# Genetics of Childhood Disorders: XXIX. Autoimmune Disorders, Part 2: Molecular Mimicry

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The human immune system is undoubtedly one of the masterpieces of evolution. The processes of gene rearrangement and somatic hypermutation allow for the generation of an immense range of binding specificities in both antibodies and T-cell receptors. Almost any foreign material which find its way into the human body can be targeted and removed or destroyed with exquisite specificity. However, the immune system has not arisen in isolation but is the result of a biological arms race, conducted over millions of years, between man and the microorganisms that can enter the body and cause disease. As the immune system has developed, microorganisms have evolved strategies to subvert or evade its surveillance.

For the microbes, one logical tactic in this battle has been the development of camouflage. If the immune system cannot distinguish an invading microbe from its own tissues, then the battle is all but won. It is therefore logical that microbial or viral pathogens should evolve surface antigens that share sequence homology with normal cellular proteins, or at least present a similar surface structure to the immune surveillance mechanisms.

An inevitable consequence of this argument is that if an immune response should be mounted against the pathogen's antigens, then damage to host tissues will occur. This tissue damage may continue even if the invading organism that triggered the immune response has been cleared completely from the system.

This is the basis of the "molecular mimicry" hypothesis of autoimmune disease. An infectious agent gains access to the body and instigates an immune reaction that eventually clears the pathogen from the system. However, the antimicrobial antibodies continue to recognize native proteins bearing cross-reactive epitopes and continue to cause tissue damage. The binding to host proteins leads to cellular damage and the release of more autoantigen. This results in reamplification and spreading of the immune response. In the most fulminate cases, autoimmune destruction of the tissue results.

Since this hypothesis was first proposed in the early eighties, a huge body of evidence has accumulated supporting the view that a number of diseases are caused by molecular mimicry. Over the next several months, this column will review autoimmune disorders. The coverage of this topic is due to the recent resurgence of interest among researchers, clinicians, and families in autoimmunity hypotheses and their possible involvement in the etiologies of childhood neuropsychiatric disorders.

A large amount of data has demonstrated both structural similarities and antigenic cross-reaction of various bacterial, viral, and protozoan antigens with proteins in human tissues or cellular components of those tissues. Much circumstantial evidence links the onset or exacerbation of autoimmune disease with recent infections. In animal models, immunization with either viral peptides or their tissue antigen homologues can result in the development of autoimmune tissue destruction that closely mimics certain autoimmune diseases. Similarly, autoimmunity can be triggered very efficiently in certain animal models by systemic viral infections. A direct cause-and-effect relationship for infection and naturally occurring autoimmune disease in humans still eludes us. Nonetheless, a presumptive role of infectious organisms is now accepted in many autoimmune diseases, including insulin-dependent diabetes mellitus (coxsackie viruses), HLA-B27–associated ankylosing spondylitis (various Gram-negative bacteria), Guillain-Barré syndrome (*Campylobacter*), myasthenia gravis (herpesvirus), lyme disease arthropathies (*Borrelia*), and multiple sclerosis (various viruses).

Multiple sclerosis (MS) is a prime example of an autoimmune disease in which the circumstantial evidence for a viral trigger is becoming almost overwhelming. As yet, however, there is still no "smoking gun." MS is caused by the immunological destruction of myelinated nerves. It has a strong genetic element to its etiology, with almost two thirds of sufferers carrying the HLA DR2 allele. Monozygotic twins have a 30% concordance rate (10-fold higher than dizygotic twins have). The fact that the concordance rate in monozygotic twins is not 100% strongly suggests that environmental factors play an important role. There is also an intriguing finding that individuals who migrate from an area of high incidence to one of low incidence before their 15th birthday carry the lower risk factor, while those who migrate after this age retain the high risk factor.

The course of the disease follows a cyclical pattern of activity and remission, with exacerbations often following viral infections. The main target of the immunological effectors in MS is the myelin basic protein (MBP) and proteolipid-protein components of the myelin sheath, although the oligodendrocyte antigen transaldolase, and other minor components, are also targeted by autoantibodies. It is likely that the minor antigens targeted in MS result from epitope spreading during the course of the disease.

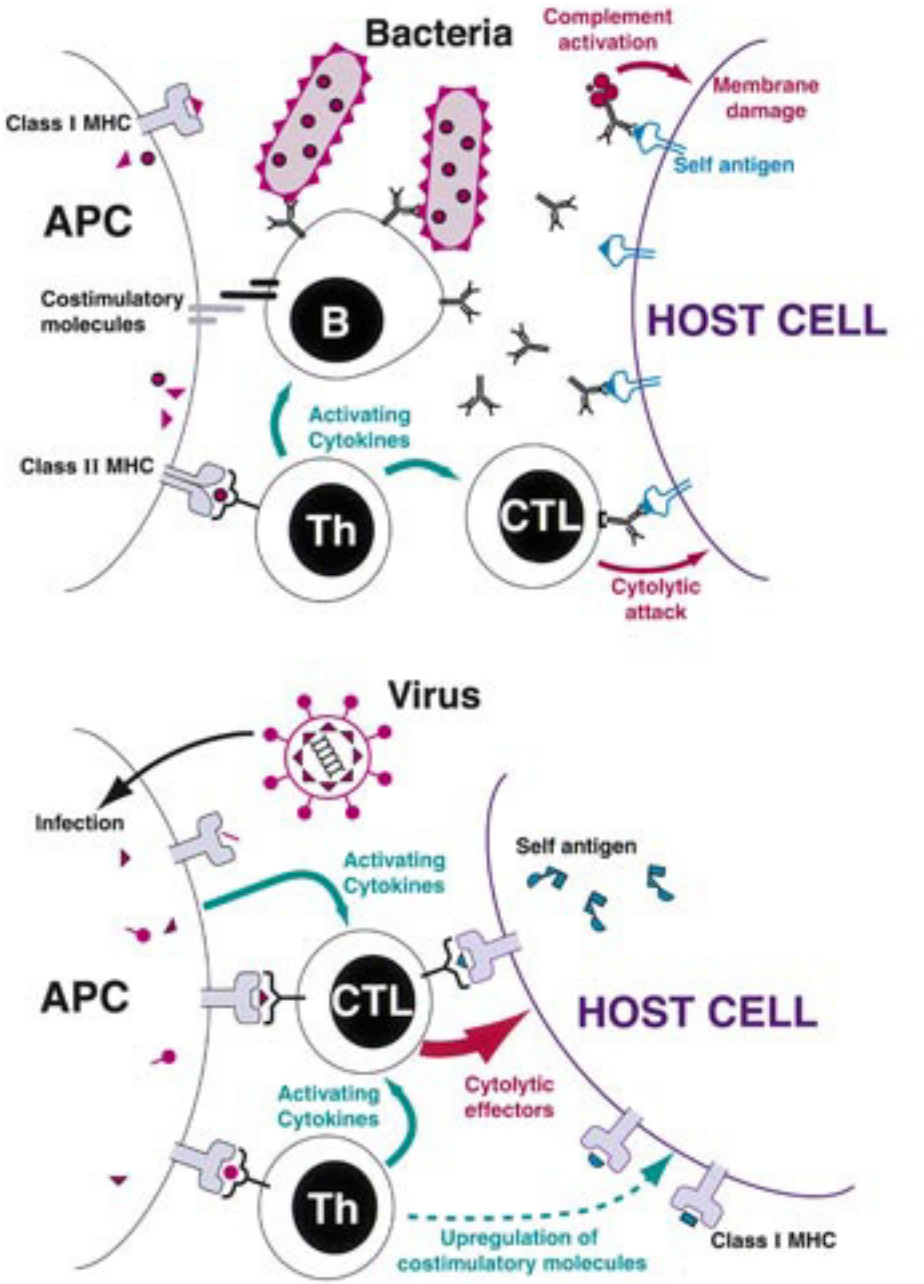


**Fig. 1** Molecular mimicry and autoimmunity resulting from infection. A somewhat simplified network of immune activation, leading to immunological damage to host tissues, is shown. Cellular damage occurs following a bacterial or viral infection, in which the invading pathogen carries an epitope (represented as triangles) which is immunologically indistinguishable from a host-derived peptide, or surface molecule structure. In the upper portion of the figure, a bacterial infection stimulates a humoral immune response, with the B cell binding directly to a bacterial coat protein via its surface immunoglobulin. Other bacterial epitopes, processed by the antigen-presenting cell (APC), stimulate helper T cells (Th) to secrete cytokines that drive the differentiation of the B cell to become a plasma cell, secreting large amounts of antibody. The antibody helps to clear the bacteria from the system, but also binds to a cell-surface antigen on host cells, resulting in either cellular damage, mediated by complement or cytotoxic T cells (CTL), or inappropriate signaling (either activating or blocking activation) through the antibody-bound receptor. In the bottom portion, a viral infection results in the activation of class I–restricted cytotoxic T cells (CTL) by direct stimulation from the APC, and secondary activating signals from the major histocompatibility complex (MHC) class II-restricted helper T cells (Th). The activated CTL are then capable of lysing any virally infected cells, but also any host cells displaying the self peptide, which is mimicked by the viral epitope, even in the absence of virus.

Immunization with MBP, or its component peptides, is sufficient to induce experimental allergic encephalomyelitis (EAE), which closely mirrors MS, in animal models. The epitopes that are recognized by the majority of autoantibodies and self-reactive T cells in MS have been mapped to amino acids 84–103 of MBP, and homologies to peptides within this region are found in protein components of hepatitis B virus, influenza, adenovirus, Epstein-Barr virus, papillomavirus, and, most recently, human herpesvirus 6. For example, the encephalitogenic MBP peptide sequence Tyr-Gly-Ser-Leu-Pro-Gln occurs in the polymerase protein of hepatitis B virus. A 10 amino-acid peptide of HBV polymerase containing that sequence, when injected into New Zealand rabbits, can cause EAE with very similar pathology to MS including both humoral and cellular immune responses to MBP.

The genetic linkage of MS to the HLA DR2 allele and the genetic linkage of other autoimmune disorders to other HLA alleles can be explained to a large extent by major histocompatibility complex (MHC) restriction. Foreign antigens are not presented to the immune system as whole molecules. Instead, they are first cleaved by antigen-presenting cells into short peptides. These peptides in turn associate with MHC molecules inside the cell and are only then brought to the cell surface as a complex where they are recognized by the T cells as a peptide-MHC complex. To a large extent, the immunogenicity of particular peptide fragments are determined by their capacity to fit into the peptide-binding groove of the MHC molecules borne by the cell. Thus, small differences in the MHC proteins will still allow them to bind the peptide, but will now present slightly different epitopes on the surface of the cell for recognition by antibodies. The putative cross-reactive peptide sequence may be effectively presented to the immune system by only one particular MHC allele. If you do not have that specific MHC allele, then that specific peptide will not be present on the surface of the cell. This is thought to be the basis of the genetic restriction, which is associated with many autoimmune diseases.

As has been mentioned, there is a strong linkage in the case of MS between the class II molecule HLA DR2 and disease susceptibility. Similarly, HLA DR4 is associated with an increased risk of rheumatoid arthritis and HLA DQ8 with diabetes. The strongest HLA association with autoimmune disease is that of ankylosing spondylitis with HLA B27, although in this case the HLA molecule actually bears the cross-reactive epitope itself and is not simply presenting it to the immune system. It should be noted that the microbial peptides implicated in the development of an autoimmune response do not necessarily have to share exactly the same sequence to elicit cross-reactivity. Two quite disparate sequences that bind in the groove of the MHC can potentially present a similar molecular surface to the scanning T cells and, therefore, will elicit a cross-reactive response. In the case of certain viral peptides known to mimic MBP epitopes, as few as 4 out of 11 amino acids need match the cognate MBP peptide sequence for cross-reactivity to be detectable.

Although molecular mimicry provides a simple and credible model for the initiation of autoimmunity, it cannot be sufficient in itself to cause disease. The process of tolerance to self-antigen must also be overcome. The immune system is strongly biased against self-reactivity. Autoreactive T cells are generated continually by the hematopoietic system but are largely removed by antigen-induced apoptosis before they can escape into the peripheral tissues, a process referred to as clonal deletion. Autoreactive B cells are not destroyed but are rendered anergic to normal stimuli. In addition, there are immune effector cells that actively suppress autoreactive responses, a phenomenon referred to as peripheral tolerance. All these systems must be broken down for autoimmunity to become a pathogenic process. This fact is highlighted by the finding that T cells bearing receptors that bind the encephalitogenic peptides of MBP are found frequently in normal individuals, but no evidence of autoimmune damage is found even during viral infections. The autoreactive cells must therefore be effectively suppressed by a mechanism that is presumably defective, or lacking, in individuals with MS.

It should be stressed that there are also several other credible theories, which might explain the linkage between infection and autoimmunity. "Bystander activation" refers to the aberrant activation of rare autoreactive cells due to an over-robust immune response occurring during an infection. In effect, the autoreactive cells receive activation and proliferation signals not meant for them. "Epitope spreading" is the process of the sequential development of an immune reaction to epitopes neighboring the initiating antigen, a well-documented process in both normal immune responses and systemic autoimmune disease. For instance, many viruses use intracellular structures as assembly frameworks for the construction of new viral particles. These associations may well bring the cellular components into highly immunogenic immune complexes. Indeed, transient autoantibody production to cytoskeletal antigens is a common finding during viral infections. "Mistaken self" refers to the misexpression of antigens normally resident in immunologically privileged sites, or the release of normally cryptic antigens, by the process of immunological damage which inevitably follows a robust antimicrobial response. Other potential contributory factors include the inappropriate overexpression of class II HLA molecules or the excessive release of proinflammatory cytokines.

We can expect a great deal of argument about the physiological relevance of each theory, but it is likely that all the mechanisms outlined above will be found to contribute, to varying degrees and in varying combinations, to the complex array of autoimmune diseases currently recognized.

## WEB SITES OF INTEREST

http://www.pharminfo.com/pubs/msb/autoimm.html
http://www.aarda.org/index.html
http://www.sciencenews.org/sn_arc97/6_21_97/fob1.htm

## ADDITIONAL READINGS

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