

Autoimmune diseases and infections

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ABSTRACT

Autoimmune disease occurs when a response against a self-antigen(s) involving T cells, B cells, or autoantibodies induces injury systemically or against a particular organ. In fact, autoantibodies as well as B- and T-lymphocytes bearing specific receptors for self antigens are found in health individuals. Autoimmune disease is an aggressive and harmful immune reaction against autologous tissue. Both the humoral and cellular part of the immune response are involved, since autoantibodies, as well as auto-reactive T-cells are present. Although an autoimmune response occurs in most persons, clinically relevant autoimmune disease develops only in susceptible persons. Infectious agents and/or their products have been implicated in the pathogenesis of autoimmune and chronic inflammatory diseases. Since infections generally occur well before the onset of symptoms of autoimmune disease, linking a specific causative agent to a particular autoimmune disease is difficult. This difficulty raises the question of whether autoimmune diseases really can be attributed to infections. A vast quantity of literature documenting appearance or exacerbation of autoimmune disease after viral infection has accumulated in recent years. No single causative microorganism or mechanism can be held responsible for the spectrum of clinical manifestations of autoimmune disease, which can range from being organ-specific (e.g. autoimmune hepatitis, Hashimoto's thyroiditis, etc.) to system-wide (e.g. systemic lupus erythematosus).

Key words: autoimmunity, autoimmune diseases, infections

The etiology of autoimmune diseases remains largely unknown. It is generally accepted that the etiology of autoimmune disease is multifactorial, and that environmental, genetic (genetic background accounts for only about one third of the risk of autoimmune disease) and humoral factors are of prime significance. There are considerable data

supporting the role of infection in a variety of autoimmune diseases (1).

Immunologists have long suspected that viral and bacterial infections may be able to initiate autoimmune responses. Many different microorganisms (e.g., streptococci, Trypanosoma, Cytomegalovirus, Coxsackie virus B3 etc.) have been associated with autoimmune diseases (2,3).

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The concept of virus-induced autoimmune disease is supported by a wide range of experimental and clinical observations. A vast quantity of literature documenting appearance or exacerbation of autoimmune disease after viral infection has accumulated in recent years (e.g., hepatitis C virus) (4).

Recently, great interest has been the association with pancreatropic viruses infection, such as mumps virus. The association of infections and autoimmune diseases has long been recognized and in fact the first human autoimmune disease described (paroxysmal cold haemoglobinuria) was considered a consequence of syphilis.

Many of the immune diseases associated with infection have a genetic component, suggesting that genetic susceptibility may play a role in the development of pathologic immune responses to microorganisms.

To address the question of whether autoimmune diseases can be induced by infections, first autoimmunity needs to be defined. Most autoimmune diseases develop without apparent cause, fluctuate inexplicably over many years, and may even disappear (3).

Autoimmune disease as a pathological disorder has to be distinguished from auto-immu-

nity, which might serve physiological functions. Understanding of autoimmune diseases is hindered by the fact that some level of autoimmunity, in the form of naturally occurring autoantibodies and self-reactive T and B cell, is present in all normal persons. Thus, on a proportional basis, developing autoimmune disease is the relatively uncommon consequence of a common autoimmune response (4).

The best evidence so far that infections can induce autoimmune diseases comes from animal models. In most animal models of autoimmunity, including myocarditis, disease has been transferred to native animals with autoimmune cells (splenocytes or T cells), autoantibodies, or both, which provides compelling evidence that infections induce autoimmune diseases by immune-mediated mechanisms. In addition to antigen-specific mechanisms, nonspecific mechanisms could also lead to autoimmunity after infection.

To better understand the relationship between infection and autoimmune disease, it was established a mouse model of myocarditis, or inflammation of the heart, induced by Coxsackie virus B3 (CB3) infection. After mice was infected with CB3, autoantibodies are produced against cardiac myosin, the major component of heart muscle.

Disease	Infection
Multiple sclerosis	Epstein Barr virus (EBV), measles virus
Lyme arthritis	Borrelia burgdorferi
Type 1 diabetes	Coxsackie virus B4, rubella virus, cytomegalovirus (CMV), mumps virus
Immune haemolytic anaemia	EBV, Mycoplasma pneumoniae
Rheumatoid arthritis	Escherichia coli, Mycobacterium, EBV, hepatitis C virus (HCV)
Lupus erythematosus	EBV
Myocarditis	CB3, CMV, Chlamydia
Rheumatic fever/myocarditis	Streptococci
Polyarteritis nodosa	Hepatitis B and C viruses, Human Immunodeficiency virus
Chagas' disease/myocarditis	Trypanosoma cruzi
Myasthenia gravis	Herpes simplex virus, HCV
Guillain-Barré syndrome	CMV, EBV, Campylobacter spp.
Rheumatic arthritis	Escherichia coli, mycobacteria, EBV, hepatitis C virus (HCV)
Spondylarthropaties	Enterobacteriaceae, Klebsiella spp.
Reactive arthritis	Retroviruses
Crohn's disease	Mycobacterium paratuberculosis
Celiac disease	Adenoviruses
Psoriasis	Retroviruses, streptococci
Henoch-Schöenlein purpura	β-haemolytic streptococcus
Kawasaki disease	Staphylococcus aureus, streptococci
Yersinia pseudotuberculosis	

TABLE 1. Infections in humans associated with autoimmune diseases (1)

Adjuvants (usually bacterial, e.g. *Mycobacterium* in complete Freund's adjuvant) activate the innate immune response in the same pathogen-specific manner when administered with self-antigen, this process results in organ-specific autoimmune disease in animal models (4).

Viruses have long been postulated as the most likely environmental agents involved in the pathogenesis of autoimmune disease in susceptible individuals. Viral infections often result in the syndrome of autoantibodies that do not lead to tissue injury or clinical symptoms, but viral infections may also precede organ damage and the development of frank autoimmune disease.

The fact that clinical autoimmunity develops much less often after a viral infection than do autoantibodies reflects the absence, in some individuals, of additional factors that are needed to produce autoimmune disease.

The concept of virus-induced autoimmune disease is supported by a wide range of experimental and clinical observations. Of great interest recently has been the association between infection with pancreatropic viruses such as mumps virus, Coxsackie virus B3, or congenitally acquired rubella and the later development of type 1 diabetes mellitus (5-7).

Another clinical observations is the appearance of serum antibodies to DNA, erythrocytes, lymphocytes, neutrophils, platelets, immunoglobulin, cytoskeleton, smooth muscle and thyroglobulin after Epstein-Barr virus infection.

Autoantibodies in infectious mononucleosis (IM) are common, e.g. in one study, 97% and 66% IM patients had antibodies to cytoskeletal and nuclear antigens, respectively. Such observations are linked to the possible appearance of diverse autoimmune syndromes (immune thrombocytopenia, Sjögren syndrome, Guillain-Barré syndrome, SLE) after infectious mononucleosis. Other observations include the hepatic and extrahepatic autoimmune features of hepatitis B, A and C virus infections (including cryoglobulinemia, glomerulonephritis, arthritis and vasculitis) and the appearance of acute immunogenic thrombocytopenic purpura following vaccination for measles, chickenpox, mumps, and smallpox with live-attenuated vaccine. The origins of autoimmunity in systemic lupus erythematosus (SLE) are thought to involve both genetic and environmental factors.

Antecedent infection with many different microbes is often associated with the development of autoimmune disease in humans, but the pathogenic mechanisms involved, if any, are unknown. Most of the microbes associated with autoimmune disease have been viruses, particularly cytomegalovirus (CMV), Epstein Barr virus, and varicella-zoster virus. The rheumatic fever represents an autoimmune response triggered by streptococcal infection and mediated by cross-reactivity between streptococcal and cardiac myosin. A relatively new finding suggests a possible viral etiology for Sjögren syndrome. The Epstein-Barr virus must be considered in view of the history of infectious mononucleosis in many Sjögren syndrome patients. Reiter's syndrome and Lyme diseases are chronic immune-mediated inflammatory diseases that are clearly induced by infectious agents. Infection with *Campylobacter* spp. is a common antecedent of the Guillain-Barré syndrome.

An association of rheumatoid arthritis with various organisms, including mycoplasma, Epstein-Barr virus, parvovirus, and rubella, has been suggested. Type 1 diabetes mellitus, a metabolic disease caused by immune destruction of the pancreatic beta cells, has also been associated epidemiologically with various infectious agents, including rubella and Coxsackie virus. Recently, cross reactivity of T cell clones to both Coxsackie protein and glutamic decarboxylase (GAD65), a pancreatic islet beta cell protein and type 1-associated antigen, has provided molecular evidence for the association of type 1 diabetes with Coxsackie virus (8-10). In addition, various viral and bacterial peptides are able to activate myelin basic protein specific T cell clones, which were isolated from patients with multiple sclerosis.

A role for superantigens, which can be of viral or bacterial origin, has also been postulated. Superantigens are products of infectious agents that activate a large proportion of the host's T cells by interaction with the MHC and the variable domain of the beta-chain of their antigen receptors. Recently, isolation of islet infiltrating lymphocytes from the pancreas of patients with newly onset type 1 diabetes provided suggestive evidence that a superantigen may be involved in the origin of this disease (8).

Epidemiological and clinical data support the hygiene hypothesis according to which the decrease of infections observed over the last

three decades is the main cause of the incessant increase in immune disorders.

How can infections induce autoimmune diseases? Various mechanisms by which pathogens could induce autoimmune or immune-mediated diseases have been suggested. The organism may directly generate an immune response by its continued presence. If they do cause disease, several mechanisms may explain the association between viruses and autoimmune disease. To stimulate a complete autoimmune response, two signals (antigen specific and antigen non-specific), are necessary. Infectious agents can cause autoimmune disease by different mechanisms.

Mechanisms of induction of autoimmune disease by infectious agents could be: molecular mimicry; expression of modified cryptic or new antigenic determinants; superantigens; increased processing and presentation of autoantigens; cytokine release and immune activation; lymphocyte activation

A mechanism often called to explain the association of infection with autoimmune disease is molecular mimicry, that is, antigens or more properly epitopes of the microorganism closely resemble self-antigens. The term molecular mimicry denotes that peptide epitopes of an infectious agent have sequence homology with self-epitopes, therefore the foreign peptides can activate naïve autoreactive T cells specific for the corresponding self-epitopes (11-14). Molecular mimicry is considered an important pathogenic mechanism in rheumatic fever, in Guillain-Barré syndrome, in type 1 diabetes mellitus, in rheumatoid arthritis, in the spondylarthropathies, in multiple sclerosis, in Chagas's disease and in herpes simplex keratitis (15-18).

The induction of an immune response to the microbial antigen thus results in cross-reaction with self-antigens and induction of autoimmunity. Although epitope-specific cross reactivity between microbes and self-tissues has been shown in some animal models, molecular mimicry has not been clearly demonstrated to occur in human diseases (19,20).

Another possibility is that microorganisms expose self-antigens to the immune system by directly damaging tissues during active infections. This mechanism has been referred to as the "bystander effect". However, whether pathogens mimic self-antigens release sequestered self-antigens, or both, is difficult to determine.

Viral infections can induce damage to host tissues by direct (e.g., viral replication) or indirect (e.g., nitric oxide) mechanisms.

The purpose of immunological memory is to protect the host from reinfection to control persistent infections, and, through maternal antibody, to protect host's immunologically immature offspring from primary infections. Immunological memory is an exclusive property of the acquired immune system, where in the presence of CD4 T cell help, T cells and B cells clonally expand and differentiate to provide effector systems that protect the host pathogens.

The initial autoantigenic epitope for some lupus patients directly cross-reacts with a peptide from the latent viral protein Epstein-Barr virus nuclear antigen-1 (EBNA-1). Animals immunized with either the first epitope of 60 kDa Ro or the cross-reactive EBNA-1 epitope progressively develop autoantibodies binding multiple epitopes of Ro and spliceosomal autoantigenes. These data support the hypothesis that some humoral autoimmunity in lupus patients arises through molecular mimicry between EBNA-1 and lupus autoantigens and provide further evidence to suspect an etiologic role for Epstein-Barr virus in SLE (21-23).

The best described antigen-specific mechanism is molecular mimicry, whereby some component of the offending virus resembles the host structure on a molecular level, thus providing the template for antibody formation that may crossreact with self-antigen. Several of the antigen non-specific signals include costimulatory cell surface markers as well as the generation of a multitude of cytokines. Theoretically, viruses may play a role in eliciting either or both of these signals.

CMV has been associated with the increased production of rheumatoid factor, antiphospholipid antibodies, cold agglutinins, antimyosin antibodies, antiendothelial cell antibodies and antiganglioside antibodies. One study found an increased incidence of anti-CMV antibodies among patients with systemic lupus erythematosus.

Neutralizing antibodies induced by CMV are directed primarily against the major envelope protein of CMV, glycoprotein B (gB). Antibodies to CMV gB share some homology with rheumatoid factor, thus providing a theoretical relationship between CMV infection and autoimmune disease.

It was reported an increased incidence of antibodies to Sm antigen and antibodies to ribonucleoprotein (RNP) among naturally CMV-infected individuals, as well as an increase in antibodies to U1-70 kD.

Microbial antigens have the potential to initiate autoreactivity through molecular mimicry, polyclonal activation, or the release of previously sequestered antigens (24-26).

In the Guillain-Barré syndrome and its variants, antibody cross-reactivity has been demonstrated between human gangliosides and lipopolysaccharides of *Campylobacter* spp.

In autoimmune diabetes, T cells recognize both a peptide derived from the autoantigen glutamic acid decarboxylase and a highly analogous peptide from Coxsackievirus P2-C protein.

In multiple sclerosis, T cells react with both a peptide from the autoantigen myelin basic protein and peptides from Epstein-Barr virus, influenza virus type A, and human papillomavirus.

In these examples infection could cause the initiation activation of the lymphocytes that mediate these diseases and autoantigen could sustain the activation that persists even after the eradication of the infectious agent.

Microbial infection can also cause polyclonal activation of autoactive lymphocytes. Microbes that kill cells can cause inflammation, the release of sequestered antigens.

It is clear that inflammation, even in the absence of infection, can trigger polyclonal activation and autoreactivity.

Chronic inflammatory demyelinating polyneuropathy is a rare disease. The pathogenesis of the demyelination is thought to be immune mediated but the mechanism is uncertain. Antecedent infections are reported in 35% of the patients with chronic inflammatory demyelinating polyneuropathy, especially cytomegalovirus (CMV) infectious. The CMV infection probably triggers an immune reaction against components of peripheral nerve myelin.

A decrease in the activity of C4, which is involved in the neutralization of viruses and the dissolution of immune complexes, could contribute to the development of diabetes just as much as to other autoimmune diseases. The alternative pathway is initiated by structures on microbial surfaces. Alternately, the organism may induce an immune response, possibly by

revealing self antigens that are normally sequestered from the immune system, and this autoreactive response then becomes self-sustaining.

The role of superantigens in the pathogenesis of autoimmune diseases is far from clear. Superantigens are proteins produced by bacteria, mycoplasma and virus-infected cells which can link T cell receptor with the V region of the b chain of MHC class II molecules. As a result, superantigens can activate a large number of T lymphocytes of different antigenic specificities and they are potent immune stimulating molecules. Animal models also provide evidence that infectious agents may play a role in either initiating or in protecting the host from the development of autoimmune disease.

The knowledge developed through research into the mechanisms by which infectious agents break tolerance to self antigens should provide information about the underlying basis of autoimmunity.

Investigation of the role of pathogens in the development and regulation of the immune response in autoimmune or chronic immune-mediated inflammatory diseases may lead to new preventive or therapeutic strategies for these diseases.

T lymphocytes play a decisive role in the course and clinical outcome of viral CNS infection. The etiopathogenesis of childhood chronic autoimmune disease is, in most cases, unknown (27-31).

De Libero et al. (2005) demonstrate that bacterial infection leads to increased synthesis of autologous glycolipids that are recognized by CD1-restricted human T cells, indicating that recognition of inducible self-glycolipids could be a mechanism for microbial detection. This mechanism also may provide a connection between infection and autoimmunity (32). □

Conclusion

The study of animal models has clearly shown that infections may trigger autoimmune diseases.

Infectious agents can cause autoimmune diseases by different mechanisms, which fall into two categories: antigen-specific, in which pathogen products or elements have a central role e.g. superantigen or epitope (molecular) mimicry, and antigen non-specific, in which the pathogen provides the appropriate inflammatory setting for "bystander activation".

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