IMMUNOLOGY

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Immune tolerance

One of the remarkable properties of the normal immune system is that it can react to an enormous variety of microbes but does not react against the individual's own (self) antigens. This unresponsiveness to self-antigens, also **called immunological tolerance,** when tolerance to self is lost immune responses can damage the body, a condition known as autoimmune diseases, like lupus erythematosus , some forms of diabetes. despite the fact that the molecular mechanisms by which lymphocyte receptor specificities are generated are not biased to exclude receptors for self-antigens. In other words, lymphocytes with the ability to recognize self-antigens are constantly being generated during the normal process of lymphocyte maturation. many self-antigens have ready access to the immune system, so unresponsiveness to these antigens cannot be maintained simply by concealing them from lymphocytes. It follows that there must exist mechanisms that prevent immune responses to self-antigens. These mechanisms are responsible for one of the cardinal features of the immune system namely, its ability to discriminate between self and nonself (usually microbial) antigens.

Immunological tolerance to different self antigens may be induced when developing lymphocytes encounter these antigens in the generative (central) lymphoid organs, a process called central tolerance, or when mature lymphocytes encounter self antigens in peripheral (secondary) lymphoid organs or peripheral tissues, called peripheral tolerance

Central tolerance is a mechanism of tolerance only to self antigens that are present in the generative lymphoid organs namely, the bone marrow and thymus. Tolerance to self antigens that are not present in these organs must be induced and maintained by peripheral mechanisms.

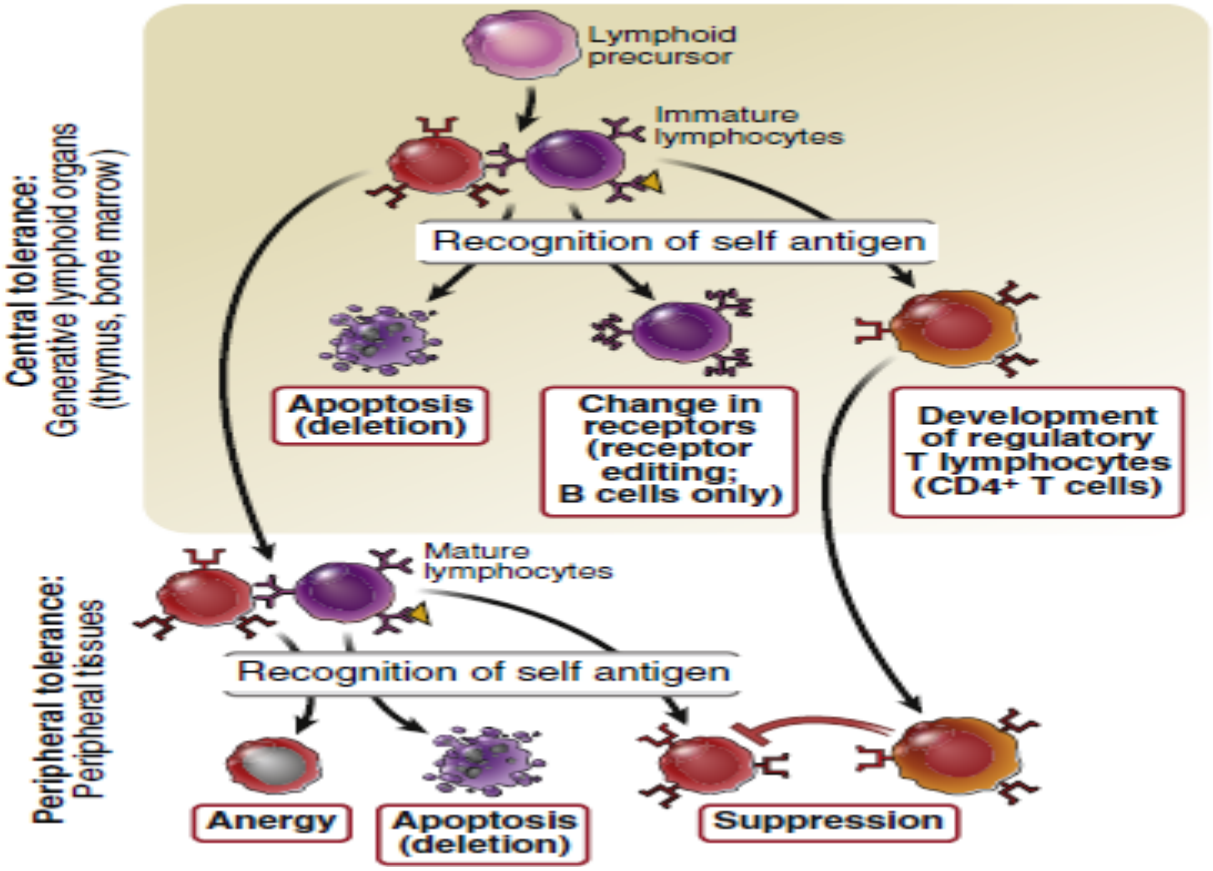
Central tolerance

Central tolerance occurs during the early differentiation of B cells in the bone marrow and T cells in the thymus. Normally, both B and T cells that bind self-epitopes at distinct

early stages of development meet an apoptotic death(process of programmed cell death that occurs in multicellular organisms), thus eliminating large numbers of potentially self-reactive cells before they enter the circulation. B cells express surface lgM as their BCRs. Epitope recognition by BCRs of developing B cells within the bone marrow triggers their apoptotic death , a process known as **negative selection.** Also the binding of peptide-MHC complex (MHC I or MHC II) by TCRs of single positive (CD4,CD8) thymocytes causes them to undergo apoptotic death . This process removes many potentially autoreactive B and T cells before they enter the periphery . A major caveat imposed on central tolerance is that not all self-epitopes are to be found in the primary lymphoid organs, especially those self epitopes that arise after lymphogenesis, such as those that arise during puberty. Other means are needed to prevent the auto reactive cells among them from inflicting damage on the body.

Peripheral tolerance

Several additional mechanisms, collectively called peripheral tolerance, control or eliminate autoreactive B and T cells after they exit the bone marrow or thymus



Hypersensitivity Reactions

Excessive or inappropriate immune responses sometimes lead to host tissue damage resulting from prolonged or repeated antigen exposure. These reactions, called hypersensitivity reactions, cause tissue injury by the release of chemical substances that attract and activate cells and molecules resulting in inflammation. These reactions are classified into four hypersensitivity types depending on the mechanism(s) that underlie the tissue damage . the first three types involve antigen-antibody reactions, whereas the fourth is antibody-independent, involving cell-mediated immune responses only.

TYPES OF HYPERSENSITIVITY REACTIONS

Hypersensitivity reactions are classified on the basis of the principal immunologic mechanism that is responsible for tissue injury and disease.

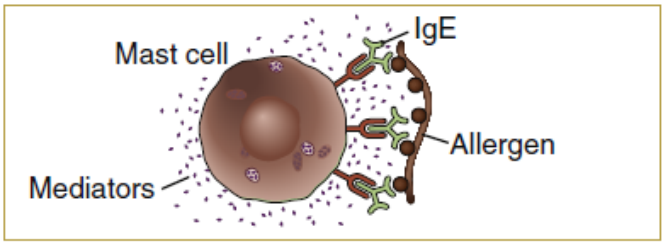
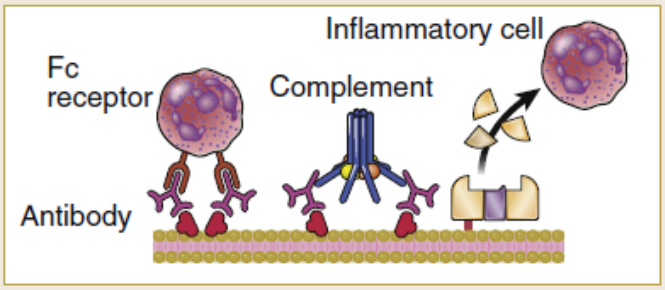
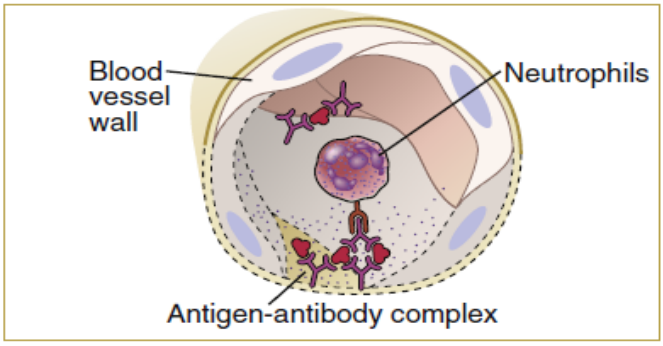
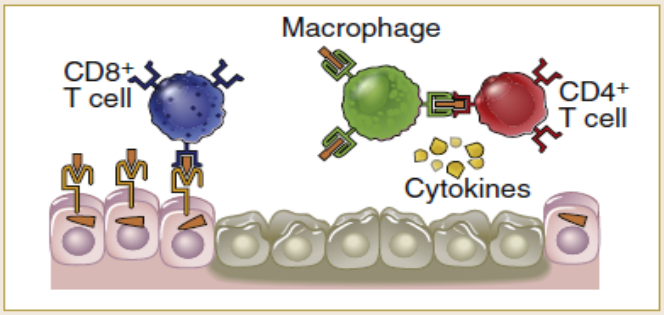
1- Immediate hypersensitivity, or type I hypersensitivity, is a type of pathologic reaction that is caused by the release of mediators from mast cells. This reaction most often depends on the production of immunoglobulin E (IgE) antibody against environmental antigens and the binding of IgE to mast cells in various tissues.

2- Antibodies other than IgE that are directed against cell or tissue antigens can damage these cells or tissues or can impair their function. These diseases are said to be antibody mediated and represent **type II hypersensitivity**.

3- Antibodies against soluble antigens may form complexes with the antigens, and the immune complexes may deposit in blood vessels in various tissues, causing inflammation and tissue injury. Such diseases are called immune complex diseases and represent **type III hypersensitivity**.

4- Some diseases result from the reactions of T lymphocytes, often against self-antigens in tissues. These T cell–mediated diseases represent **type IV hypersensitivity**.

This classification scheme is useful because it distinguishes the mechanisms of immune-mediated tissue injury. In many human immunologic diseases, however, the damage may result from a combination of antibody-mediated and T cell–mediated reactions, so it is often difficult to classify these diseases neatly into one type of hypersensitivity.

Type of hypersensitivity	Pathologic immune mechanisms	Mechanisms of tissue injury and disease
Immediate hypersensitivity (Type I)	Th2 cells, IgE antibody, mast cells, eosinophils 	Mast cell-derived mediators (vasoactive amines, lipid mediators, cytokines) Cytokine-mediated inflammation (eosinophils, neutrophils, lymphocytes)
Antibody-mediated (Type II)	IgM, IgG antibodies against cell surface or extracellular matrix antigens 	Complement- and Fc receptor-mediated recruitment and activation of leukocytes (neutrophils, macrophages) Opsonization and phagocytosis of cells Abnormalities in cellular function (e.g., hormone or neurotransmitter receptor signaling)
Immune complex-mediated (Type III)	Immune complexes of circulating antigens and IgM or IgG antibodies deposited in vascular basement membrane 	Complement- and Fc receptor-mediated recruitment and activation of leukocytes, and tissue damage secondary to impaired blood flow
T cell-mediated (Type IV)	1. $CD4^+$ T cells (cytokine-mediated inflammation) 2. $CD8^+$ CTLs (T cell-mediated cytolysis) 	1. Macrophage activation, cytokine-mediated inflammation 2. Direct target cell lysis, cytokine-mediated inflammation