IMMUNOLOGICAL ASPECTS OF AUTOIMMUNE DISEASES*

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Autoimmune diseases, by definition, are diseases in which the immune destruction of one's own (autologous) tissues is the main pathophysiologic feature. The term, however, has been used in clinical medicine in a much broader sense. Thus, when antibodies to one's own antigens (auto–antibodies) are found in a given condition, the condition is said to be autoimmune. This is acceptable to the immunologists as long as it is noted that further investigations should be initiated in order to show that autoimmunity is indeed the main etiologic factor in the pathogenesis of the disease. Once there is evidence that this is the case, the condition becomes a bona fide autoimmune disease. In order to provide a guideline for establishing the etiologic role of autoimmune processes in various conditions, a set of criteria was proposed by Witebsky.[1, 2] This is known as the Witebsky's postulate and the criteria are as follows:

1. Autoantibodies must be found in many patients with the disease and the autologous antigen (s) to which the autoantibodies are reactive must be identified or even isolated.

2. Experimental animals injected with a comparable preparation of autologous antigens must be shown to develop the disease.

3. The pathologic findings in the experimental model must be identical to or resemble those found in the human disease.

4. The disease in the experimental animals must be passively transferable by serum or viable lymphoid cells from affected animals to normal animals.

These criteria, admittedly, have not been satisfied in most diseases in which autoimmunity has been implicated. In these diseases, it is fair to say that the demonstration of autoantibodies is a signal that autoimmune processes may be etiologic. For the sake of simplicity the sequence of pathophysiological events may be viewed as shown in Figure 1.

It is fair to say that when the criteria according to Witebsky's postulate are satisfied in a given disease, it is likely that the sequence of events mentioned is responsible for the pathogenesis of that disease. The initial events leading to the failure of the immune homeostasis in each disease should be elucidated. The relative roles of the humoral and cell mediated immune systems could be indicated by whether the disease is passively transferable with viable lymphoid cells or with serum and by the correlation between the levels of autoantibodies and the severity of the disease.

Immunological homeostasis

The immune machinery of the body normally does not show an immune response to the antigens contained in and on the tissues of the body. This is described as the phenomenon of self tolerance. It implies that the immune machinery recognizes "self" and "not self"

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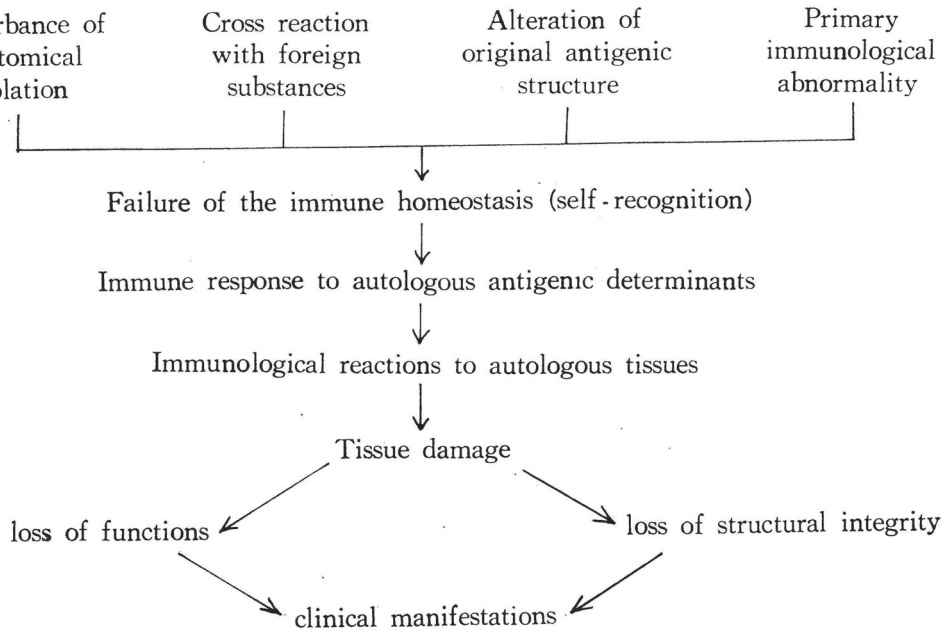


Fig. 1. Pathophysiological events in autoimmune diseases.

antigens. In immunological homeostasis, this capacity to recognize is maintained by mechanisms built into the immune system. Though these mechanisms are not as yet elucidated, it is important to give due consideration to them in a discussion of pathogenesis of autoimmune diseases.[2]. The phenomenon of self recognition and tolerance is an important feature of the immune system. It must be accounted for in any hypothesis on the mechanisms of antibody formation. The number of hypotheses postulated so far is fairly large. In this discussion only two reasonable hypotheses will be considered. These include the clonal selection hypothesis [3] and the Darwinian selection hypothesis. [4]

1. The clonal selection hypothesis accounts for self tolerance by postulating suppression of clones of cells which are predetermined to respond to autologous antigens. According to this hypothesis, the immune machinery contains clones of immunologically competent cells (ICC's). Each clone originates from one single precursor cell and contains genetic information for the synthesis of antibody specific to only one antigen. There exist enough clones of cells for the synthesis of specific antibodies to the large number of distinct antigens present in nature. At certain critical stages early in the development of these clones of cells, the cells are susceptible to destructive interaction with antigens present during that period of time (in the paranatal periods for most species studied). Thus clones of cells containing genetic information sufficient to mount an immune reaction against self-antigens will be destroyed since these antigens are present during the critical period. These clones are said to become the "forbidden clones". When the animals

are fully developed immunologically, there are no clones of cells for mounting the immune reaction to any self antigens or any antigens artificially introduced during the critical period early in the development. The latter was demonstrated by experiments reported by Billingham et al.,[4] who were able to induce tolerance to specific antigens by administration of the antigens into animals in the newborn period.

2. The Darwinian selection theory[5] accounts for self tolerance by the effects of the presence of a large amount of self antigens. According to this hypothesis, the effectiveness of an antigen in stimulating an immune response depends on its initial modifications by the macrophages. Thus it was assumed that only antigen fragments complexed with an RNA produced by the macrophages are effective in inducing an immune response. The intact natural form of antigenic molecules is not able to induce the ICC's to mount an immune reaction. Furthermore, the intact antigenic molecules competitively inhibit the induction by the effective form of antigen (i.e. antigen fragment–RNA complex). Thus the ratio between the intact antigen and the antigen–RNA complex is important in determining the level of the immune response. With the administration of an optimal dose of antigen, most of the antigenic molecules will be "processed" by the macrophages; thus they will be in the form of Ag–RNA complex. When an excessive amount of the antigen is present however, the limit of the function of the macrophages may be exceeded and more and more antigens will be in the intact, thus ineffective, form. In this latter situation the immune response will be inhibited by the excessive amount of intact antigenic molecules. The antigens of one's own tissues are undoubtedly constantly present in large amounts and may suppress the appropriate immune response in the manner described above.

Possible causes of the failure of immunological homeostasis

Whatever may be the actual mechanisms eventually shown to be operative in maintaining the immunological homeostasis, the interference with their normal operations will lead to autoimmunity. Observations, so far, suggest that this interference may be brought about in one of several possible ways in the autoimmune diseases. The major possibilities are briefly discussed as follows:

1. Disturbance of normal anatomical isolation. There are tissues in the body which are thought to be anatomically isolated form accessibility by the ICC's. These are often termed the privileged sites and include the uvea, the spermatozoa in the tubular systems of the testes and other sites. Thus substances unique to these sites are not in constant contact with the ICC's and may not be recognized by these ICC's as self antigens. When this anatomical isolation is disturbed (by infection, trauma or other causes), first contact between these substances and the ICC's may result in an immune response to these substances. The formations of antispermatozoa antibodies in "autoimmune" orchitis and of antithyroglobulin antibodies in Hashimoto's thyroiditis are believed to be due to this disturbance of anatomical isolation.[6, 7]

2. Cross reaction of autologous substances with foreign substances.

The immune response induced by bacterial antigens and other substances may lead to immunological cross–reactions to

autologous antigens. Certain antigens of streptococci, for example, were shown to have antigenic similarity with basement membrane in the glomerulus and sarcolemma of the myocardium. Specific antibodies in response to infection by streptococci elaborating these antigens may cross react to these host tissue components. This cross-reaction has been implicated in rheumatic heart disease and in acute glomerulonephritis.

3. Alteration of original antigenic structure. The alteration of the antigenic structure of autologous tissues may lead to the failure of the ICC's to recognize the altered antigens as self-antigens. These alterations may be brought about by viral infection, by certain drugs and by other sources of cell injury. This alteration of antigenic structure has been implicated in lupoid hepatitis (chronic lymphocytic hepatitis or chronic active hepatitis)[8] and in some cases of acquired hemolytic anemia.

4. Primary immunological abnormality. Abnormality of the immune system itself may lead to indiscriminate immune response and thus autoimmunity. One would expect that in this situation the autoimmune reaction would be systemic rather than organ specific. Systemic lupus erythematosus is a systemic disease believed to be due to autoimmune reactions involving many organ systems. SLE has been shown to be inheritable disease and the patterns of inheritance are associated with other diseases with immunological abnormality.[9,10]

Autoimmune tissue damage

Antibody-mediated, as well as cell-mediated, immunological reactions may cause tissue damage,[7,11] particularly when the antigen (s) involved is a component of that tissue. Among the best investigated autoimmune diseases (Hashimoto's thyroiditis, allergic encephalomyelitis, etc.), the cell-mediated immunological reactions are believed to play a predominant role. This theory is supported by several lines of evidence. In the experimental animal models available, passive transfer of the disease could be accomplished by the transfer of lymphoid cells but not often by the transfer of serum.[12] The histology of the lesions is often characterised by mononuclear cell infiltration typical of lesions due to cell-mediated reaction.[7] In a few selected diseases however, antibodies may play a predominant role (acquired hemolytic anemia, autoimmune thrombocytopenic purpura, etc.).

Autoantibodies may cause tissue damage in the autoimmune diseases in many ways. The most outstanding ways include cytolysis (hemolysis, lysis of target cells) and vasculitis. Cytolysis by antibodies requires the activation of the complement system best studied in the phenomenon of immune hemolysis.[13] Vasculitis also requires the activation of the complement system, particularly the C3, C5, C6 and C7 components.

The cell-mediated immune reactions can cause tissue damage by their cytotoxic and cytolytic effects. These effects, as well as the accumulation of a large number of mononuclear cells at the site to increase the intensity of tissue destruction, are accomplished by the release of several non-immunoglobulin substances called lymphokines.[14-16]

Summary

The demonstration of autoantibodies in a disease does not establish the etiologic role of autoimmune processes.

One should be alerted by the presence of autoantibodies and investigate further. The disturbance of the homeostatic mechanisms of the immune system can result from various causes. This disturbance results in an immune response to autologous tissue antigens. Immunological reactions involving autologous tissue antigens are responsible for the destruction of the tissues. Cell-mediated immune reactions probably play a more significant pathogenic role in most autoimmune diseases than do immunoglobulin -mediated immune reactions.

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