Autoimmune Disease: Mechanisms

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The immune system provides protection against infectious organisms and repairs tissue damage induced by infections or physical damage. Autoimmune disease occurs when the immune response inflicts damage to tissues in the body.

Introductory article

Article Contents

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Introduction

The immune system specifically recognizes and eliminates foreign agents thereby protecting the host against infection. During maturation of the immune system, immune cells that react against self-tissues are eliminated providing an immune system that is 'tolerant' to self. Historically, autoimmunity or reactivity of the immune system to self-antigens was thought of as an aberrant response. More recently, researchers have realized that autoimmunity is a natural phenomenon, with self-reactive antibodies and autoimmune cells present in all normal individuals. Anti-self responses are usually generated in the process of mounting an immune response to foreign antigens, but autoimmune disease results only if autoimmunity is poorly regulated. A combination of genetic predisposition and environmental factors contribute to the development of autoimmune disease. Although individual autoimmune diseases are relatively uncommon, as a group they affect approximately 5–8% of the population in the United States and are the third most common category of disease in industrialized countries following cardiovascular disease and cancer. Because many autoimmune diseases start at a relatively young age and continue throughout life, they have a disproportionate affect on public health with an estimated annual cost of over 100 billion dollars in the United States alone. Furthermore, most autoimmune diseases are chronic in nature requiring a lifetime of care. Understanding the mechanisms that lead to dysregulation of the immune response resulting in autoimmune disease is necessary to develop better therapies to treat and possibly even prevent these diseases.

Genetics

The development of autoimmune disease depends on a combination of genetic and environmental factors (**Figure 1**). Most autoimmune diseases are thought to be polygenic, involving more than one gene. The idea that individuals are genetically predisposed to develop autoimmune disease arose from clinical reports that patients often describe a family history of autoimmune diseases. For example, patients with the autoimmune thyroid diseases, Graves' disease or Hashimoto's thyroiditis, have a family history of developing one or the other of these diseases. Patients with autoimmune thyroid disease are also more likely to develop other autoimmune diseases like systemic lupus erythematosus (lupus), pernicious anaemia, type I diabetes or Addison disease. There is also a higher probability that other family members without autoimmune disease will develop increased levels of autoantibodies. The fact that autoimmune diseases cluster in families and in individuals suggests that common mechanisms increase autoimmunity in genetically susceptible individuals. Thus, defects in genes that regulate inflammation, for example, could increase the susceptibility of developing an autoimmune disease. **See also**: Autoimmune Disease: Genetics

Human lymphocyte antigen, or HLA haplotype, is the best available predictor of developing an autoimmune disease. The likelihood of developing similar autoantibodies relates directly to sharing HLA haplotypes with family members and the probability is even greater if two haplotypes rather than one are shared. HLA haplotype, or the major histocompatibility complex (MHC) in mice, is proposed to increase autoimmune disease by enhancing antigen presentation in the periphery resulting in increased T-cell activation. Genes outside of the MHC also contribute to the risk for developing autoimmune disease. Extensive studies of type I diabetes mellitus and lupus or their animal models, have revealed a number of non-MHC genes that contribute to susceptibility. Common susceptibility loci have been found for a number of different autoimmune diseases, including diabetes and myocarditis, suggesting that shared genes are involved in the pathogenesis of autoimmune diseases. Recent evidence suggests that many of the genes conferring susceptibility control immunoregulatory factors.

Studies of the prevalence of autoimmune disease in monozygotic and dizygotic twins indicate that environmental factors are also necessary for the development of disease. If an autoimmune disease is due entirely to genes, then its concordance rate in identical monozygotic twins should be 100% and its concordance in nonidentical

dizygotic twins 50%. However, if autoimmune disease is due to environmental factors, the concordance rate should be similar in monozygotic and dizygotic twins. Comparison of the occurrence of autoimmune diseases in genetically identical, monozygotic twins found a concordance rate in the range of 10–50% in different studies and 2–40% for dizygotic twins. The low disease concordance in monozygotic twins ($<50\%$) indicates that environmental agents are important in the development of autoimmune diseases. Thus, heredity accounts for only about one-third of the risk of developing an autoimmune disease, while noninherited, environmental factors account for the remaining 70% risk (**Figure 1**).

Environment

External environmental factors such as hormones, diet, drugs, toxins and/or infections are important in determining whether an individual will develop autoimmune disease. Environmental agents are able to amplify autoimmunity in genetically susceptible individuals and to break tolerance in genetically resistant individuals, thereby increasing the risk of developing autoimmune disease (**Figure 2**). **See also**: Autoimmune Disease

Hormones

Most autoimmune diseases are more prevalent in women than men. Conservative estimates indicate that nearly 80% of individuals with autoimmune diseases are women. Exceptions include diabetes mellitus, ankylosing spondylitis and inflammatory heart disease, which occur more frequently in men. Hormones are obtained from external sources like diet (i.e. soy), drugs (i.e. birth control pills) or skin products in addition to production of steroids by the body. Sex hormones (natural and synthetic) directly interact with cells of the immune system via receptors on the surface or inside immune cells. Steroid hormones, including oestrogens and androgens, are known to influence antibody production and immune cell proliferation. Thus, hormones can amplify or inhibit the immune response. Women produce elevated antibody responses compared to men, while men often develop more severe inflammation. Most of our understanding of sex differences and the immune response is derived from studies conducted in animal models. Many animal models show a sex-bias in prevalence and severity of disease that is similar to human autoimmune diseases. Understanding how sex hormones regulate the immune response is an area of avid research.

Diet

Any number of environmental agents present in our diet, such as chemical food additives or pesticides, could interfere with regulation of the immune response contributing to the development of autoimmune disease in genetically susceptible individuals. One dietary component that has been shown to increase autoimmune disease is iodine. The increased prevalence of autoimmune thyroid disease in United States and Western European populations has been associated with increased use of iodized salt. Iodine binds to the thyroid hormone precursor, thyroglobulin, making it a target for the immune system resulting in increased autoantibodies against thyroglobulin and recruitment of inflammation to the thyroid gland.

Coeliac disease resulting from gluten-sensitivity also has the hallmarks of an autoimmune disease. Genetically susceptible individuals develop hypersensitivity to wheat gluten and similar proteins of barley, rye and oats resulting in inflammation of the intestine and autoantibodies against the enzyme transglutaminase as well as calreticulin and actin. Although considerable progress has been made

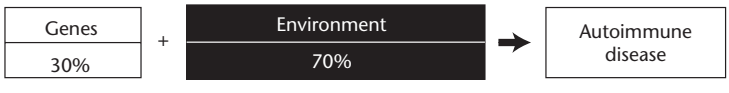

Figure 1 The development of autoimmune disease depends on a combination of genetic and environmental factors like hormones, diet, toxins, drugs and infections. Genetic predisposition accounts for only about one-third of the risk of developing an autoimmune disease, while noninherited environmental factors account for the remaining 70% risk.

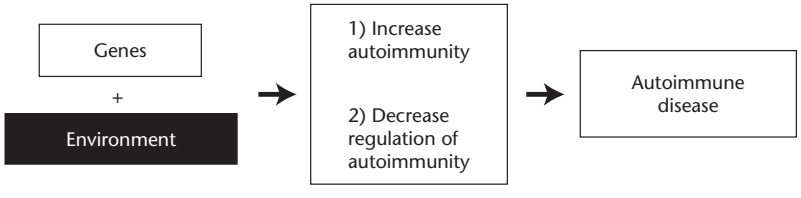

Figure 2 Alterations in mechanisms that regulate inflammation, whether due to genes and/or environment, contribute to the progression from autoimmunity to autoimmune disease. Autoimmune responses are usually generated in the process of mounting an immune response to foreign antigens, but autoimmune disease results only if autoimmunity persists and is poorly regulated.

regarding the molecular basis of coeliac disease, many questions remain regarding its status as an autoimmune disease. An important question is whether other autoimmune disorders can be initiated by immune responses to foreign, yet unidentified, antigens.

Toxins/drugs

For quite some time, toxins like heavy metals or drugs intended for therapy have been associated with disease syndromes resembling autoimmune diseases. For example, drugs like procainamide and hydralazine can induce autoantibodies and lupus-like disorders in patients. Penicillamine has been associated with myasthenia gravis and α-methyldopa is known to cause a form of haemolytic anaemia. However, in all cases of drug-induced autoimmune diseases described thus far, the disease disappears when the drug is removed.

Various heavy metals, such as mercury, silver or gold, can induce an autoantibody response to cell nuclear antigens in susceptible strains of mice. By yet unknown mechanisms, mercurial compounds have been shown to exacerbate autoimmune disease in experimental animal models. Recently, administration of mercuric chloride to susceptible strains of mice was found to increase autoantibodies and cell-mediated autoimmunity in a collagen-induced model of arthritis. These findings suggest that environmental factors like the microbial component of adjuvant in the collagen-induced model and mercury exposure can act synergistically to promote autoimmune disease.

Infections

Bacterial and viral infections were some of the first agents associated with autoimmune diseases more than a century ago. However, most of the clinical evidence linking autoimmune diseases with preceding infections is only circumstantial. For example, diabetes has been associated with coxsackievirus and cytomegalovirus infections, multiple sclerosis with Epstein–Barr virus and measles virus infections, rheumatoid arthritis with mycobacteria and Epstein–Barr infections and myocarditis with coxsackievirus and cytomegalovirus infections, to name a few. Since infections generally occur well before the onset of signs and symptoms of autoimmune disease, linking a specific causative agent to a particular autoimmune disease is difficult. The most direct evidence that infectious agents can induce autoimmune disease is the development of disease in experimental animals following inoculation with self-antigens in combination with adjuvant containing uninfectious microbial antigens. The fact that multiple, diverse types of microorganisms are associated with a single autoimmune disease suggests that infectious agents induce autoimmune disease through common mechanisms.

Several mechanisms have been proposed for how infections can lead to autoimmune disease including direct viral damage, release of cryptic self-peptides, antigenic spread, molecular mimicry, bystander activation and the adjuvant effect. Molecular mimicry is the concept that antigens of the microorganism closely resemble self-antigens and so when an infection occurs autoimmunity is also induced. Bystander activation may occur when the immune response is nonspecifically stimulated by the infection resulting in activation of autoimmunity in genetically susceptible individuals. The adjuvant effect describes the specific activation of the innate immune response by microbial antigens as occurs, for example, during administration of adjuvants in vaccines. A number of autoimmune diseases can be induced experimentally by administering self-antigen with adjuvant, such as rheumatoid arthritis with collagen, multiple sclerosis with myelin basic protein and myocarditis with cardiac myosin. Animal models of autoimmune disease, whether induced with adjuvants or chemicals, spontaneous as in the nonobese diabetic (NOD) mouse or biobreeding (BB) rat models of diabetes or genetically engineered models, provide valuable information on the mechanisms leading to disease and the efficacy of therapeutic strategies designed to combat autoimmune disease. **See also**: Autoimmune Disease: Animal Models

Autoimmune Disease

A common feature of all autoimmune diseases is the presence of autoantibodies and inflammation, including mononuclear phagocytes, autoreactive T lymphocytes and plasma cells (autoantibody producing B cells). Autoimmune diseases can be classified as organ-specific or nonorgan-specific depending on whether the autoimmune response is directed against a particular tissue like the thyroid in Hashimoto's thyroiditis, or against widespread antigens such as cell nuclear antigens in lupus. **See also**: Autoimmune Disease; Autoimmune Disease: Animal Models; Autoimmune Disease: Diagnosis

Antibody-mediated damage

Antibodies or immunoglobulins are a family of glycoproteins present in the serum and tissue fluids of all mammals. Antibodies can be carried on the surface of B cells, acting as receptors, or free in the blood or lymph. Specific binding of antigens (self or foreign) causes B cells to produce large amounts of antigen-specific antibody. These antibodies provide critical protection against infectious microorganisms immediately following infection and are the key protective immune response induced by vaccination. Similarly, self-reactive or autoantibodies are important in clearing cellular debris induced by inflammation or physical damage to the body.

A common feature of all autoimmune diseases is the presence of autoantibodies, which are an important factor in the diagnosis or classification of the autoimmune

disease. Due to the chronic nature of most autoimmune diseases, autoantibodies appear long before clinical symptoms, providing a good predictive marker for the potential to develop disease. In fact, the risk of developing an autoimmune disease rises from about 10% if one autoantibody is present to around 60–80% if three autoantibodies are present for a particular autoimmune disease.

Autoantibodies can induce damage to the body by binding to self-tissues, activating the complement cascade and inducing lysis and/or removal of cells by phagocytic immune cells. This occurs in certain forms of haemolytic anaemia when autoantibodies bind to red blood cell surface antigens inducing lysis of red blood cells. Autoantibodies can also interact with cell-surface receptors, altering their function. Autoantibodies to the acetylcholine receptor block transmission at the neuromuscular junction resulting in myasthenia gravis, while autoantibodies to the thyrotropin receptor block thyroid cell stimulation resulting in Graves' disease. Self-antigen, autoantibodies and complement can combine to form injurious immune complexes that deposit in vessels or joints as is observed in lupus, inflammatory heart disease and arthritis.

Cell-mediated damage

Damage induced by cells of the immune system play a major pathogenic role in many autoimmune diseases. The predominant infiltrating cells include phagocytic macrophages, neutrophils, self-reactive CD4+ T helper cells and self-reactive CD8+ cytolytic T cells, with smaller numbers of natural killer cells, mast cells and dendritic cells. Immune cells damage tissues directly by killing cells or indirectly by releasing cytotoxic cytokines, prostaglandins, reactive nitrogen or oxygen intermediates. Tissue macrophages and monocytes can act as antigen-presenting cells to initiate an autoimmune response, or as effector cells once an immune response has been initiated. Macrophages act as killer cells through antibody-dependent cell-mediated cytotoxicity and by secreting cytokines, such as tumour necrosis factor (TNF) or interleukin (IL)-1, which act as protein signals between cells. Macrophages and neutrophils damage tissues (and microorganisms) by releasing highly cytotoxic proteins like nitric oxide and hydrogen peroxide. Cytokines and other mediators released by macrophages recruit other inflammatory cells, like neutrophils and T cells, to the site of inflammation.

CD4+ T cells have been classified as T helper 1 (T_H1) or T helper 2 (T_H2) cells depending on the release of the cytokines interferon-γ (IFN-γ) or IL-4, respectively. IFN-γ is a proinflammatory cytokine associated with many organ-specific autoimmune diseases like type I diabetes and thyroiditis, while IL-4 activates B cells to produce antibodies and is associated with autoantibody/immune complex-mediated autoimmune diseases like lupus and arthritis. Suppressor or regulatory T-cell populations, including activated CD25+CD4+ regulatory T cells, exist in peripheral tissues and are important in controlling inflammation and autoimmune responses by killing autoreactive cells. These regulatory cells also secrete anti-inflammatory cytokines like IL-10 and transforming growth factor (TGF)-β that further inhibit T_H1 immune responses, thereby reducing inflammation and autoimmune disease. If regulation of self-reactive T-cells and autoantibody production by regulatory T-cell populations is disrupted by environmental agents like infections or toxins, then chronic autoimmune disease may result.

Tolerance

Mechanisms of self-tolerance, defined as a state of nonresponsiveness to self, can be divided into central and peripheral tolerance. In central tolerance, immature lymphocytes in the bone marrow (B cells) and thymus (T cells) that recognize self-antigens with high affinity die by apoptosis or programmed cell death. In peripheral tolerance, mature self-reactive lymphocytes are inactivated, killed or turned off by regulatory mechanisms including functional anergy, ignorance and suppression by regulatory T cells. Defects in tolerance leading to autoimmune disease may occur in one or multiple tolerance mechanisms. For example, changes in the apoptotic cell death process, resulting in inappropriate cell death or survival or disturbances in clearing apoptotic cells, are thought to be involved in the pathogenesis of a number of autoimmune diseases such as rheumatoid arthritis, lupus and Hashimoto's thyroiditis. **See also**: Autoimmune Disease

Common Mechanisms

Several features are similar between all autoimmune diseases suggesting that common pathogenic mechanisms lead to the development of autoimmune disease in genetically susceptible individuals. A number of these common mechanisms have already been discussed in this review. A feature common to all autoimmune diseases is that they cluster in families and in individuals. Although genes are important in determining the likelihood of developing autoimmunity, in most cases environmental agents are also necessary for autoimmune disease to develop (**Figure 1**). For example, in animal models of arthritis, disease does not develop in genetically susceptible animals unless adjuvant with microbial and self-peptides is administered. Although some animals (and humans) develop autoimmune diseases spontaneously due to genetic defects, these models are not thought to closely represent most cases of human autoimmune disease. Autoimmune diseases also display a strong sex-bias, with antibody-dependent systemic autoimmune diseases occurring more often in females, while inflammation is often more severe in males. Thus, endogenous and exogenous sex hormones are able to alter the

immune response, impacting the progression to autoimmune disease. Infectious microorganisms have long been considered important aetiologic agents in the development of autoimmune disease. Although their role in patients has been difficult to substantiate, animal models have demonstrated that some autoimmune diseases can be induced by infectious agents such as inflammatory heart disease following coxsackievirus infection. That many diverse microorganisms have been associated with a single autoimmune disease (e.g. viral, bacterial and parasitic infections associated with inflammatory heart disease) and one type of microorganism associated with many different autoimmune diseases (e.g. coxsackievirus infection associated with diabetes, thyroiditis and inflammation in the heart) further indicates that infections may induce autoimmune disease by common pathogenic mechanisms. That is, the inflammatory response to infection is more important than the particular infectious agent in triggering autoimmune disease.

Innate immunity

Activation of the innate immune system is essential for the development of a protective adaptive immune response against infection and for the development of autoimmune disease. Innate immune cells produce responses to particular classes of pathogens via pattern recognition receptors (PRR), such as Toll-like receptors (TLR). Interaction of pathogen-associated molecular patterns (PAMP) on microorganisms with PRR on antigen-presenting cells (APC) like macrophages and dendritic cells results in the upregulation of surface molecules essential for antigen presentation and the production of proinflammatory cytokines. Microbial components of adjuvants, like lipopolysaccharide (LPS) or the mycobacteria in complete Freund's adjuvant, activate the innate immune response when administered with self-antigens resulting in autoimmune disease in animal models such as collagen-induced arthritis or cardiac myosin-induced myocarditis. Inoculation of adjuvants without self-antigen does not usually result in the development of autoimmune disease. Microorganisms not only stimulate the immune response by stimulating PRR like TLR2 and TLR4, but also provide self-antigens to the immune system by damaging tissues, both of which are necessary for the development of autoimmune disease in animal models. Recent studies in animal models have demonstrated that stimulating the innate immune response is critical for the later development of autoimmune disease. Thus, exposure to environmental agents that alter or influence the innate immune response may increase the risk of developing an autoimmune disease in genetically susceptible individuals.

Proinflammatory cytokines

Another pathogenic mechanism common to autoimmune diseases is the increased production of the cytokines TNF and IL-1β. These proinflammatory cytokines are produced during the innate and adaptive immune response and act in a long-range endocrine manner, affecting immune cells far removed from the site of infection or inoculation. If TNF or IL-1β levels are increased by inoculation of mice with the adjuvant LPS (which stimulates TNF and IL-1β production) or with either cytokine, autoimmune disease can be increased in genetically susceptible strains of mice or tolerance broken in genetically resistant strains. This indicates that genetic resistance to developing autoimmune disease can be overcome by environmental factors like infections or adjuvants that increase proinflammatory cytokines. Some epidemiological evidence for this exists in studies of individuals from regions of the world where the incidence of autoimmune disease is low (i.e. the Equator) moving to regions where autoimmune diseases are more common (i.e. the Northern hemisphere) who go on to develop autoimmune disease. Since only the environment changed and not the genetic background of the individual, environment appears to exert a dominant influence on whether an individual will develop an autoimmune disease (**Figures 1** and **2**). Furthermore, autoimmune disease can be prevented in humans or animal models if TNF or IL-1 levels are reduced using neutralizing monoclonal antibodies. Recent clinical therapies blocking TNF have produced remarkable effects in reducing the severity of autoimmune diseases like rheumatoid arthritis, inflammatory bowel disease, ankylosing spondylitis, psoriasis and multiple sclerosis. Experience has shown, however, that it is difficult to turn off an ongoing autoimmune response and intervention during the earliest stages of antigen recognition is likely to be necessary for successful treatment or prevention of disease. **See also**: Autoimmune Diseases: Gene Therapy; Autoimmune Disease: Treatment

Regulating the immune response

The induction of an immune response must be followed by downregulation of the response to maintain homeostasis of the immune system and to prevent or reduce tissue damage. Likewise, inflammation associated with autoimmune disease can be reduced or possibly even prevented if proinflammatory responses are appropriately downregulated. Multiple inhibitory pathways keep the immune response in check including the inhibitory receptors CTLA-4 and Tim-3, anti-inflammatory cytokines like IL-10 and TGF-β and specialized cells like regulatory T cells. Recently, it has been demonstrated that signals leading to both activation and regulation of the immune response are initiated during innate immunity. In adjuvant-induced animal models of autoimmune disease, depletion of regulatory T cells increases inflammation while administering these cells can reduce or even prevent disease. Thus, the balance between effector T cells and regulatory T cells may determine whether autoimmune disease develops or

persists. Recently, microbial stimulation of TLR was found to decrease the number of regulatory T cells, which could be one explanation for the link between infection and the development of autoimmune disease. Thus, alterations in mechanisms that regulate inflammation, whether due to genes or environment, may contribute to the progression from autoimmunity to autoimmune disease.

Immunotherapy

Patients usually come to medical attention only after antigenic spread and autoimmune escalation have greatly expanded the immune response, making it difficult to intervene at the point of initiation of disease. In the past, therapies for autoimmune diseases have included immunosuppressive or antiviral/antibacterial treatments. Recent therapies, however, are selectively targeting pathways common to a number of autoimmune diseases. Therapies include treatments that target proinflammatory cytokines like TNF and IL-1β, block costimulatory molecules or use therapeutic vaccination with regulatory T cells. Recently, familiar oral medications, such as statins and angiotensin blockers, widely used to treat other disease conditions such as allergy and hypertension, have been shown to inhibit autoimmune inflammation. Since multiple effector mechanisms contribute to the immunopathogenesis of autoimmune diseases, it is likely that several effector mechanisms will need to be targeted to effectively treat autoimmune disease. **See also**: Autoimmune Diseases: Gene Therapy

Further Reading

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