# Genetics of Childhood Disorders: XXVIII. Autoimmunity, Part I

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The immune system fights infection by recognizing and destroying invading pathogens. To do this effectively, it must distinguish between proteins that are foreign and those that are not. Once this skill is acquired, the immune system is able to recognize foreign antigens and initiate an immunological response against them while ignoring proteins that are not foreign.

Occasionally the immune system malfunctions and attempts to destroy self-proteins, mistaking them as foreign. This phenomenon is known as autoimmunity. Autoimmune diseases comprise a group of more than 75 chronic and disabling illnesses that can target almost any of the body's tissues. It has been suggested that a subset of neuropsychiatric disorders result from autoimmune processes. The next several columns will review how the immune system normally functions and what happens when it malfunctions in autoimmune reactions. The importance of this area lies in the recent hypothesis that vulnerable individuals may develop several psychiatric disorders including Tourette's syndrome and obsessive-compulsive disorder through an autoimmune process. It is important for us as clinicians to understand this phenomenon and how it might arise as well as the controversies that exist in the current debate.

The immune system can be divided into two distinct arms: the innate and the adaptive systems. Innate immunity is the more primitive component and is found in many organisms. It refers to systems that are already in place and that do not require any further modifications to operate. Skin is a good example of innate immunity. Another is the ability of phagocytic lymphocytes to recognize certain proteins such as bacterial lipopolysaccharide molecules and to engulf organisms that have these proteins on their surfaces.

Over the millennia pathogens have been evolving mechanisms to evade detection while mammalian immune systems have been evolving more sophisticated means of destroying them. Adaptive immunity is a more recently evolved immune mechanism. It differs from the innate mechanisms by having the capacity to recognize millions of different antigens associated with specific proteins, thereby generating a more specific immune response. In addition, an adaptive immune response takes several days to develop, in contrast to the innate response, which is always present and therefore immediate (Fig. 1). Finally, once an adaptive response is mounted against a specific antigen, a memory of that antigen is maintained throughout the life of the organism, making possible a more rapid response to subsequent infections.

Three cells are critical for the adaptive response: B cells, T cells, and antigen-presenting cells (APCs). B cells are the lymphocytes that produce antibodies: the proteins—also called immunoglobulins—that bind to foreign antigens. Their production is one of the important early steps in signaling the detection of a foreign protein.

T cells are divided into two types based on the expression of specific receptors on their cell surfaces. T cells with CD8 receptors are called killer T cells. These cells are responsible for the destruction of cells that are infected with pathogens. T cells with CD4 receptors on their surfaces are called helper T cells. These cells provide signals to antibody-producing B cells and instruct them to make antibodies.

The third cell type critical to the adaptive immune response, the APCs, present antigens either to T cells or to B cells within the lymphoid tissues, thus informing them of an ongoing infection. When viruses or other foreign pathogens are engulfed by an APC, the proteins that make up the organisms are digested into small peptides of only 10 to 15 amino acids in length. These smaller peptides are bound to specific proteins, members of the major histocompatability complex class of proteins (MHC I or MHC II). Once the peptide associates with the MHC proteins, the resulting immune complexes are transported to the surface of the APCs. The presentation of these protein-peptide complexes on the cell surface activates a small subset of T cells and B cells that are programmed to recognize the foreign peptide.

In general there are two types of infection, each of which requires a different immune response: cell-mediated and humoral immunity. Killer or cytotoxic T cells become activated in cell-mediated immunity. These lymphocytes seek out infected cells and target them for destruction. In humoral immunity, B cells become activated through T helper cell stimulation. The B cells secrete specific antibodies directed against the antigens, and these antibodies initiate their own sequence of immune events to combat the foreign proteins.

Cell-mediated immunity is exemplified by the mammalian response to viral infections. Viruses specialize in getting inside the host's cells and using the host cell's genetic material to replicate. There is not much that can be done to save a cell once it has been infected with a virus. The immune strategy that has evolved is simply to destroy the infected cells. APCs also become infected with the viruses that cause the more wide-

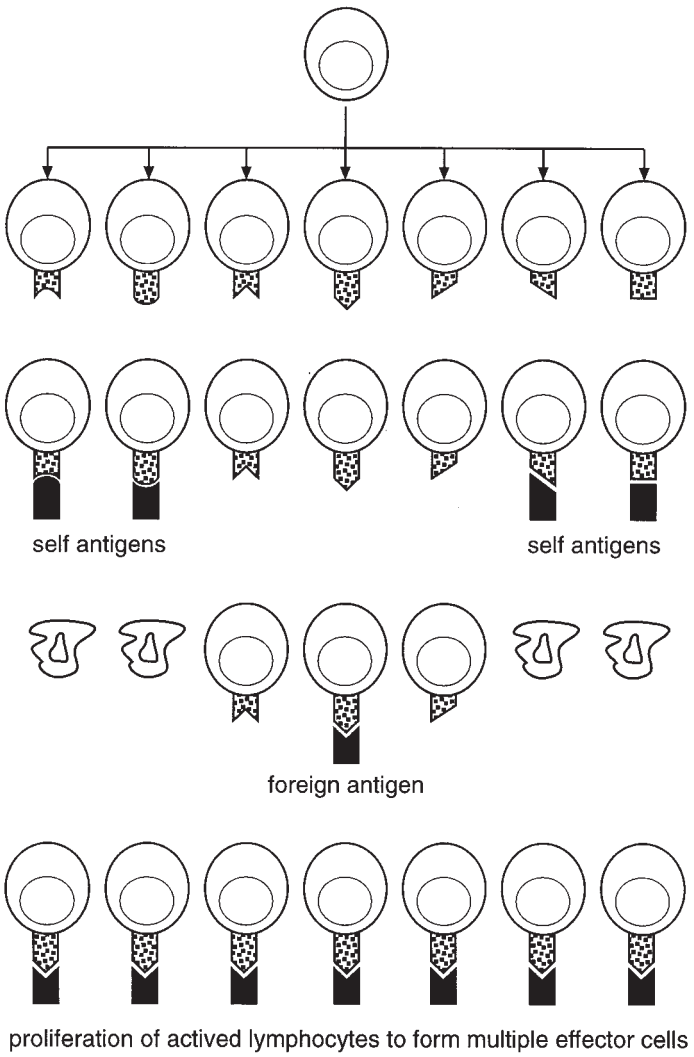


**Fig. 1** The clonal selection hypothesis. During development of lymphocytes, a single progenitor cell gives rise to many different lymphocytes, each with a different receptor on its surface to allow for specificity in recognizing antigens. Immature lymphocytes that bear receptors that recognize self-proteins are removed during their development by a process termed *programmed cell death* or *apoptosis*. The remaining cells survive and mature. At a later date, one or more of these may be stimulated by foreign antigens. Those that are stimulated will proliferate and produce an army of identical lymphocytes that help to eliminate the foreign antigens.

spread infection. The APCs digest portions of the infecting pathogen into peptides, bind these peptides to MHC I proteins, and present these immune complexes on their cell surfaces.

Killer T cells that recognize the MHC I-peptide complexes then become activated. They multiply in lymphoid tissue and move into the circulation in search of other virally infected cells that carry similar MHC I-peptide complexes on their cell surface. The close apposition of T cells with infected cells stimulates the secretion of several signaling molecules that activate the apoptotic (cell death) pathway in targeted cells. In this way, virally infected host cells are destroyed as a means of combating the infection.

Certain viruses have learned to evade the APC system; they remove all MHC I proteins from the cell surfaces. A parallel strategy has evolved in mammalian cells in response to these specialized viruses. Natural killer cells recognize cells that lack MHC I proteins and specifically target them for destruction.

In the second type of infection, which stimulates a humoral immune response, the host's cells are not infected. Instead, the pathogen replicates in the extracellular space outside of the

cell. As with cell-mediated immunity, APCs engulf some of the pathogenic organisms and digest them. Once again, small peptides are attached to MHC proteins for presentation on the cell surface of the APCs. This time, however, the peptides are attached to the MHC II class of proteins.

The APCs migrate to lymphoid tissues and the peptide-MHC complexes are again recognized, but this time by helper T cells. The activated T cells in turn stimulate specific B cells to produce antibodies against the peptide displayed on the surface of the APCs. Antibodies are secreted into the circulation and bind to the pathogens when they encounter them. As the antibodies bind to the extracellular pathogens, larger immune complexes accumulate and attract phagocytic cells that ingest the pathogens. In this way, a humoral response is mounted that helps to clear the bacterial infection.

As mentioned above, it is critical for the immune system to recognize the difference between foreign antigens and antigens that are not pathogenic, but part of the self. *Tolerance* is the term used to describe how the body learns to differentiate self from foreign antigens. When B and T cells are first generated (B cells in bone marrow, T cells in the thymus gland), each cell expresses a specific receptor on its surface. Each is unique, but as a group they are capable of recognizing virtually all possible antigens, including those on the cells of the self. Cells that recognize and target self-antigens for destruction must be eliminated if the body's own tissues are to be protected from an immune response.

Three different mechanisms have been proposed to explain how tolerance arises: ignorance, apoptosis, and anergy. The simplest of the tolerance mechanisms is ignorance, which occurs when the immune system is never exposed to certain proteins and thus does not react to them. This happens with immune privileged sites such as the eye, brain, and testes. In addition, certain proteins are sequestered, or hidden, inside the cells and thus never presented to the immune system.

The majority of B and T cells that recognize self-proteins are eliminated when they are still immature through a second tolerance mechanism. The developing immune cells that recognize self-proteins on cell surfaces are deleted from the immune repertoire through genetically programmed cell death—apoptosis. A slightly different situation is thought to happen to immature B and T cells that are exposed to soluble self-proteins. These cells become unresponsive or anergic to the antigen. Anergy is a third form of tolerance.

The net result of these processes is that the immune cells that might respond to self-proteins are either shielded so they do not know the self-proteins exist, or are killed or prevented from maturing. When tolerance mechanisms operate normally, only a fraction of the B and T cells that are born actually develop into mature lymphocytes. That is, only the immature cells that have not encountered self-antigens during earlier stages of development mature normally. They migrate from the bone marrow, where they are born to the peripheral lymphoid tissues, where they develop into mature immune cells.

We now turn to some of the ways that tolerance fails. Sequestered or hidden antigens such as those on intracellular proteins are likely not to have been recognized as self-proteins because the immature T or B cells were never exposed to them. If these proteins are later released into the circulation, they may elicit an autoimmune response. For example, the eye disease, sympathetic ophthalmia, occurs after serious trauma to an eye. The release of proteins from this normally privileged site leads to an immune response directed against the released proteins that are also present within the good eye. The resulting autoimmune response often leads to damage and blindness in the undamaged eye. Immunosuppressant medication and the immediate removal of the damaged eye can help to prevent an autoimmune reaction.

Superantigens have also been put forward as an etiological explanation for certain autoimmune disorders. Some bacteria or viruses produce toxic peptides. These toxins are potent stimulators of T cells. They inappropriately bind to, and activate, a significant subset of the population of T cells. As described above, the typical presentation of antigen to T cells occurs through APCs. Superantigens circumvent these normal mechanisms by forming an inappropriate bridge between MHC II proteins on the APC and the T cell receptor on T cells. The bridge that is formed activates the T cells even though the T cell receptors would never have recognized the MHC proteins. Superantigens are thus capable of eliciting an enormous immune response by activating approximately 1 in 10 T cells. The activation and expansion of these T cells results in the release of large amounts of inflammatory cytokines as well as the stimulation of antibody-producing B cells.

The final mechanism to be discussed is molecular mimicry. The idea of molecular mimicry is based on the observation that certain epitopes are shared by both a foreign antigen and a protein in the host. The individual responds normally to the foreign protein by producing antibodies directed against it. However, the antibodies then cross-react with host tissues and target them for destruction.

Paraneoplastic cancers are an important example of this process. Paraneoplastic neurological disorders are autoimmune disorders that occur in patients with specific types of malignancies. The tumor cells in these malignancies inappropriately produce certain proteins that are normally found only within neurons in the CNS. When these proteins are expressed by the tumor cells, they act as immunogens and initiate an autoimmune process. High titers of antibodies are secreted as the body attempts to eradicate the tumor cells. Unfortunately, the antibodies also recognize the protein normally expressed in the CNS. They bind to it and compromise its usual neuronal function. These patients often present with neurological symptoms rather than symptoms more directly related to the underlying

tumor. When the underlying malignancy is removed or effectively treated, the neurological symptoms frequently disappear.

## WEB SITES OF INTEREST

http://www.pharminfo.com/pubs/msb/autoimm.html
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