destructive to islet beta cells which would then release their autoantigens.⁶¹ Increased levels of IFN- γ in Behçet syndrome have been suggested to upregulate NK cell activities.⁸³ Likewise, the induction of cellular immune response in blister formation as well as increased autoantigen gene expression in cultured keratinocytes has been associated with excessive production of IFN- γ in bullous pemphigoid.^{84,85}

The regulatory roles of cytokines such as IL-1 and TNF- α in the development of RA are of interest. High levels of IL-1 in the synovial fluid suggest that this cytokine plays a crucial role in this disease. In response to IL-1, synovial fibroblasts of RA patients produced MCAF (monocyte chemotactic and activating factor) and PGE₂, suggesting that IL-1 may involve in macrophage accumulation and both pain and edema associated with rheumatoid synovitis.^{86,87} If treatment of RA patients with methotrexate (MTX) has resulted in reduced IL-1 levels of synovial fluid,⁸⁸ this treatment regiment might decrease the severity of RA. Furthermore, one of the TNF- α activities in RA may be associated with hyaluronan (HA), a marker of synovial proliferation, since increased HA production is significantly correlated with increased levels of this cytokine.⁸⁹ The most important role of this cytokine in RA is perhaps related with its ability to induce IL-1 production, but suppress GM-CSF production, suggesting that downregulated TNF- α production would be beneficial.⁷⁷ Indeed, injection of anti-TNF- α antibodies before or during the arthritis process significantly suppressed the severity of collagen-induced arthritis in mice.⁹⁰

The role of microorganisms

Certain microbial antigen-derived peptides which are presented by MHC class II molecules share homology with self peptides derived from HLA-DR α , suggesting that microbial peptide-activated T cells may be able to recognize self-antigen presented by MHC class II and initiate autoimmune response. This phenomenon is termed as the antigenic mimicry. For example, in ankylosing spondylitis, *Klebsiella* organisms can modify HLA-B27 negative to -B27 positive like persons, suggesting that infection due to these organisms may enhance the individual susceptibility to develop this autoimmune disease.⁹¹ Other microenvironmental antigens such as a 75 kD heat shock protein (Hsp70) of *Trypanosoma brucei*, RfbA protein of *Salmonella typhimurium*, and periplasmic protein of *Treponema pallidum* have shown to have amino acid homology at certain position with HLA-DR α sequence, implying that these antigens may trigger the development of certain autoimmune diseases.⁹²

The antigenic mimicry hypothesis seems to rely on the existence of HLA-DR expression, but it may not always be the case for the development of certain autoimmune diseases such as RA. Some of the population carrying HLA-DR1 or DR4 β do not develop this disease, suggesting that a definite conclusion to show

a correlation of HLA-DR expression and RA is scanty.⁹³ In fact, mycobacterium-induced infection shows similar features seen in this autoimmune disease. Thus, elevated levels of rheumatoid factors, agalactosyl immunoglobulin G, and antibodies to mycobacterial Hsp65 can be detected in this infection, suggesting that rheumatoid arthritis is a slow bacterial infection.^{94,95} The mechanism(s) underlying this phenomenon is unknown and needs to be elucidated further. It has been postulated that microbial antigens originated from extra-articular sites such as the gut or lung would be processed and presented by synovial APC to activate T cells which in turn trigger synovial macrophages to release tissue-damaging mediators.⁹⁵ Perhaps, the slow bacterial infection may also be a good candidate in explaining the pathogenesis of Behçet's syndrome, since high levels of IgA and IgG antibodies from patients with this disease react with 65 to 70 kD heat shock protein (Hsp) derived from *Streptococcus sanguis*.⁹⁶ It is unclear how these microbial antigens induce this disease. Yet, it may be that the pathogenesis of Streptococcal HSP65-induced Behçet syndrome is similar to that of Mycobacterial-induced RA, since *S. sanguis*-derived Hsp65 shares homology to Mycobacterial Hsp65 and high levels of antibodies specific to both microbial antigens can be observed in both autoimmune disorders.⁹⁶ Of interest, Hsp60-derived amino acids 336-351 and 136-150 which are T epitopes of this syndrome were able to induce uveitis in Lewis rats,⁹⁷ suggesting that mycobacterial infections may induce both autoimmune diseases.

CONCLUSION

Distinct mechanisms implicated in the induction of autoimmune response have been proposed; however, it seems that none of them is able to explain satisfactorily and exclusively the occurrence of a single autoimmune disease. It is safely to say that the induction of autoimmune response is a complex interaction involving many possible pathways. Of important, other effector molecules such as complements, idiotypic antibodies and adhesion molecules may also play a crucial role in the induction of these diseases. Fresh ideas with substantial evidences, at the present time, are desperately needed to delineate this phenomenon. A slow bacterial infection as a possible etiology of the autoimmune diseases is perhaps one of the examples to open the dead lock, since it may provide a direction for future therapeutic bimodal. It should also be kept in mind that previously described works in elucidating the mechanisms of autoimmune response were mainly carried out in the animal models,

extrapolation of these findings in humans remains speculative and needs to be investigated further.

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