Principles of autoimmunity: Part I - Induction of autoimmunity

Raj Raghupathy

Mechanisms of immunological self-tolerance normally protect us from self-reactive immune responses, and the immune system generally directs its arsenal against foreign antigens. However, failures of immunological tolerance do occur and thus inappropriate self-reactive or autoimmune responses and diseases do occur. Autoimmune diseases affect about 5-7% of adults and have implications on health and socio-economic aspects considering their debilitating effects. The first of this two-part article discusses mechanisms that normally eliminate or control potentially self-reactive lymphocytes and then discusses events that lead to the loss of one or more of these preventive mechanisms that eventually result in autoimmunity and autoimmune damage. The second part of the article is directed at discussing mechanisms of autoimmune tissue damage and basic principles of immunologic treatment of autoimmune diseases. In other words, Part I of this article describes why autoimmune diseases occur, while Part II deals with how autoimmune damage is mediated as well as principles of immunologic treatment of autoimmune diseases.

Key words: autoimmunity, autoimmune diseases, immunological tolerance

Bull Kuwait Inst Med Spec 2006;5:22-25

This two-part article, *Principles of autoimmunity*, is designated as CME/CPD. Readers who study it, answer the questions related to it on page 29, and send a copy of the Answer Sheet (page 54) to the CME Center of KIMS become eligible for 1 CME/CPD credit in Category 1 in the MPC Program of KIMS. To claim credit, the reader has to be registered in the MPC Program, the answer sheet should be received by the CME Center before 31st May 2007, and all questions should have been attempted. Readers would then receive a certificate from the CME Center indicating the credit data.

The immune system exists to guard us against microbial invasions. It is responsible for defending us from the constant threats of infections. In fact, the role of the immune system is to attack and eliminate 'non-self' while at the same time leaving 'self' undisturbed. To fulfill this role, the immune system is equipped with the ability to distinguish between self and non-self; it has specialized molecules and cells that detect and distinguish self and non-self as well as molecules and cells that attack and eliminate non-self.

Interestingly, while one might think that lymphocytes in the immune system recognize only 'foreign' or non-self antigens, this is not entirely true. Most T cells and B cells recognize foreign antigens but some T and B cell receptors do indeed recognize self antigens. Thus, self-reactive lymphocytes are produced and do exist, and obviously this is potentially dangerous. What if self-reactive lymphocytes get activated? Would these cells not attack the body's own cells, tissues and organs, and cause deleterious autoimmune responses?

In this two-part article, we will discuss mechanisms that normally eliminate or control potentially self-reactive lymphocytes, that is, mechanisms that prevent reactions against self-antigens. We will then discuss events that lead to the loss of one or more of these preventive mechanisms that eventually result in autoimmunity and autoimmune damage. Thus, in Part I of this article published here, we will discuss why autoimmune diseases occur. In Part II appearing on pages 26 to 29, we shall discuss how autoimmune damage is mediated, as well as principles of immunologic treatment of autoimmune diseases.

Immunological Tolerance

As lymphocytes undergo development within each individual, the antigen-specific receptors on T lymphocytes and the immunoglobulins in B lymphocytes are generated afresh, with specificities for all kinds of antigens. Initially this is a random process with T cell receptors

Professor of Immunology, Faculty of Medicine, Kuwait University, and Consultant Immunologist, Mubarak Al-Kabeer Hospital, Kuwait.

Correspondence: Prof. Raj Raghupathy, Department of Microbiology, Faculty of Medicine, Kuwait University, P.O. Box 24923, Safat. Kuwait 13110; Tel.: 965 5319602, email: raj@hsc.edu.kw

(in T cells) and immunoglobulins (in B cells) being generated with a large and diverse variety of antigen specificities; these specificities will of course include those against non-self and those that are potentially reactive for self antigens. The immune system has a selective method by which T and B cells that are specific for non-self are allowed to persist while those that are self-reactive are eliminated. This method is referred to as *immunological tolerance* and the immune system is in a state of *tolerance*—the normal state in which immunity is maintained for use against infections and foreign antigens, i.e. non-self, and not for reactions against self.

Immunological tolerance is established by a process called *thymic education*; a process that teaches immune cells what is self and thus, what is non-self. As early developing T cells circulate around the body, they undergo a 'negative selection' in which T cells which have receptors specific for 'self' antigenic peptides are given a death signal and undergo apoptotic death. Generally about 99% of early T cells that begin the developmental process are actually eliminated due to self-reactivity.

B cells also undergo a form of negative selection in the bone marrow; B cells expressing immunoglobulins specific for self antigens are eliminated. These methods of eliminating self-reactive T and B cells are referred to as *central tolerance*. Clearly this process is not foolproof; surely not all the millions of self antigens can be expressed in the thymus and bone marrow, thus T and B cells with specificity for self antigens can and do survive negative selection. Many such lymphocytes with the ability to recognize and bind self antigens still enter the blood circulation. To handle this potential and real problem, peripheral tolerance mechanisms operate to control or eliminate these cells at the level of secondary lymphoid organs, i.e. in the periphery. These mechanisms include those such as *anergy*, a state of induced non-responsiveness to self antigens; if such mechanisms did not exist, for example, for self-reactive cytotoxic T (Tc) cells, presumably these cells could kill cells that express the self antigens. *Clonal anergy* refers to the maintenance of self-reactive T cells in a non-responsive state. Besides anergy, peripheral tolerance is also maintained by the presence of suppressor or regulatory cells that inhibit autoreactive lymphocytes.

Bypass of Immunological Tolerance

Thus, the immune system is equipped with both central (in the primary lymphoid organs) and peripheral (in secondary lymphoid organs and in circulation) tolerance mechanisms to prevent and control autoimmunity. Given these mechanisms, one might imagine that autoimmunity would not occur; how then do we develop autoimmune reactions? Clearly, while mechanisms of self-tolerance normally protect an individual from potentially self-reactive lymphocytes, there are failures; these failures result in inappropriate responses of the immune system against self antigens, a process termed autoimmunity. The existence of autoimmune diseases is proof that neither central nor peripheral mechanisms of tolerance are entirely successful.

How then is self tolerance bypassed or broken? Several situations can lead to the bypass or breakage of self-tolerance. These include:

1. Molecular mimicry
2. Exposure of hidden antigens
3. Formation of new antigens
4. Loss of suppressor function
5. Epitope spreading
6. Cytokine dysregulation
7. Polyclonal activation of B cells

MOLECULAR MIMICRY

A number of viruses and bacteria have been shown to possess antigenic determinants that are identical or similar to normal host cell components; such 'molecular mimicry' has been shown between polio virus and the acetylcholine receptor, papilloma virus and the insulin receptor, measles virus and myelin basic protein, to name a few. In fact, peptides from the myelin basic protein, a molecule expressed on myelin sheaths enclosing nerve fibres, are mimicked by peptides from several viruses including influenza, polyoma, poliomyelitis and hepatitis B viruses. Infection with some of these viruses expressing peptides that mimic self components such as myelin basic protein, may induce autoimmunity to those self components. An example of molecular mimicry leading to autoimmunity is heart damage that sometimes follows rheumatic fever, an inflammatory disease that develops from pharyngeal infection with *Streptococcus* *pyogenes*. Antibody responses generated against antigens of *S. pyogenes* cross-react with antigens of the heart valve and cross-reactive antibodies generated against the bacterial antigens can cause damage that can impair cardiac function.

Another example of molecular mimicry in autoimmune diseases is Type 1 diabetes mellitus, a condition in which the immune system attacks and destroys pancreatic islet β cells which secrete insulin. Antigenic cross-reactivity has been demonstrated between the pancreatic islet β cell enzyme glutamate decarboxylase and the viruses Cocksackie virus and cytomegalovirus. This antigenic cross-reactivity results in the stimulation of T lymphocytes which attack and destroy the pancreatic islet cells, leading to diabetes mellitus.

Cross-reactive *stress proteins* are also believed to be involved in the pathogenesis of some autoimmune diseases. These are a series of evolutionarily preserved proteins expressed in increased amounts by cells when subjected to a range of different stresses such as heat, hypoxia and physical trauma. Stress proteins induced by heat are called heat shock proteins (HSPs) and are found in cell types from bacteria to humans. Thus, in the case of bacterial infections, the host immune system may mount an immune response to bacterial HSPs. These anti-bacterial HSP antibodies may cross-react with human HSPs in an apparent autoimmune response. In rheumatoid arthritis, for example, T cell responses have been demonstrated against one such heat shock protein, HSP70 which cross-reacts with proteins in the Epstein Barr virus and *E. coli*.

EXPOSURE OF HIDDEN ANTIGENS

The second situation that leads to breakage of self-tolerance is when an immune response occurs to antigens that are usually 'hidden' from the immune system. During thymic education described earlier, induction of tolerance to self antigens involves only those antigens that are 'seen' by developing T cells in the thymus. Thus, when previously hidden antigens are revealed, they could well become targets for T cell responses. The immune system does not normally 'see' these so called sequestered (or hidden) antigens. For example, spermatozoa are not normally exposed to the immune system because the seminiferous tubules are sealed off during fetal development and also because sperms arise late in development and are not, therefore, seen in the thymus during lymphocyte development. During thymic education of T cells and negative selection of B cells in the bone marrow, these sequestered antigens are not encountered by T cells and B cells. Thus, T and B cells specific to spermatozoal antigens do persist in the body but do not normally encounter these antigens; however, if these antigens are exposed due to testicular injury or after vasectomy when sperm antigens are released into the circulation, these self antigens will be viewed as foreign and may be attacked by immune cells. This has been suggested to lead to immunologically-mediated infertility in males.

The testis is thus an example of an immunologically privileged site, i.e. a site which is sheltered from the immune system. The anterior chamber and cornea of the eye, the brain and the uterus are other examples. The cornea, for instance, is sheltered from the immune system due to low exposure to vasculature, but if the cornea is breached by injury or infection, the immune system gains access to this site and may view actual self antigens as foreign, and may mount immunological attack. Similarly the release of heart-muscle antigens after myocardial infarction has been shown to lead on occasion to the formation of autoantibodies.

FORMATION OF NEW ANTIGENS

Sometimes 'new' antigens, also known as neoantigens, are formed by modification of self antigens by chemical binding with another reactive molecule; this may result in provocation of the immune system and subsequent immunological attack which is similar to that seen in autoimmune tissue damage. For example, several drugs are capable of binding to erythrocyte cell surfaces in the body, creating neoantigens—examples of such drugs include penicillin, cephalosporins, salicylic acid, sulfonamide and streptomycin. These neoantigens on erythrocyte surfaces may stimulate the production of antibodies which may bind to erythrocytes and cause complement-mediated lysis of erythrocytes, a condition called drug-induced hemolytic anemia.

LOSS OF SUPPRESSOR FUNCTION

Some autoimmune responses are kept under control by the action of suppressor cells; loss of this suppressor function can result in a lack of control over this response and subsequent autoimmunity. This has been proposed to be one mechanism for the induction of autoantibodies against nucleic acids and chromosomal proteins seen in systemic lupus erythematosus (SLE). Aside from peripheral tolerance maintained by regulatory T cells, other factors such as hormones and cytokines may be involved in restraining potentially autoreactive cells under normal conditions. Presumably a deficiency in any of these hormones (e.g. steroids) and cytokines (e.g. transforming growth factor-β) may increase susceptibility to autoimmunity, by allowing the restrained autoreactive cells to get activated.

EPITOPE SPREADING

Epitope spreading is yet another mechanism that triggers autoimmune reactivity. Sometimes infections in tissues can result in the induction of defensive immune reactions that are geared to destroy the microbes, but in doing so, result in damage to neighboring tissues. This damage to an unintended target (i.e. host tissues) is often referred to as 'innocent bystander' damage. For example, infections of areas rich in myelin, such as the myelin sheath that encloses neuronal axons can result in the triggering of immune responses that cause innocent bystander destructtion of the myelin sheath; this may result in the activation of new responses to myelin itself leading to further destruction of this important barrier and subsequent infiltration by immune molecules and cells.

CYTOKINE DYSREGULATION

Cytokine dysregulation has also been suggested to be responsible for triggering anti-self responses. Some cytokines such as interferon-γ (IFNγ) can induce the expression of Class II HLA molecules on cells that do not normally express these molecules; when Class II HLA molecules are induced inappropriately, these molecules may then present self antigens that are not normally presented to T cells, leading to responses against self. For example, pancreatic β cells of individuals with insulin-dependent diabetes mellitus express high levels of class II HLA molecules, whereas healthy β cells do not express Class II HLA molecules. Similarly, thyroid cells from those with Graves' disease have been shown to express Class II molecules on their cell membranes. Class II HLA molecules are normally expressed only on antigen-presenting cells (i.e. macrophages, dendritic cells and B cells) and the inappropriate expression of these molecules on pancreatic cells or thyroid cells, induced by inappropriate production of the cytokine IFNγ, may lead to the activation of T helper cells to peptides from pancreatic cells or thyroid cells respectively. This would further lead to the activation of B cells or cytotoxic T cells against self antigens.

POLYCLONAL ACTIVATION OF B CELLS

Several viruses and bacteria can induce non-specific polyclonal activation of B lymphocytes; if B cells specific for self antigens are activated randomly autoantibodies can be produced. For example, in infectious mononucleosis, caused by the Epstein-Barr virus, several autoantibodies are induced by non-specific polyclonal B cell activation. This pool of autoantibodies often includes rheumatoid factor, anti-nuclear antibodies and antibodies to T cells and B cells.

From the above discussion, it should be clear that while immunological tolerance for self antigens is generally effective in preventing autoimmune reactivity against self, mechanisms of tolerance are not always successful and that tolerance can be bypassed or breached by any of the mechanisms described above. When tolerance is bypassed, autoantibodies and/or autoreactive T cells can be generated and when these are produced, autoimmune disease may result. Autoimmune diseases affect about 5-7% of adults and have a major health and socio-economic impact considering their debilitating effects. Having discussed how autoimmunity can be induced, we shall discuss how immunological damage is mediated in autoimmune disease in Part II of this article, published on pages 26 to 29.