Interactions between infections and autoimmunity have been recently viewed in a bidirectional way: some evidence supports the role of infections as a cause of autoimmunity, but it was also suggested that infections may play a role in protecting from autoimmune diseases (ADs). However, the latter is not the focus of this review, because the so-called “hygiene hypothesis” was a theoretical hypothesis that was debunked even by its proposers. They stated that “the hygiene hypothesis remains a credible but nonspecific explanation for observed variations over time, place and persons at risk for developing atopic allergic disorders” and called for more prospective studies. However, this theory generated quite a lot of confusion among some doctors and parents on the real need to prevent and to treat infections in children. Therefore, in this article, we will briefly review the state of the evidence demonstrating the causative role of infections in ADs. This review differs from other recently published reviews in that it highlights the point of view of specialists in infectious diseases on this topic.

Autoimmunity is a physiological and, at low doses, even a beneficial event contributing to defense against infections. Autoreactive cells of adaptive immunity are normally present in human blood and tissues. Self-epitopes are recognized by the autoreactive cells when tissues are damaged by an infection. Furthermore, the availability of altered-self danger signals further released through autoimmune mechanisms increases the host innate and adaptive response to the invading pathogen.

ADs are the detrimental facet of these physiological mechanisms, and they result from multiple synergistic factors. Many ADs develop when a person with a genetic susceptibility encounters environmental triggering factors. The role of genetics in the pathogenesis of ADs has been well documented, but the absence of a complete concordance in identifying the genetic susceptibilities encounters environmental triggering factors. As a general rule, Koch’s postulates, or even their reinterpretation in the era of molecular diagnostics, are unlikely to be applicable to establish that an infectious agent is the cause of an AD, because clinical manifestations may appear even years after the acute infection, so that it may be difficult to establish a relationship.

In most cases, the infectious origin of AD is supported by the following factors: onset of the disease after an infection, seasonal trend and recovery of the microorganism, or of its nucleic acid sequences, in the affected tissues.

MAIN MECHANISMS TRIGGERING AUTOIMMUNITY AFTER INFECTIONS

The main nonmutually exclusive mechanisms are molecular mimicry, bystander activation, epitope spreading and polyclonal activation of B cells. Molecular mimicry grants T-cell and B-cell receptors flexibility, thymic selection and recognition of the largest number of antigens. However, microbial antigens with homology with self-antigens can stimulate the autoreactive T cells and trigger an autoimmune mechanism. This potentiality does not necessarily cause autoimmunity, if the recognition of a shared antigen does not occur together with an infection. Bystander activation is triggered by antigen-presenting cells, which stimulate and induce the proliferation of autoreactive T and B cells by presenting them the self-epitopes of the damaged tissues, in the presence of an inflammatory environment.

Epitope spreading occurs after bystander activation triggering an immune response against a different portion of the same protein or of a different protein. Epitope spreading is a helpful physiologic mechanism. In fact, if the set of responding T cells is large, the possibilities that the pathogen may escape the immune mechanisms with a single mutation into an immunogenic epitope are limited. The largest number of antigens is a helpful physiologic mechanism. In fact, if the set of responding T cells is large, the possibilities that the pathogen may escape the immune mechanisms with a single mutation into an immunogenic epitope are limited. However, the most common environmental factors acting in childhood are the infectious agents. As a general rule, Koch’s postulates, or even their reinterpretation in the era of molecular diagnostics, are unlikely to be applicable to establish that an infectious agent is the cause of an AD, because clinical manifestations may appear even years after the acute infection, so that it may be difficult to establish a relationship.

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AUTOIMMUNE DISEASES WITH A STRONG EVIDENCE OF AN INFECTIOUS ETIOLOGY

Rheumatic fever is the disease in which the causal relationship between an...
infection and an AD has been more clearly recognized. Rheumatic fever is the result of an immune response to the antigens of group A β-hemolytic streptococcus (GABHS) after pharyngitis or after a skin infection. Antibodies against the M protein of the GABHS cross-react with cardiac myosin, tropomyosin, laminin and other cardiac proteins in rheumatic carditis and with cerebral basal ganglia in Sydenham chorea or in Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections. Tissue damage occurs through a mechanism of molecular mimicry, but also through a persistent immune response which leads to bystander activation, because the streptococcal antigen may persist in the infected tissue for a long time. Even if the pathophysiology is not completely understood, human leukocyte antigen class II haplotypes have been shown to confer susceptibility to rheumatic fever. Therefore, rheumatic fever is considered the paradigmatic model of interplay between an infection and genetic susceptibility in the genesis of an AD.

Poststreptococcal acute glomerulonephritis is another severe noninfectious immune-mediated complication of GABHS infection. Unlike rheumatic fever, poststreptococcal acute glomerulonephritis is not clearly defined as an AD. Proposed mechanisms include the glomerular deposition of circulating immune complexes, as well as in situ formation of immune complexes resulting from antibodies directed against streptococcal antigens deposited in the glomerulus or against glomerular antigens (glomerular basement membrane components laminin and type IV collagen) with a mechanism of molecular mimicry. On the basis of differences in M protein serotypes, it is commonly believed that different strains of GABHS are intrinsically rheumatogenic (mainly M-serotypes 1, 3, 5, 6, 14, 18, 19 and 24), or nephritogenic (mainly M-serotypes 4, 12 and 25), because epidemiologic data show that the epidemiology of poststreptococcal acute glomerulonephritis differs from that of acute rheumatic fever.

Another AD with strong evidence in favor of an infectious etiology is myocarditis. Even if a large proportion of cases of myocarditis in infants has no known etiology, common viral infections, namely human enteroviruses (eg, coxsackievirus), adenovirus, parvovirus B19, herpesviruses (eg, human herpesvirus 6, cytomegalovirus [CMV]), HIV and hepatitis C virus, have been associated with the development of myocarditis. The detection of viral genome from myocardial biopsies and several studies on animal models suggest that viral myocarditis results, in an early phase, from myocardial damage due to the direct infection of the myocytes, with a consequent expression of cryptic antigens or modified myocardial proteins. Antibodies and specific T lymphocytes directed against viral, rather than myocardial, antigens trigger a sub-acute phase characterized by a postviral autoimmune activation which can last from weeks to several months, even after virus clearance. Several nonviral pathogens, including bacteria (eg, Borrelia burgdorferi, Mycoplasma pneumoniae, Streptococcus pneumoniae, Neisseria meningitidis), protozoa (eg, Trypanosoma cruzi, Toxoplasma gondii) and fungi (eg, Candida spp., Aspergillus spp, Cryptococcus spp.), may induce autoimmune myocarditis.

Immune-mediated polyradiculoneuropathies, such as Guillain-Barré syndrome and chronic inflammatory demyelinating polyradiculoneuropathy, are disorders resulting from an autoimmune reaction against peripheral nerve antigens. Autoantibodies directed against several gangliosides (eg, GM1, GD1b, GalNAc-GD1a and GT1) of distal motor nerve terminals and spinal anterior roots cause the progressive impairment of nerve conduction through several mechanisms, such as by blocking axonal sodium channels and by triggering an acute and chronic inflammation. Epidemiologic data show consistent evidence that in about 50–82% of children with Guillain-Barré syndrome the disease occurs 1–6 weeks after bacterial or viral infection. The strongest evidence is available concerning the causative role of Campylobacter jejuni, even if pediatric studies suggest other potential infectious triggers such as coxsackieviruses, Chlamydia pneumoniae, CMV, Mycoplasma pneumoniae.

It is well known that acute innate thromboctopenia in childhood is often associated with a preceding viral illness. As in myocarditis, immune thrombocytopenia may result from the direct infection of megakaryocytes, because some viruses such as HIV and CMV can infect megakaryocytes. However, autoimmune mechanisms may also be involved. Molecular mimicry between viral and platelet antigens is the best-known mechanism, because IgG against varicella-zoster virus, HIV, hepatitis C virus and Epstein-Barr virus cross-react with platelet antigens, such as glycoproteins IIb/IIIa and Ib/IX. However, antiviral antibodies cross-reacting with platelet glycoproteins are not always present. The pathophysioloxy of virus-associated immune thrombocytopenia is not completely elucidated. Other mechanisms have also been proposed, such as desialylation of platelet antigens or immune complex absorption on platelet surface and consequent platelet destruction.

**AUTOIMMUNE DISEASES WITHOUT DEFINITIVE EVIDENCE OF THEIR RELATIONSHIP WITH AN INFECTIOUS AGENT**

Several other AD have been investigated for a possible link with an infectious agent. One of the most intriguing topics is the development of type 1 diabetes in genetically susceptible individuals after viral infection. Although mumps, rubella, rotavirus, CMV have been implicated in the pathogenesis of type 1 diabetes, several studies and a recent meta-analysis of 33 molecular studies highlight the role of enteroviruses (particularly coxsackievirus B) in the development of islet cell-associated autoantibodies and in the clinical onset of type 1 diabetes. This relationship is supported by the detection of enterovirus RNA in blood and in Langerhans’ islets of patients at the onset of type 1 diabetes. However, some studies reach conflicting results, thus the role of enteroviruses in the pathogenesis of type 1 diabetes needs to be further confirmed. Similarly, there is consistent, but not definitive, evidence of the association between adenovirus and celiac disease, between parvovirus B19 and Hashimoto thyroiditis, between Porphyromonas gingivalis, Escherichia coli and Proteus mirabilis infections and rheumatoid arthritis and between herpes simplex virus and stromal keratitis.

**CONCLUSIONS**

There is strong evidence of the role played by some infections in the development of autoimmunity and of some overt ADs. Therefore, every effort should be made to prevent and treat these infections whenever possible. Further research is still needed to elucidate a causal relationship between other infections and ADs.

**REFERENCES**


