Autoimmune diseases

Autoimmune diseases occur when there is a loss of self-tolerance, the immune system's ability to discriminate self from non-self. In the generally accepted model by which T cells become capable of distinguishing self from non-self, the cells acquire this ability during their passage through the thymus. Any T cells that will target host cells are eliminated by deletion or other mechanisms in the thymus. This makes it unlikely that the T cell will attack its own tissue cells. However, when this process goes awry, loss of self-tolerance leads to the production of antibodies against self (autoantibodies) or a response by sensitized T cells against a person's own tissue antigens. Autoimmune reactions, and the diseases they cause, can be cytotoxic, immune complex, or cell-mediated in nature.

Cytotoxic Autoimmune Reactions

Multiple sclerosis is one of the more common autoimmune diseases, affecting mostly younger adult women in temperate areas. It is a neurological disease in which autoantibodies, T cells, and macrophages attack the myelin sheath of nerves. This compromises nerve impulse conduction and leads to scarring. Symptoms range from fatigue and weakness to, in some cases, eventual severe paralysis. There is considerable evidence of genetic susceptibility from several genes that interact. The etiology of multiple sclerosis is unknown, but epidemiological evidence indicates that it probably involves some infective agent or agents acquired during early adolescence.

Immune Complex Autoimmune Reactions

Systemic lupus erythematosus is a systemic autoimmune disease involving immune complex reactions, which mainly affects women. The etiology of the disease is not completely understood, but afflicted individuals produce antibodies directed at components of their own cells, including DNA, which is probably released during the normal breakdown of tissues, especially the skin. The most damaging effects of the disease result from deposits of immune complexes in the kidney glomeruli. Crippling rheumatoid arthritis is a disease in which immune complexes of IgM, IgG, and complement are deposited in the joints. In fact, immune complexes called rheumatoid factors may be formed by IgM binding to the Fc region of normal IgG. These factors are found in 70% of individuals suffering from rheumatoid arthritis. The chronic inflammation caused by this deposition eventually leads to severe damage to the cartilage and bone of the joints.

Cell-Mediated Autoimmune Reactions

Insulin-dependent diabetes mellitus is a common condition caused by immunological destruction of insulin-secreting cells of the pancreas. T cells are clearly implicated in this disease; animals that are genetically likely to develop diabetes fail to do so when their thymus is removed in infancy.

The fairly common skin condition psoriasis is an autoimmune disorder characterized by itchy, red patches of thickened skin. As many as 25% of patients develop psoriatic arthritis. Several topical and systemic therapies such as corticosteroids and methotrexate are available to help control psoriasis of the skin. Psoriasis is considered to be a TH1 disease and can be treated effectively with immunosuppressant that target T cells and especially the cytokine TNF-α (an important factor in inflammation). For psoriatic arthritis, as well as rheumatoid arthritis, the most effective treatments are injections of monoclonal antibodies that inhibit TNF-α.

Reactions to Transplantation

The inherited genetic characteristics of individuals are expressed not only in the color of their eyes or curl of their hair, but also in the composition of the self-molecules on their cell surfaces. Some of these are called histocompatibility antigens.The most important of these self- molecules are known as the major histocompatibility complex (MHC). In humans, these genes are called the human leukocyte antigen (HLA) complex. We saw that most antigens can stimulate an immune reaction only if they are associated with an MHC molecule.

A process called HLA typing is used to identify and compare HLAs. Certain HLAs are related to an increased susceptibility to specific diseases; one medical application of HLA typing is to identify such susceptibility.

* Another important medical application of HLA typing is in transplant surgery, in which the donor and the recipient must be matched by tissue typing.

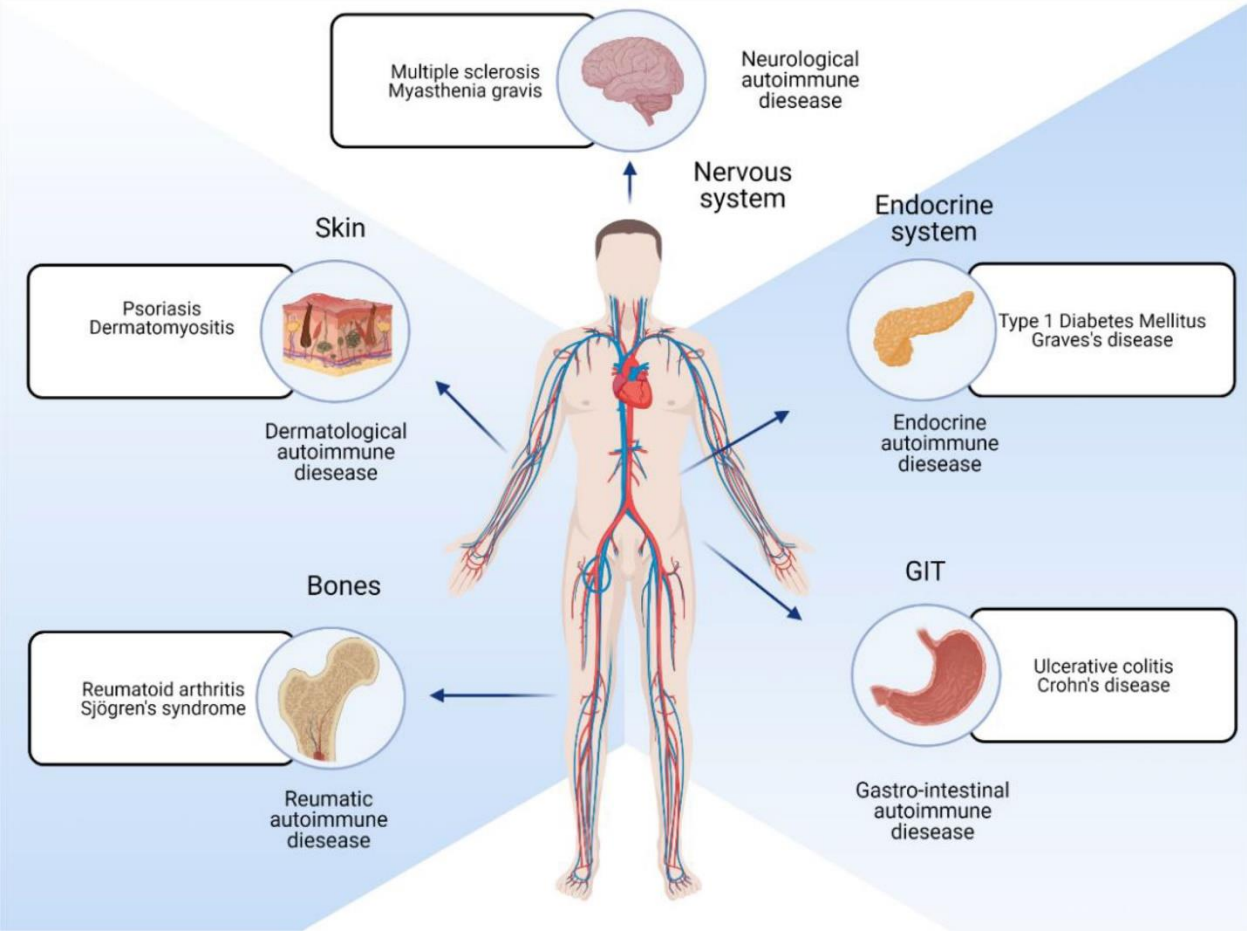
In serological tissue typing, the laboratory uses standardized antisera or monoclonal antibodies that are specific for particular HLAs.

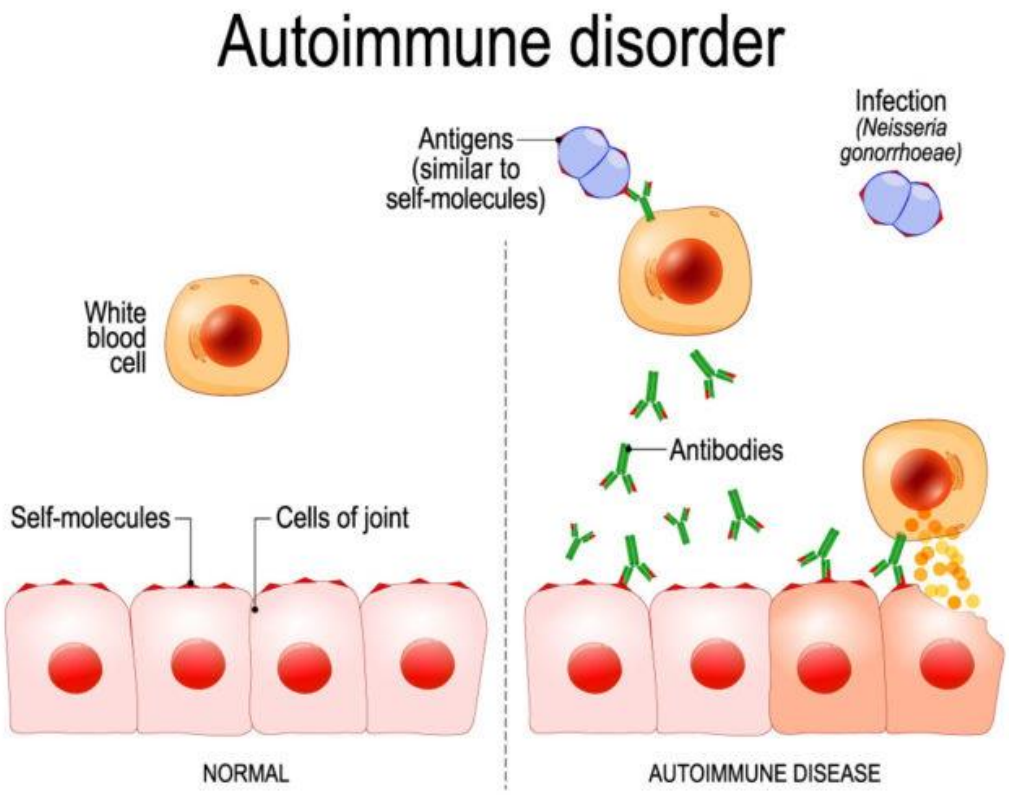
A newer, more accurate technique for analyzing HLA is the use of polymerase chain reaction (PCR) to amplify the cell's DNA. If this is done for both donor and recipient, a match between donor DNA and recipient DNA can then be made. Having

such a DNA match and matching ABO blood type between the donor and the recipient should result in a much higher success rate in transplant surgery.

Other factors may be involved in the success of a transplant, however. According to one hypothesis, the body's reaction to transplanted foreign tissue may be a response to surgery damaged cells. In other words, tissue rejection may result from a learned reaction to the danger signal posed by damaged cells, rather than a learned reaction to non-self.

Transplants recognized as non-self are rejected—attacked by T cells that directly lyse the grafted cells, by macrophages activated by T cells, and, in certain cases, by antibodies, which activate the complement system and injure blood vessels supplying the transplanted tissue. However, transplants that are not rejected can add many healthy years to a person's life.




Autoimmune disorder
Infection
(Neisseria
gonorrhoeae)
Antigens
(similar to
self-molecules)
White
blood
cell
Antibodies
Self-molecules
Cells of joint
NORMAL
AUTOIMMUNE DISEASE