Review

Autoimmunity

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Autoimmune diseases comprise a large, diverse group of diseases characterized by a humoral or cell-mediated immune response against the constituents of the body's own tissues. In cases in which the host is sensitized with a tissue-specific antigen, a single pathological immune reaction occurs in the target organ. In those cases in which the host is sensitized with either a single tissue nonspecific or many tissue-specific antigens, several pathological immune reactions occur in many target organs. Examples of each type of autoimmune disease are shown in Tables 1 and 2. This classification is arbitrary, and in certain patients a combination of immunological reactions may be detected. Furthermore, what is considered organ-specific presently may turn out to be multiorgan diseases in the future.

Within the organ-specific autoimmune diseases, there is a group (Table 3) of diseases in which the patients produce autoantibodies directed against different cell surface receptors.[1–5] Autoantibodies will bind these cell surface receptors and impair their physiologic function. The common feature to all these diseases is the cross-linking of cell surface receptors, which occurs after binding the autoantibody.[3] Moreover, this immunological reaction increases the metabolic degradation of these receptors. Abnormal receptor function may result from receptor blockade or decrease in the number of receptors available due to increased degradation of these molecules. In some cases, the autoantibody has been shown to possess activity somewhat similar to the receptor involved; for example, insulin-like activity for autoantibodies against insulin-receptor.[6] Although experimental evidence is not available as yet, it is tempting to speculate that pemphigus autoantibodies also bind to epidermal cell surface receptors important in cell-to-cell adhesion. It has been shown that pemphigus autoantibodies induce acantholysis[7] or epidermal cell detachment[8,9] when tested in vitro.

The autoimmune diseases shown in Tables 1 and 2 share two common pathogenetic mechanisms, ie, one, a loss of self-tolerance, and two, the activation of B or T cells. The result of these defects is the induction of a hypersensitivity state. The hypersensitivity states have been classified into four major types.[10] There may be in situ antigen-antibody reactions with complement activation, which leads to tissue damage (Type II). Antigen-antibody complexes may also circulate as immune complexes and become trapped in various organs resulting in complement activation and tissue damage (Type III). This mechanism is thought to be responsbile for the renal disease and vasculitis seen in systemic lupus erythematosus. T-cells may alone become activated, leading to a delayed-type hypersensitivity reaction (Type IV), as may be found in Hashimoto's thyroiditis.

Tolerance to Self-antigens

Immune tolerance may be thought of as a homeostatic mechanism maintained by the interaction of the immune system and the host antigens. When this homeostasis is broken, the immune system is activated, resulting in reactions against host antigens and causing disease. This is the "Horror Autotoxicus" described by Ehrlich at the turn of the century.[11] Immune tolerance is an incompletely understood mechanism whereby the immune system of an animal recognizes self-antigens and remains unresponsive to them. Tolerance involves a genetic endowment, a long-lasting immunological memory

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TABLE 1. *Organ-specific Autoimmune Diseases*

Chronic lymphocytic thyroiditis
Diabetes mellitus (insulin-resistant)
Myasthenia gravis
Pemphigus vulgaris
Bullous pemphigoid
Goodpasture's syndrome
Graves' disease

toward self-antigens after fetal exposure and active immunological mechanisms that protect the animal from responding against self. Tolerance may be defined as an antigen-specific immunological unresponsiveness, either cell-mediated or humoral of a host animal; to an antigen to which it would otherwise respond.

One of the earliest theories of tolerance was proposed by Jerne in 1955.[12] He postulated that preformed antibody was present in the fetus prior to postembryonic antigenic stimulation. Animals exposed to antigens after birth will develop proliferating antibody producing cells, specific for the immunizing antigen. Antibodies that react with self-antigens will be eliminated.

The theory of clonal selection was introduced by Burnet in 1959.[13] He proposed that contact of lymphocytes with self-antigens during fetal life (or for a short time after birth) would lead to the destruction and elimination of those clones that would be autoreactive. Another term that he proposed for this process was "functional elimination." Self-lymphocytes sensitized to self-antigens are destroyed, rendering the hosts unable to respond to their own tissue antigens. This theory is generally accepted presently, although it does have some unanswered observations. It is known, for example, that circulating autoantibodies against self-antigens may be detected under normal conditions, ie, autoantibodies against thyroglobulin.

Other theories have been discussed to explain immune tolerance. Extensive cross-linking of cell surface receptors for antigen, induced by the tolerogen will induce unresponsiveness of the cells involved in the immune response. Other investigators believe that normal serum contains blocking factors, perhaps immune complexes, which abrogate the immune response to antigens. Finally, the modulation of the immune response and tolerance toward self- and nonself-antigens may be one of the functions of suppressor T-cells.

TABLE 2. *Organ Nonspecific Autoimmune Diseases*

Systemic lupus erythematosus
Rheumatoid arthiritis
Scleroderma
Sjögren's syndrome

TABLE 3. *Autoimmunity Involving Specific Receptors*

Disease	Receptor
Myasthenia gravis	Acetylcholine receptor
Insulin-resistant diabetes	Insulin receptor
Graves' disease	TSH-receptor
Pemphigus vulgaris	Epidermal cell-surface receptor
Some atopic individuals	β-Adrenergic receptor

Although the exact mechanism of immunological tolerance remains unknown, there are some basic principles already confirmed experimentally. These are: (1) Tolerance is learned by the immune system. Immune tolerance is an acquired trait, and is not strictly a genetic phenomenon. This was shown by Owen in 1945 in experiments with chimeric calves, having fetal cross-circulation and mutual tolerance to blood groups and skin grafts.[14] (2) Tolerance is easier to induce in young animals. The younger an animal is, the easier it is to tolerize. (3) High doses of antigen induce tolerance, whereas low doses are immunogenic. Likewise, some antigens may display both low-dose and high-dose tolerance, and in some animals, multiple small doses of antigen will induce tolerance. (4) Tolerance is separate and distinct for the T and B arms of the immune system. It is extremely difficult to induce and maintain B-cell tolerance requiring 10–100 times the usual dose of antigens for immunization. Tolerance is usually short-lived. The T-cell system is tolerized at low doses of antigen, and also at extremely high doses of antigen. The low-dose tolerance may be related to the generation of specific suppressor T-cells. High-dose tolerance is due to an immunological overload of antigen and a "freezing" of all antigen-specific responses of T and B cells and hence, unresponsiveness.

Animal Models of Autoimmunity

The basic defects that may cause the break in tolerance leading to disease states have come from the study of animal models. The best known model of multisystem autoimmune disease is the New Zealand mouse derived from a strain taken to Australia for cancer research in 1959.[15] This strain has the following general features[16,17]: (1) early immunologic maturation; (2) humoral hyper-responsiveness early in life; (3) loss of tolerance to foreign and self-antigens early in life; (4) impaired cell-mediated immunity late in life; (5) loss of recirculating thymocytes; (6) loss of thymic-derived suppressor activity; (7) spontaneous production of antithymocyte antibodies; and (8) spontaneous development of circulating immune complexes, including antibodies to DNA.

Two inbred colonies derived from the New Zealand mice have been studied in detail. One is the NZB/NZB cross, that is a model of autoimmune hemolytic anemia and has the following features[18]: (1) autoimmune hemolytic anemia early in life leading to reticulocytosis and splenomegaly later in life; (2) low incidence of both ANA and positive LE preparations; (3) development of glomerulonephritis late in life; and (4) cytotoxic IgM antibodies for T-cells. The other mouse colony is the NZB/NZW F_1 generation. These mice show features similar to human systemic lupus erythematosus.[18] These are: (1) high incidence of both ANA and LE preparation; (2) severe immune-complex glomerulonephritis; (3) low levels of antibodies to erythrocytes and thymocytes; (4) high antibody titer to both DNA and RNA; and (5) a more severe disease found in female mice.

Dermatological Models of Autoimmunity

There are dermatological diseases that are examples of organ-specific and organ nonspecific autoimmune diseases. Organ-specific models would include pemphigus vulgaris and bullous pemphigoid; these diseases show a highly specific autoimmune reaction directed against the skin. Pemphigus vulgaris is a disease in which there is an autoantibody to a cell surface glycoprotein of differentiating keratinocytes. Normal individuals are tolerant to this epidermal antigen. If tolerance to this antigen is lost, patients will manufacture pathogenic antiepidermal antibodies. Bullous pemphigoid is another highly specific autoimmune dermatological disease. These patients become sensitized to an antigen normally found at the cutaneous basement zone (BMZ) and produce anti-BMZ autoantibodies. Like in pemphigus vulgaris, these patients have lost their immune tolerance to this self-antigen.

The organ nonspecific autoimmune diseases are best represented by systemic lupus erythematosus. Many antigen-antibody systems have been detected in the sera of those patients involving DNA, RNA, RNP, Sm, Ro, La, etc. There are many reviews dealing with this subject already published in this and other journals.[19–23] Other organ nonspecific autoimmune diseases are dermatomyositis, Sjögren's syndrome, and scleroderma, where the antigenic components are not well defined.

Autoimmune Diseases—Pathogenesis

Numerous theories have been proposed to explain the development of autoimmunity in experimental animals and man. Some of these theories are similar and overlap in a spectrum. Since most of these entities are so diverse and variable, it is difficult to select a unifying theory to link the spectrum of autoimmunity. Here we will restrict our discussion to what appears to be the most important factors in the pathogenesis of the autoimmune diseases.

Genetic Factors

The genetic control of the immune response must be considered in the pathogenesis of autoimmunity. Recognition and processing of antigens by the immune system of an animal is a genetically controlled mechanism.[24] For example, in man the major histocompatibility complex, also called the HLA system, controls the synthesis of cell surface molecules grouped in four loci: HLA-A, HLA-B, HLA-C, and HLA-D. These molecules, which are phenotypic products of the major histocompatibility complex, can be identified in vitro. Any individual may be typed according to their HLA haplotype.

Recent work has demonstrated the importance of various HLA genes that control the immune response (Ir genes), or predispose to disease susceptibility. Many associations of diseases with certain HLA typings have been described, but the most impressive are in the HLA-A8 and HLA-B27 loci. HLA-A8 is increased in young females with myasthenia gravis, Graves' disease, and insulin-resistant diabetes.[25–26] A high incidence of HLA-B27 haplotype is seen in patients with Reiter's syndrome, juvenile rheumatoid arthritis, and ankylosing spondylitis.[27] Pemphigus vulgaris also has a high association with HLA-DRW4 in the Jewish population,[28] whereas bullous pemphigoid and lupus erythematosus show no consistent HLA associations.

A genetic hypothesis to explain the autoimmune phenomenon found in patients with systemic lupus erythematosus has been proposed by Quimby and Schwartz.[29] According to these authors, a set of genes will make the host animal predisposed to develop autoimmunity, and another set of genes will confer the phenotype characteristics to the autoimmune disease. Both classes of genes would consist of multiple unlinked dominant and recessive components with structural and modifier genes possible in both classes.

Viral Factors

A viral theory for the development of autoimmunity has been described previously.[30] A virus may trigger autoimmunity by different mechanisms. Some of these may involve the nonspecific polyclonal stimulation of B-cells with a resulting overproduction of antibodies and autoantibodies.[31] In other cases, the virus may combine with the host DNA and be expressed on the surface of infected cells. These neoantigens may sensitize the host's immune system to respond to both self and viral antigens. Neoantigens can also be formed by conjugation of viral and host cell coats as shown by Burns and Allison.[32] It is known that C-type viral particles are found

in many organs of New Zealand mice and the kidneys of patients with lupus erythematosus.[23,33] It is conceivable that these viral particles may be present but not causally related to the pathogenesis of the disease.

Adjuvants and Bacterial Injections

Adjuvants and bacterial infections may also play an important role in the pathogenesis of autoimmune diseases. Nonspecific polyclonal activators such as *Escherichia* lipopolysaccharide or tuberculin may stimulate B-cells to produce antibodies, escaping normal regulatory control mechanisms.[34] Complete Freund's adjuvant is a nonspecific activator of T-cells.[34]

Bacterial infections, especially the chronic type, may be the source of substances that may act as polyclonal activators or adjuvants in the induction of autoimmune disease. Furthermore, self and bacterial antigens may cross react and consequently trigger the autoimmune reaction as seen in rheumatic heart disease.[35–36]

Suppressor T-cells

Thymus derived lymphocytes constitute a functionally heterogeneous population of cells. Some T-cells provide helper functions for B-cell activation, another suppresses B-and T-cell activation and finally a group capable of directly killing target cells.[37–38] Abrogation of some of these subpopulation of T-lymphocytes may originate and perpetuate autoimmune reactions against self-antigens. For example, lack of suppressor T-cells that modulate B-cell activation may lead to the overproduction of autoantibodies. Recent studies[39–42] have shown that peripheral blood lymphocytes from patients with SLE or juvenile RA are unable to generate suppressor T-cell function in vitro. It is unknown whether this defect in suppressor T-cell has a primary or secondary relation to the autoimmune reactions present in these patients.

Antilymphocyte Antibodies

Lymphocytes from patients with active SLE show a low or absent suppressor activity and a poor mixed lymphocyte reaction response when tested in vitro.[43] This defect may result from the cytotoxic effect of circulating autoantibodies. Several reports have shown that the serum of patients with SLE eliminates suppressor T-cell functions from peripheral blood lymphocytes of normal individuals.[44–45] This cytotoxic serum factor can be absorbed out using T-cells but not with non-T-cells. Furthermore, this factor has been identified in both IgG and IgM immunoglobulin classes.

Other Theories of Autoimmunity

Drugs or degradation products of self-antigens may bind to tissue constituents forming a hapten-carrier complex which then triggers autoimmunity.[46–47] Drugs inducing lupus-like syndromes or hemolytic anemia are well documented in the clinical literature.[46,48] In some cases, self-antigens, are sequestered from the immune system by a biological barrier-membrane. If the permeability of this membrane is altered, active sensitization and autoimmunity may occur,[49] eg, encephalomyelitis triggered by sensitization to myelin basic protein, or orchitis due to autosensitization to sperm.

Defects in thymic hormones,[50,51] thymus atrophy,[52] or faulty antigen-processing by macrophages[53] as the cause of autoimmunity are postulated by some investigators. Finally some authors[54–56] think that autoimmunity may result from disturbances in the equilibrium between idiotypes and anti-idiotype antibodies present in the host animal.

Summary

Autoimmune diseases are entities in which the host becomes sensitized to self-antigens mounting a humoral and/or cell-mediated immune response to target tissues. The basic defect in all autoimmune diseases is manifested by loss of immune tolerance to self-antigens. Immune tolerance under normal conditions is a complex biological phenomenon not fully understood as yet. Many theories to explain autoimmunity have been postulated. In an individual patient, however, many of these theories may be found to be correct. Dermatological research is just beginning to explore this area using dermatologic organ-specific autoimmune diseases as experimental models.

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