Histopathology

Lecture 10

Diseases of Immunity

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Diseases of Immunity

OVERVIEW

Diseases of the immune system take many forms, including hypersensitivity reactions, autoimmune disorders, and immunodeficiency states. Hypersensitivity reactions occur as one of four types (types I–IV). Autoimmune diseases are the result of a failure in the immune system to recognize self-antigens, resulting in production of antibodies that react against normal components of cells. Most of the autoimmune diseases are associated with one or more specific antibodies, which can be identified by laboratory tests to aid in diagnosis. Immunodeficiency states can be hereditary or acquired. The concepts of immunity are also important in regard to transplantation efforts. This Lecture will discuss hypersensitivity reactions only.

HYPERSENSITIVITY REACTIONS

Overview: There are four types of hypersensitivity reactions, each of which has a different mechanism. These four types of hypersensitivity reactions will be discussed below

TYPE I HYPERSENSITIVITY REACTION

Mechanism: Exposure to an antigen results in the formation of IgE. The antigen reacts with CD4+ cells, which differentiate to TH2 cells. TH2 cells release interleukin-3 (IL-3), IL-4, and IL-5. IL-5 stimulates eosinophils, and IL-4 activates IgE-producing B cells. The IgE binds to mast cells. Subsequent exposure to the same antigen results in binding of the antigen to IgE bound to mast cells, with the consequence of degranulation of the mast cells and release of mediators (e.g., histamine). The release of mediators causes increased vascular permeability, leading to edema and increased smooth muscle contraction and eventually to bronchoconstriction (Figure 1).

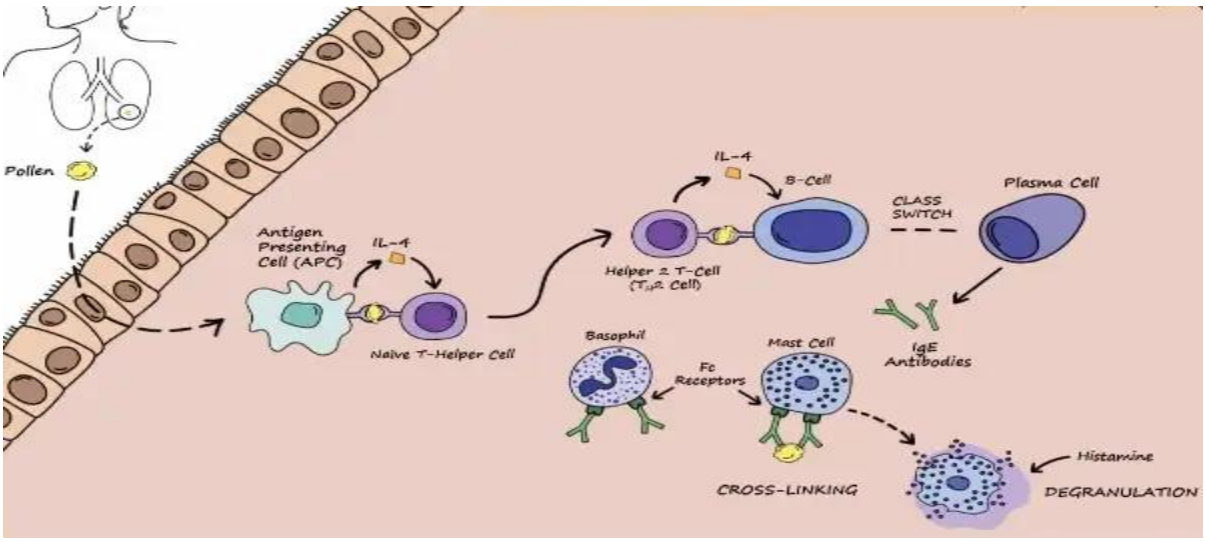

Figure 1. **Mechanism type I Hypersensitivity.**

Causes: Penicillin, angiotensin-converting enzyme (ACE) inhibitors, intravenous (IV) contrast and other drugs, proteins (e.g., insect venoms), and food.

Clinical presentation of type I hypersensitivity reaction: Symptoms and signs include abrupt onset (within 30 minutes of exposure to antigen) of rash, nausea and vomiting and facial swelling, and hypotension and tachycardia.

TYPE II HYPERSENSITIVITY REACTION

Overview of general mechanism: Antibodies directed against target antigens on cells or in extracellular matrix. The target antigens may be endogenous or absorbed exogenous antigens. **Specific mechanisms**: There are three specific mechanisms by which type II hypersensitivity reactions occur. The three mechanisms are complement-dependent reactions, antibody dependent cell-mediated cytotoxicity, and antibody-mediated cellular dysfunction.

■ Complement-dependent reactions

Mechanism: Antibody bound to antigen can fix complement and cause direct lysis of the cell through production of the membrane attack complex (MAC), or the complement can coat cells with C3b (an opsonin) and promote phagocytosis of the antigen (Figure 2).

Example: Glomerulonephritis

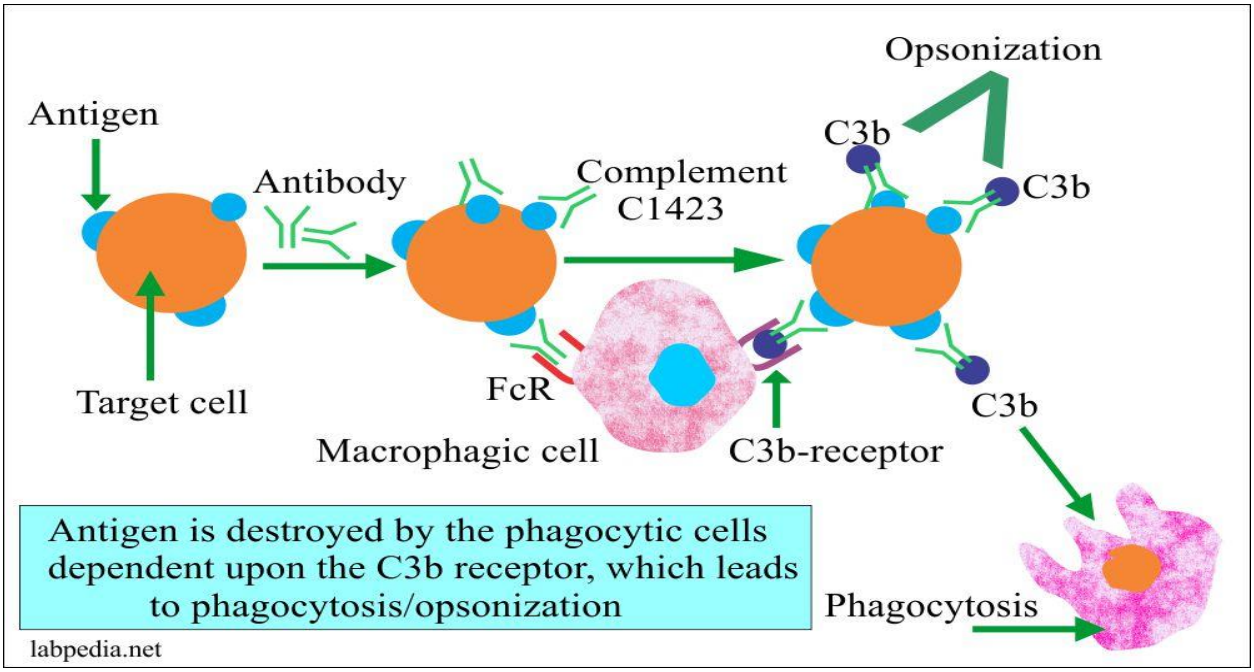

Figure 2. Complement-dependent reactions.

■ **Antibody-dependent cell-mediated cytotoxicity**

Mechanism: Cell types that bear receptors for the Fc portion of IgG, such as neutrophils, eosinophils, macrophages, and natural-killer (NK) cells, mediate removal of antigen (Figure 3).

Examples: Transfusion reactions, and autoimmune hemolytic anemia.

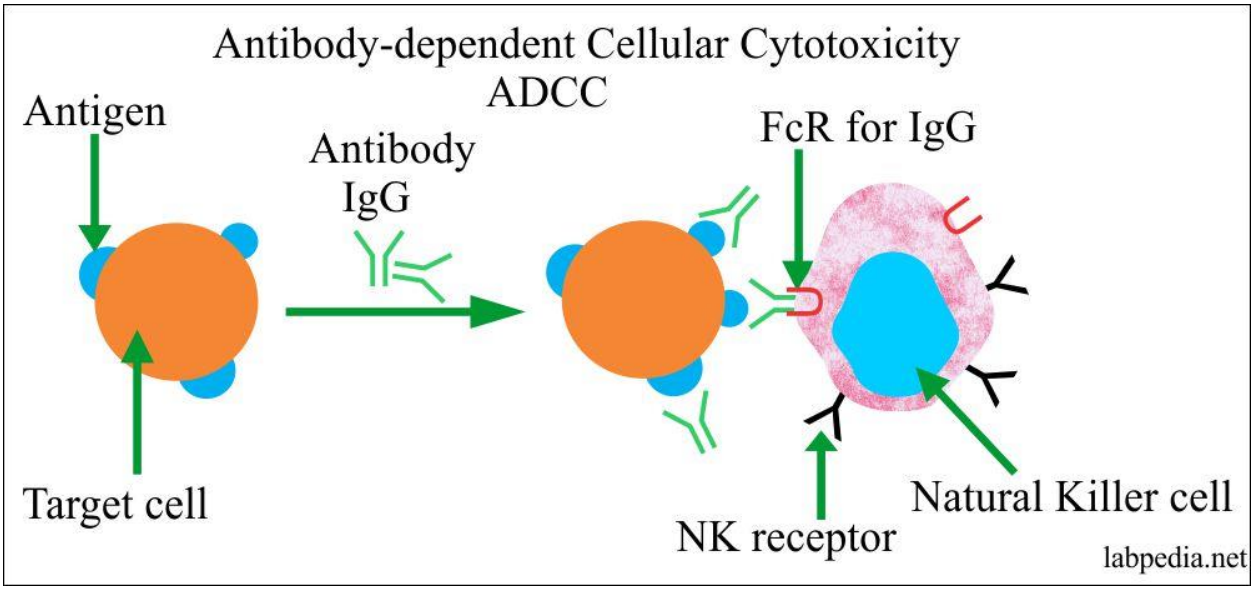

Figure 3. Antibody-dependent cell-mediated cytotoxicity

■ **Antibody-mediated cellular dysfunction**

Mechanism: Antibodies themselves affect function of the antigen.

Examples: Graves disease is due to an antibody that activates the thyroid-stimulating hormone (TSH) receptor, resulting in hyperthyroidism. Myasthenia gravis is due to antibodies against the acetylcholine (ACh) receptor, impairing neuromuscular transmission.

TYPE III HYPERSENSITIVITY REACTION

Mechanism: Antibodies bind to the antigen, forming an immune complex. The antigens can be exogenous (e.g., viral proteins) or endogenous (e.g., DNA). These immune complexes can form in situ, or they can form in the vasculature and subsequently be deposited in organs, where they cause damage. The immune complex causes activation of the complement cas cade. Note that immune complexes are commonly formed for various reasons, but only under certain circumstances do they elicit an immune reaction.

Examples: Immune–complex-mediated vasculitis and forms of glomerulonephritis.

TYPE IV HYPERSENSITIVITY REACTION

General mechanism: Mediated by sensitized T cells rather than by antibodies.

Specific mechanisms

■ **Delayed form of type IV hypersensitivity reaction**: CD4 + helper T cells (T H1 type) sensitized from previous exposure to an antigen secrete interferon γ, which activates macrophages. Activated macrophages secrete IL-12, which causes differentiation of T H1 cells.

Inciting agents: Mycobacteria, fungi, and parasites.

Examples: Tuberculin reaction and contact dermatitis.

■ **Cell -mediated cytotoxicity**: Sensitized CD8 + cells kill antigen-bearing cells. The antigens are presented by class I major histocompatibility complex (MHC) molecules. There are two mechanisms by which this occurs: the perforin granzyme system and the FAS-FAS ligand system.

Perforin-granzyme system: Perforin produces holes in the plasma membrane of cells, allowing granzyme to enter the cells. Granzyme then activates apoptosis through stimulation of caspase activity

FAS -FAS ligand system: The sensitized T lymphocytes have FAS ligand, which binds to FAS on target cells, leading to apoptosis.