Introduction to Immunology and Autoimmunity

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Autoimmune disease occurs when the immune system attacks self-molecules as a result of a breakdown of immunologic tolerance to autoreactive immune cells. Many autoimmune disorders have been strongly associated with genetic, infectious, and/or environmental predisposing factors. Comprising multiple disorders and symptoms ranging from organ-specific to systemic, autoimmune diseases include insulin-dependent diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, thyroiditis, and multiple sclerosis. There are also implications of autoimmune pathology in such common health problems as arteriosclerosis, inflammatory bowel disease, schizophrenia, and certain types of infertility. Largely of unknown etiology, autoimmune disorders affect approximately 3% of the North American and European populations, > 75% of those affected being women. This discussion provides a brief introduction to the immune system and tolerance maintenance, an overview of selected autoimmune diseases and possible mechanisms of immune autoreactivity, and a review of experimental autoimmune models. *Key words*: autoantibodies, autoimmune disease, autoimmunity, autoreactive immunity, immunity, mechanisms, tolerance. — *Environ Health Perspect* 107(suppl 5):661–665 (1999).
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Autoimmune disorders result from a breakdown of immunologic tolerance leading to an immune response against self-molecules. In most instances the events that initiate the immune response to self-molecules are unknown, but a number of studies suggest associations with environmental and genetic factors and certain types of infections. Approximately 3% of the populations in Europe and North America currently suffer from autoimmune diseases, many with symptoms of multiple disorders (*1*). This may be an underestimate, as epidemiologic studies are not available for some of the less common diseases. In addition, there are suggestions that a number of common health problems such as atherosclerosis and inflammatory bowel disease may have an autoimmune component (*2,3*). Women have a significantly higher risk of developing an autoimmune disease than men, as > 75% of those suffering from autoimmune diseases are female (*1*). Young, postpubescent women have been shown to be approximately 10 times more susceptible than men to developing autoimmune disease (*4*). Although the underlying mechanisms for this predisposition are currently being investigated, it is known that females and castrated males produce much higher levels of estrogen and reduced levels of testosterone, and it is well documented that estrogen and estrogenlike chemicals may alter the immune response (*5*). Much of the evidence supporting a role for estrogen in the development of autoimmune diseases comes from animal models rather than human studies. In autoimmune-prone mice, estrogen administration greatly enhances mortality in both males and females (*6*). Testosterone is found in much higher levels in sexually functionally males. Recent studies have found that testosterone given to lupus-prone autoimmune mice exerts a powerful suppressive effect on this disorder in both adult and prenatally treated animals, and male autoimmune MRL/*lpr* mice exhibit abnormally low testosterone levels (*7*). In this article, we provide a brief introduction to *a*) the immune system; *b*) the mechanisms by which tolerance to self is normally maintained and the ways in which these mechanisms may be broken down so that autoreactivity can occur; *c*) an overview of autoimmune diseases and possible mechanisms; and *d*) the models frequently used to study the autoimmune phenomenon.

Overview of the Immune System

The immune system is a complex set of cellular, chemical, and soluble protein components designed to protect the body against foreign substances, including infectious agents and tumor cells, while not responding to self-molecules. Foreign or self-molecules (usually proteins or carbohydrates) that evoke specific immune responses are referred to as antigens. Immune cells are located throughout the body, either in discretely encapsulated organs such as the spleen and thymus or as diffuse accumulations of lymphoid and myeloid cells as found in association with the skin and gut where they are strategically placed to monitor the entry of foreign substances. Optimal function of the immune system requires that immune cells and cell products interact with each other in a sequential, regulated manner. The distinction between self and nonself occurs through complex mechanisms that depend upon specific recognition molecules present on the surface of immunocompetent cells, in particular, T and B lymphocytes.

Nonspecific effector mechanisms that complement or amplify the specific T- and B-lymphocyte responses are also important in the immune response. These nonspecific entities serve as a first line of defense against potential pathogens and include other leukocytes such as macrophages, natural killer (NK) cells, and polymorphonuclear leukocytes, as well as soluble mediators that include complement and cytokines. A number of autoimmune diseases demonstrate characteristic aberrations in cytokine production, suggesting that these soluble mediators may play a role in both the initiation and pathogenesis of the disease (*8–10*). Therapeutic treatment with the cytokines interferon (IFN)-α and interleukin (IL)-2 have occasionally been associated with the subsequent appearance of autoimmune diseases (*11*). In addition to the complex cell–cell and cytokine interactions that are necessary in the normal functioning of the immune system, secondary factors can influence immune status. These include neurohormones and stress, both of which modulate autoimmune responses (*12*).

Many immune cell populations (e.g., B lymphocytes, T lymphocytes, NK cells) can be further divided into subpopulations on the basis of varying functional properties or states of differentiation, maturation, and activation. Most notable among these are the T-cell subpopulations, including cells that assist and amplify other immune responses (T-helper cells [Th]), downregulate other immune responses (T-suppressor [T_S] cells), or destroy cells infected with viruses or other intracellular pathogens and tumor cells (cytotoxic T [T_C] cells). The Th cells produce cytokines that regulate immune function and can be further subdivided into subpopulations that assist other T cells (Th1) or stimulate and perpetuate antibody responses (Th2).

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Immunocompetent T cells develop and mature in the thymus under the influence of thymic hormones and peptides. T cells recognize only antigens that have been processed into peptide fragments and are presented as bound to specialized cell-surface molecules, the major histocompatibility complex (MHC) proteins. MHC class I molecules are expressed on nearly all nucleated cells of the body. MHC class II molecules are constitutively expressed on antigen-presenting cells (APCs) only. However, class II expression can be induced in a variety of cell types after cytokine stimulation. The antigen recognition molecule for the T lymphocyte is the T-cell receptor (TCR), a heterodimeric transmembrane molecule containing two subunits (either αβ or γδ). The interaction between antigen, the TCR, and MHC proteins is highly complex, and T-cell activation requires signaling via the TCR and other cell-surface molecules.

Although B lymphocytes can act as APCs, their primary role is to produce antibody, which is the effector molecule for humoral-mediated immunity. Naïve, circulating B cells encounter antigen in lymph nodes or tissue-associated lymphoid tissues and become activated. B cells recognize antigen via membrane-bound antibody/immunoglobulin (Ig) molecules that act as antigen receptors. Cross-linking of Ig molecules on the cell surface initiates a signal transduction cascade and with the appropriate stimulus from Th2 cytokines, leads to activation and proliferation. These activated B cells clonally expand by repeated division, followed by differentiation into antibody-secreting plasma cells. The reader should consult any one of several excellent immunology texts for an extended discussion of these interactions (*13,14*).

Tolerance

The genetics of the TCR and antibody molecules are such that an incredible amount of diversity is generated in the antigen-binding portions of the molecule. As recombination of Ig and TCR genes occurs in a random manner, antigen-binding regions are created that are reactive with self-molecules. Thus a variety of tolerance mechanisms have evolved to distinguish self and nonself, and block the development, growth, or differentiation of autoreactive lymphocytes. There are three basic mechanisms by which self-reactive lymphocytes may be prevented from responding to self-molecules: *a*) clonal deletion, which requires the physical elimination of autoreactive lymphocytes; *b*) clonal anergy, which requires the functional elimination of autoreactive lymphocytes via downregulation of responsiveness, and *c*) suppression or inhibition of autoreactive lymphocytes via interaction with other cell types such as cytotoxic T lymphocytes or NK cells. These cells dampen the immune response to specific antigens via secretion of cytokines with negative regulatory effects, via antibody feedback mechanisms that can neutralize specific antigens and inhibit B-cell function through cross-linking of surface Ig or Fc receptors, or by the creation of antiautoantibodies (anti-idiotypes) that can recognize the antigen receptor on autoreactive B lymphocytes (*15*).

It has been suggested that T lymphocytes are the primary players in the initiation and perpetuation of both spontaneous and chemical-induced autoimmune diseases (*16,17*). This is evidenced by animal models that demonstrate that autoimmunity can be transferred via infusion of autoreactive Th cell clones and that this transfer of autoimmunity can be reversed by depletion of the Th cell clones using antibodies and complement (*18–20*).

T lymphocytes develop in the thymus from hematopoietic stem cells that do not yet express the cell-surface markers CD4 (Th cells) or CD8 (T_S or T_C cells). These early T-cell precursors randomly rearrange their TCR genes and proliferate at a very high rate, developing into a population of $CD4^+CD8^+$ (double-positive) cells. In the cortical region of the thymus, these double-positive T lymphocytes are exposed to epithelial cells that express MHC class I and II molecules. T cells that do not recognize self-MHC are deleted via programmed cell death, whereas T cells that bind to self-MHC molecules survive (positive selection), differentiate into either single-positive CD4 or CD8 cells (depending on whether they bind MHC class II or class I, respectively), and migrate into the medulla of the thymus. In the medulla, single-positive cells are exposed to autoantigens in the presence of self-MHC molecules. Those T cells that bind self-antigens with high affinity are deleted (negative selection) via TCR-mediated programmed cell death. Autoreactive T lymphocytes that are not deleted in the thymus (due to low affinity binding or responsiveness to cryptic antigens, i.e., self-antigens not present in the thymus during normal development) are usually anergized or suppressed in the peripheral lymphoid tissues.

The simplest mechanism to explain tolerance in B lymphocytes is a lack of T-cell help for self-reactive B cells as a result of successful T-cell tolerance (*21*). However, some B cells must be directly tolerized. A number of microorganisms express molecules resembling self-antigens (molecular mimicry). Furthermore, Ig genes in mature B cells may undergo somatic mutation during clonal expansion so that they become self-reactive. The fate of self-reactive B cells depends on the affinity of the Ig receptor for its specific antigen and on the nature of the antigen it encounters. When B cells encounter membrane-associated self-antigens that cross-link surface Ig receptors with high aviditiy, their surface Ig is downregulated and these short-lived cells die via apoptosis. This type of tolerance occurs most frequently in the bone marrow. However, some self-reactive B cells reach the periphery. If these cells encounter soluble antigen that is monomeric and not capable of cross-linking surface Ig receptors, they are rendered anergic via downregulation of surface IgM. This anergy may be reversible in the presence of high levels of the cell-surface antigen CD40 and IL-4 or polyclonal activators such as lipopolysaccharide and mycoplasma superantigen (*22*).

Overview of Autoimmune Diseases

Autoimmune disorders are a spectrum of diseases ranging from organ specific, in which antibodies and T cells react to self-antigens localized in a specific tissue, to systemic, which are characterized by reactivity against a specific antigen or antigens spread throughout various tissues in the body (Table 1). In

Table 1. Spectrum of autoimmune diseases and putative autoantigens.

	Disease	Autoantigen
Organ specific	Hashimoto thyroiditis	Thyroglobulin
	Thyrotoxicosis	Thyroid-stimulating hormone
	Pernicious anemia	H^+/K^+ -ATPase
	Autoimmune atropic gastritis	Intrinsic factor
	Addison disease	21-Hydroxylase
	Insulin-dependent diabetes mellitus	Glutamic acid decarboxylase 65
	Goodpasture syndrome	Type IV collagen
	Myasthenia gravis	Acetylcholine receptor
	Male infertility (few cases)	Epididymal glycoprotein FA-1
	Sympathetic opthalmia	Interphotoreceptor retinol binding protein
	Multiple sclerosis	Myelin basic protein
	Autoimmune hemolytic anemia	X antigen, glycophorin
	Ulcerative colitis	Catalase, α-enolase
	Rheumatoid arthritis	Rheumatoid factor
	Scleroderma	Topoisomerase 1, laminins
Non-organ specific	Systemic lupus erythematosus	DNA nucleotides and histones, Sm-RNP

general, Th1 cytokines such as IL-2 and IFN-γ predominate in organ-specific diseases, and the effector responses tend to occur via cell-mediated immune responses such as killing by cytotoxic T cells through the release of cytokines or through IgG and IgM antibodies directed toward cell-surface antigens, triggering Fc receptor-mediated killing. Systemic autoimmune disorders are characterized by elevated levels of Th2 cytokines such as IL-4, IL-5, and IL-10, the widespread circulation of autoantibodies and immune complex deposition, opsonization with antibody, and cell damage via complement-mediated lysis. Some autoimmune syndromes such as multiple sclerosis are not easily classified, as they demonstrate both organ-specific and systemic components. The most common targets for organ-specific autoimmune disease are the thyroid (Hashimoto thyroiditis, thyrotoxicosis), stomach (pernicious anemia, autoimmune atrophic gastritis), adrenal glands (Addison disease), and pancreas (type I or insulin-dependent diabetes mellitus [IDDM]). Systemic autoimmune disorders commonly involve the skin (scleroderma), the joints (rheumatoid arthritis), and the muscle tissue (idiopathic inflammatory myopathies [IIM]). In many instances multiple autoimmune diseases may occur in the same patient, and certain diseases are sometimes associated, such as IIM and vasculitis or rheumatoid arthritis and systemic lupus erythematosus (SLE) (*23–25*).

In recent years it has been recognized that many other diseases in a variety of target organs/tissues may have an autoimmune component. In general, the etiology of these diseases is not well understood, and multiple factors such as genetics, infectious agents, and lifestyle may contribute in some fashion to disease induction and progression. There is significant evidence that an immune response to self-antigens is involved in atherosclerosis. Increased levels of autoantibodies to heat shock protein 65/60, gangliosides, and oxidized low-density lipoproteins have been demonstrated in atherosclerotic lesions (*26–28*). The role of heat shock protein 65/60 as a candidate autoantigen is supported by animal studies in which immunization with this antigen led to the development of atheroslcerotic lesions in rabbit aorta (*29*). In addition, elevated levels of MHC class II expression and increased production of growth-promoting and chemotactic cytokines have been shown in atherosclerotic plaques (*30,31*). There is also evidence for an autoimmune pathology in schizophrenia, with immunologic abnormalities, such as increased prevalence of antinuclear and platelet-associated antibodies, altered cytokine production, and increased levels of soluble cytokine receptors being reported (*32,33*). Abnormal antibody production and autoimmunity have also been implicated in both male and female infertility and are associated with recurrent spontaneous abortion, endometriosis, premature ovarian failure, and abnormal sperm maturation (*34,35*).

Mechanisms of Autoimmune Disease

A small number of autoreactive B and T cells constitute a normal part of the immune cell pool, as the production of autoantibodies is frequently observed in normal healthy individuals. Tolerance is normally maintained by the regulatory interactions of a variety of cell types and soluble mediators. However, under certain conditions, tolerance can be broken and an autoimmune pathology may result. It is apparent that development of autoimmune disease is highly dependent on a permissive genetic background but that other triggering factors such as viral, bacterial, or chemical insult lead to altered self-reactivity. This section is meant to introduce the reader to several of the hypotheses regarding the role that genetics and environmental factors may play in breaking down the barrier to reactivity with self-antigens.

Release of Isolated Autoantigens

T cells reactive to self-antigens not present in the thymus during the early stages of T-cell development may escape thymic deletion. These antigens (cryptic or hidden antigens) generally have relatively low circulating levels or are anatomically sequestered in specific tissues (e.g., myelin basic protein or thyroglobulin) where vascular and/or cellular basement membranes constitute an effective barrier that prevents access by autoreactive cells. Induction of organ-specific autoimmune disease following tissue trauma has been frequently reported and likely occurs via tissue damage that results in the availability of previously isolated antigens, as is the case in ophthalmia following eye injury (*36*) or orchiditis following vasectomy (*37,38*). Infection with tissue-tropic pathogens such as viruses may induce similar autoimmune phenomenon, and these infections also provide the additional stimulus of the production of soluble mediators and costimulatory molecules important in the perpetuation of the immune response. This may be best exemplified in rodents and humans who develop diabetes after infection with Coxsackie B viruses (*39*).

Chemical Alteration of Self-Peptides

As discussed above, T lymphocytes that bind with low affinity to self-proteins in the thymus may not be deleted. However, these T cells are normally functionally anergized in the periphery. Responses to and presentation of these cryptic self-peptides can be enhanced under certain conditions. In a murine model of IDDM, viral infection stimulates the secretion of IFN-γ, which in turn upregulates levels of antigen-presenting MHC molecules and enhances presentation of low-affinity self-peptides (*40*). Some metals induce autoimmune disease via the creation of new high-affinity binding sites for MHC molecules on chemical-bound self-peptides, allowing activation of previously anergized T cells (*41*). Expression of altered nucleolar proteins appears to be an important step in the development of mercuric chloride ($HgCl_2$)-induced autoimmunity in a rodent model of SLE (*42*). In addition, many drugs induce autoimmunity via formation of hapten-induced autoantibodies. Compounds such as penicillin and halothane induce reactions in which hapten-specific T cells provide help to antibody-producing B cells that recognize the modified hapten but not the native form of the self-protein (*43–45*).

Molecular Mimicry

Many peptide fragments of infectious agents are homologous with host proteins and induce organ-specific autoimmune responses. A membrane protein on the β-hemolytic streptococcus bacterium has a high degree of homology with cardiac myosin, and antibodies that target the bacterium also cross-react with cardiac muscle and induce rheumatic fever (*46,47*). *Yersinia enterocolitica*, a bacterium normally associated with food poisoning outbreaks, has also been associated with various autoimmune diseases. Increased levels of antibodies to *Yersinia* have been demonstrated in patients with Graves disease or autoimmune thyroiditis (*48,49*). These antibodies cross-react with a variety of thyroid antigens (*50,51*).

Polyclonal Activators

Microbial antigens have also been implicated in the precipitation and exacerbation of systemic autoimmune diseases. Exogenous polyclonal activators may mutually stimulate T cells that react with both MHC class II-bound superantigens (peptides that activate large numbers of Th cells, promoting cytokine overproduction) on B cells and the B cells themselves, leading to the production of polyclonal Ig, some of which may be autoreactive (*52*). *Mycoplasma arthriditis* superantigen stimulates cytokine production and upregulates MHC class II expression in human T cell lines (*53*) and stimulates T lymphocytes with arthritis-associated TCR-β chains (*54*). In a rodent model, *Mycoplasma arthriditis* superantigen stimulated Th cells, resulting in polyclonal B-cell activation and/or differentiation of antigen-specific B cells (*55*).

Genetic Factors

Familial studies suggest a clear association between genetics and autoimmune diseases, particularly those with an organ-specific pathology (*56*). Further, although concordance rates between identical twins can be relatively low depending on the disease, this may be explained by nonidentity in immune repertoires because of TCR and Ig gene recombination, variations in receptor assembly, and somatic mutation of B-cell receptors. The most clearly established genetic association is with specific alleles within the MHC gene complex. Certain haplotypes (HLA-B8, DR2-DR5) tend to be associated with certain autoimmune diseases [reviewed in (*57,58*)]. However, a specific MHC haplotype is not sufficient for development of autoimmune disease, and autoimmunity-associated haplotypes are found in individuals with no clinical signs of disease.

There are also a number of non-MHC genes that may contribute to autoimmunity. Many studies have examined the possibility that predisposition for certain autoimmune diseases in the human population may lie in the germline genes for the TCR [reviewed in (*59,60*)]. The strongest evidence for TCR involvement comes from studies of sibling pairs with recurrent/relapsing multiple sclerosis. Siblings with multiple sclerosis shared specific TCR-β haplotypes at a frequency much higher than would be expected because of random segregation (*61*). TCR-α gene polymorphisms have also been associated with disease susceptibility (*62*).

Animal Models of Autoimmune Disease

Three basic types of animal models may be employed to identify the potential of environmental agents to induce autoimmune responses: *a*) organic- or chemical-induced, *b*) autoimmunization, or *c*) genetically predisposed animals (Table 2).

In models where autoimmunity is induced by exposure to chemical or biologicagents, foreign substances are used to initiate the autoimmune disease state. These may include chemicals, drugs, or biologic substances such as bacterial or viral antigens. One of the more commonly employed models of this type is the Brown Norway rat model, in which the animals are injected with nontoxic amounts of $HgCl_2$. The chemical exposure produces no overt signs of toxicity, yet the rats develop an immunologically mediated disease characterized by T-cell–dependent polyclonal B-cell activation, autoantibodies to laminin, collagen IV and other components of the glomerular basement membrane, and nephrotic syndrome with proteinuria similar to that observed in humans with autoimmune glomerulonephritis (*63*).

Autoimmunization with purified self-antigens can elicit a specific autoimmune response, particularly when adjuvants are administered in conjunction with self-proteins. A frequently used model of this type—experimental autoimmune encephalomyelitis—is induced by immunization of rodents with myelin basic protein with Freund's complete adjuvant. The resulting pathology is a Th-cell–mediated autoimmune disease characterized by central nervous system perivascular lymphocyte infiltration and destruction of the myelin nerve sheath with resultant paralysis similar to that observed in patients with multiple sclerosis (*64*).

The genetically predisposed models, whether naturally occurring, transgenic, or knockout based, tend to be the most reliable and therefore have been more commonly employed in autoimmunity research (*65*). In these models, mild to severe syndromes spontaneously develop, usually because of specific MHC allele mutations encoding class II molecules and often inducing functional abnormalities of the Th cell (*66*).

In each type of model the development and severity of symptoms have multiple components in that the presence of the disease and its progression can be influenced by age, hormonal, and/or environmental factors. In addition, there is a tendency for more than one autoimmune disorder to occur in several of the individual models. Nevertheless, a number of syndromes similar to those clinically observed in humans can be mimicked in animal models.

Table 2. Experimental models for autoimmune diseases.[a]

Autoimmune disease	Classification: Organic or chemical induction	Classification: Autoimmunization	Classification: Genetically predisposed strains
Autoimmune thyroiditis		Thyroglobulin - experimental autoimmune thyroiditis (m,r)	MRL (m) BB (r) OS (ch)
Insulin-dependent diabetes mellitus	Streptozotocin (m)		NOD (m) BB (r) DRBB (r) BN (r)
Myasthenia gravis	Penicillamine (m,r)	Acetylcholine receptor – experimental autoimmune myasthenia gravis (m,r)	
Multiple sclerosis		Myelin basic protein – experimental autoimmune encephalomyelitis (m,r,ch)	
Rheumatoid arthritis	Streptococcal cell wall (r)	CFA + type II collagen (m,r,mo) CFA + mycobacterium heat shock protein (m,r)	MRL/*lpr* (m) SCID (m) HLA B27 (r)
Systemic lupus erythematosus	Mercury (m,r,mo) Penicillamine (m,r) Procainamide (m,r)	CFA + anti-DNA antibodies (m,r)	MRL +/+ (m) MRL/*lpr* (m) MRL-mp-*lpr*/lpr (m) NZW 2410 (m) NZB/NZW (m)
Systemic sclerosis (scleroderma)			TSK (m)

Abbreviations: CFA, complete Freund's adjuvant; chicken, ch; m, mouse; mo, monkey; r, rat. [a]Table adapted from Lo (*65*), Bigazzi (*67*), and Cohen and Miller (*68*).

Summary

Many questions remain with respect to the specific etiology of a majority of the autoimmune disorders. The exact nature of the inciting antigen, the regulatory mechanisms that govern the onset and extent of the autoimmune response, the mechanisms by which spontaneous remissions and flare-ups occur, the role of environmental factors and how they initiate and perpetuate autoimmune responses, and the identity and mechanism of action of genes that predispose or accelerate autoimmunity continue to elude scientists in the field. These critical issues will be the focus of future research efforts.

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