Disease of immune system

Lec.2

Disease of immune system may result from:

1. Excessive immune responses (hypersensitivity reactions)
2. Unwanted or inappropriate immunes response (Autoimmune diseases)
3. Inadequate immune responses (immunodeficiency disease)

1–Hypersensitivity Reactions(HSR): This term originated from the idea that persons who mount immune responses against an antigen are sensitized to that antigen, so pathologic or excessive reactions represent manifestations of a hypersensitive state

Types of hypersensitivity diseases:

1–Immediate (type I) hypersensitivity

2–Antibody–mediated (type II) hypersensitivity

3–Immune complex–mediated (type III) hypersensitivity

4–T cell–mediated (type IV) hypersensitivity

1–Immediate (Type I) hypersensitivity reaction: defined as a rapidly developing immunologic reaction occurring within minutes after the interaction of antigen with (IgE) antibody that bound to the surface of mast cells in individuals previously sensitized to the antigen (Ag).

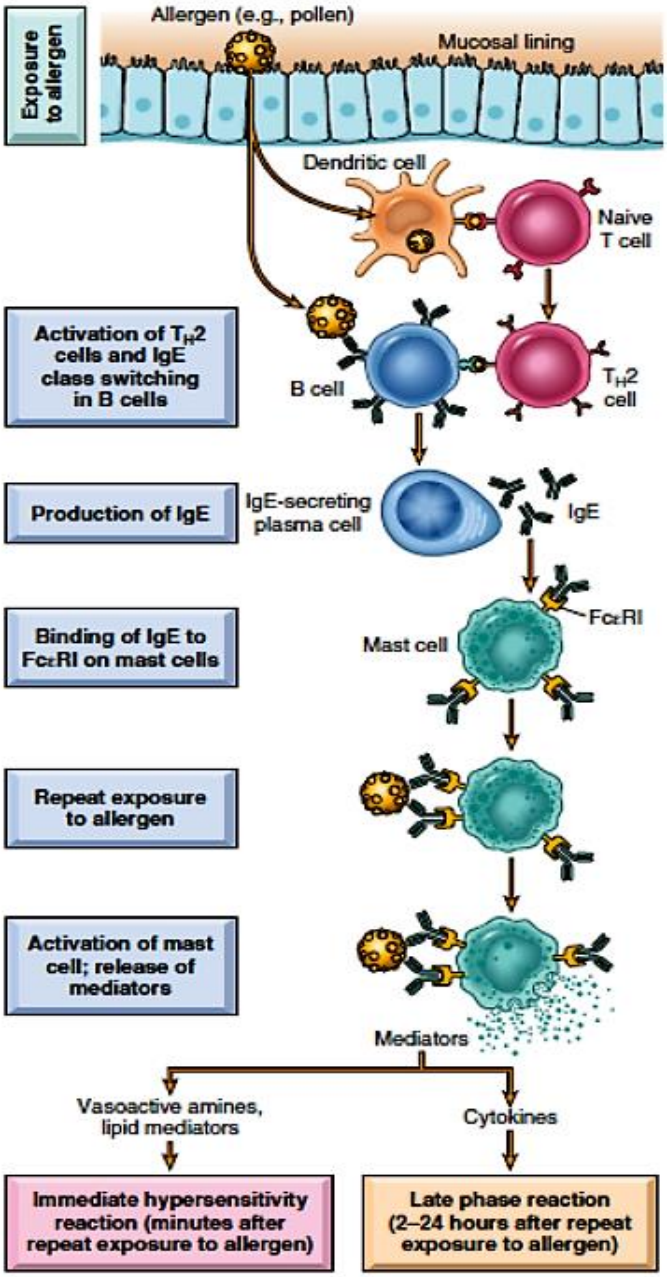
Immediate hypersensitivity may occur as a local reaction (e.g., seasonal rhinitis), severely debilitating (asthma), or even fatal (anaphylaxis).

The mediators are

1- **Vasoactive amine** released from granule stores :e.g., Histamine– vasodilation, increase permeability & increase secretion of mucus

2- **Newly synthesized lipid mediators** e.g., Prostaglandins & Leukotrienes which cause bronchospasm

3- **Cytokines** these are important for the late phase e.g. TNF & Chemokines which recruit and activate leukocytes, IL-4 & IL-5

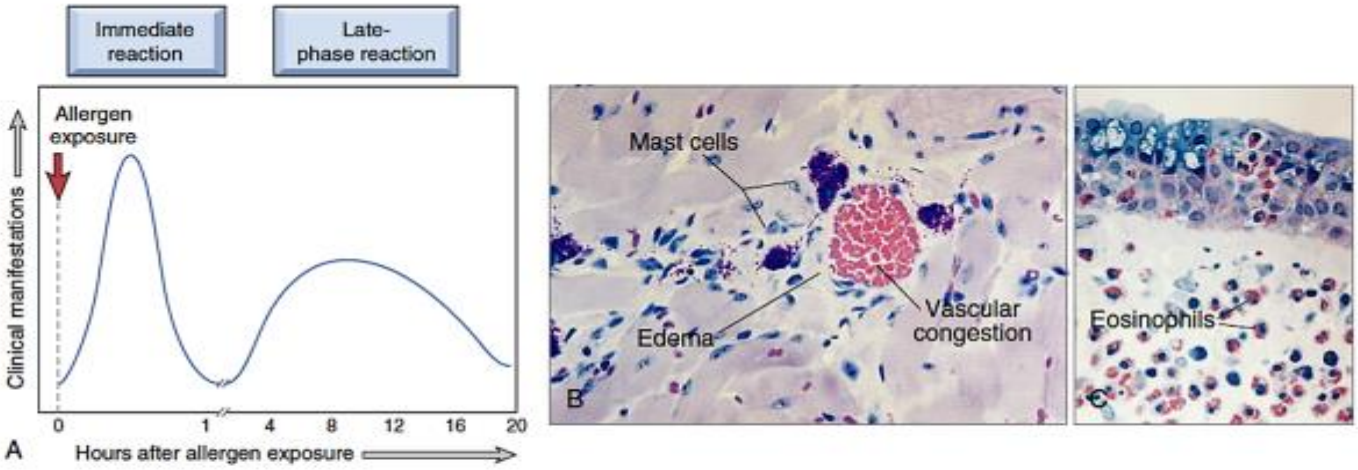


The IgE triggered reaction has two phases:

1-The immediate response: vasodilation, vascular leakage & smooth muscle contraction usually evident within 5-30 mints after exposure to allergen and subsiding by 60 minutes.

2- Late phase reaction usually set in 2-8 hours later & may last for several days characterized by inflammation & tissue destruction such as mucosal epithelial cell damage.

The dominant inflammatory cells in the late-phase reaction are neutrophils, eosinophils, and lymphocytes, especially TH2 cells. Inflammatory leukocytes are responsible for much of the epithelial cell injury in immediate hypersensitivity.



Phases of immediate hypersensitivity reactions. (A) Kinetics of the immediate and late-phase reactions. The immediate vascular and smooth muscle reaction to allergen develops within minutes after challenge (allergen exposure in a previously sensitized individual), and the late-phase reaction develops 2 to 24 hours later. The immediate reaction (B) is characterized by vasodilation, congestion, and edema, and the late-phase reaction (C) is characterized by an inflammatory infiltrate rich in eosinophils, neutrophils, and T cells.

Mast cell mediators. Upon activation, mast cells release various classes of mediators that are responsible

Examples of Disorders Caused by Immediate Hypersensitivity

Clinical Syndrome	Clinical and Pathologic Manifestations
Anaphylaxis (may be caused by drugs, bee sting, food)	Fall in blood pressure (shock) caused by vascular dilation; airway obstruction due to laryngeal edema
Bronchial asthma	Airway obstruction caused by bronchial smooth muscle hyperactivity; inflammation and tissue injury caused by late-phase reaction
Allergic rhinitis, sinusitis (hay fever)	Increased mucus secretion; inflammation of upper airways and sinuses
Food allergies	Increased peristalsis due to contraction of intestinal muscles, resulting in vomiting and diarrhea

2-Antibody-Mediated Diseases (Type II) Hypersensitivity:

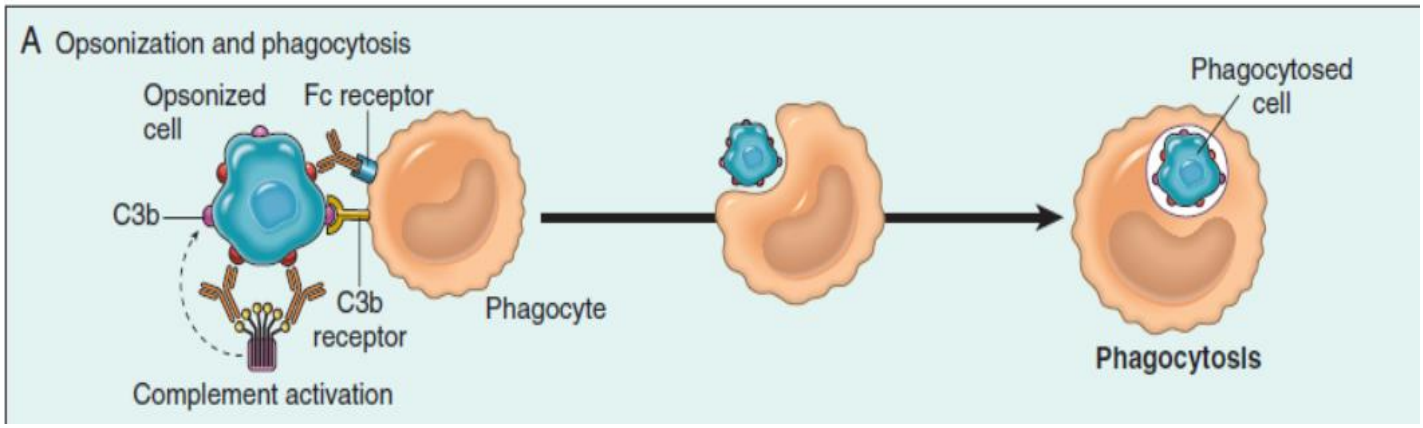
Antibody-mediated (type II) hypersensitivity disorders are caused by antibodies directed against target antigens on the surface of cells or other tissue components.

The antigens may be normal molecules intrinsic to cell membranes or extracellular matrix(endogenous), or they may be adsorbed exogenous antigens (e.g., a drug metabolite).

Antibody-mediated abnormalities are the underlying cause of many human diseases ex: myasthenia gravis (thymus), Grave's disease of thyroid & autoimmune hemolytic anemia.

Mechanisms of Antibody Mediated Disease:

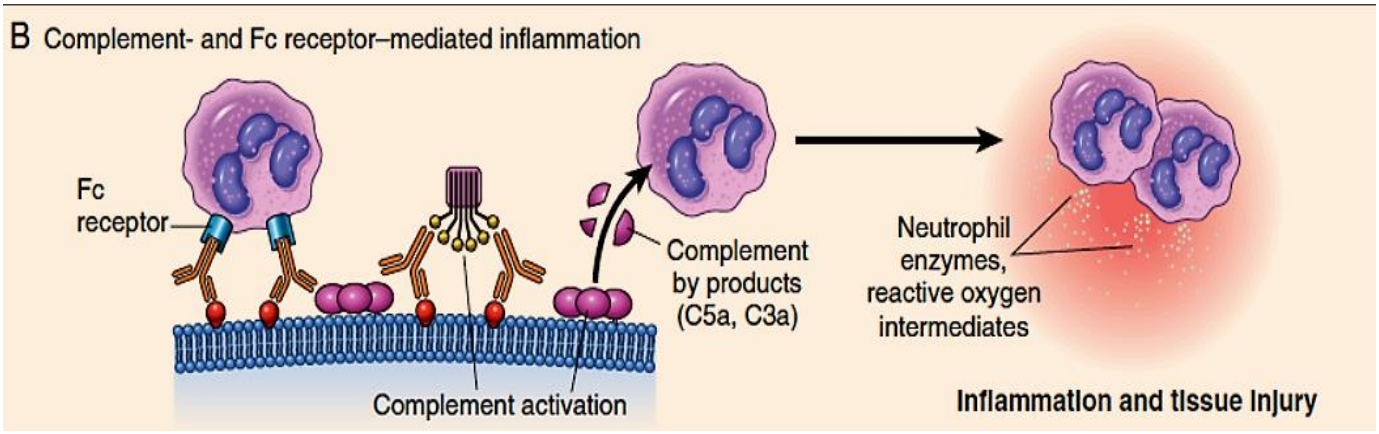
1-Opsonization & phagocytosis: when circulating cells (erythrocytes& platelets) are coated (opsonized) with auto antibodies, with or without complement proteins, the cells become target for phagocytosis by neutrophils & macrophages, these phagocytes express receptors for Fc portion of IgG Ab & these receptors bind & ingest opsonized particles & usually the opsonized cells are eliminated in the spleen



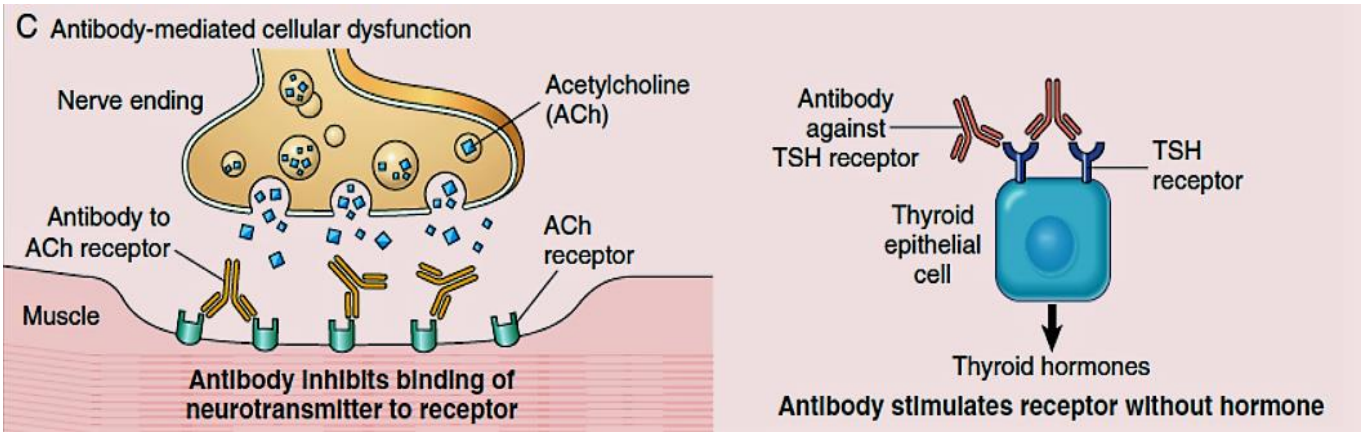
e.g., Autoimmune hemolytic anemia the targeted antigen is red blood cell membrane proteins by mechanism of opsonization and phagocytosis of red blood cells result in hemolysis, and anemia

e.g., Autoimmune thrombocytopenic purpura the target antigen is platelet membrane proteins by mechanism of opsonization and phagocytosis of platelets result in bleeding.

2-Inflammation: antibodies bound to cellular or tissue antigens activate complement system & products of complement activation recruit neutrophils & monocytes and triggering inflammation in tissues.



3. Antibody- mediated cellular dysfunction– Ab directed against cell surface receptors impaired or dysregulate cellular function without causing tissue injury or inflammation.



3-Immune complex mediated diseases (type III hypersensitivity):

Antigen–antibody (immune) complexes that are formed in the circulation may deposit in blood vessels, leading to complement activation and acute inflammation, the antigens that form immune complexes may be

-Exogenous antigens, such as infectious microbe, or

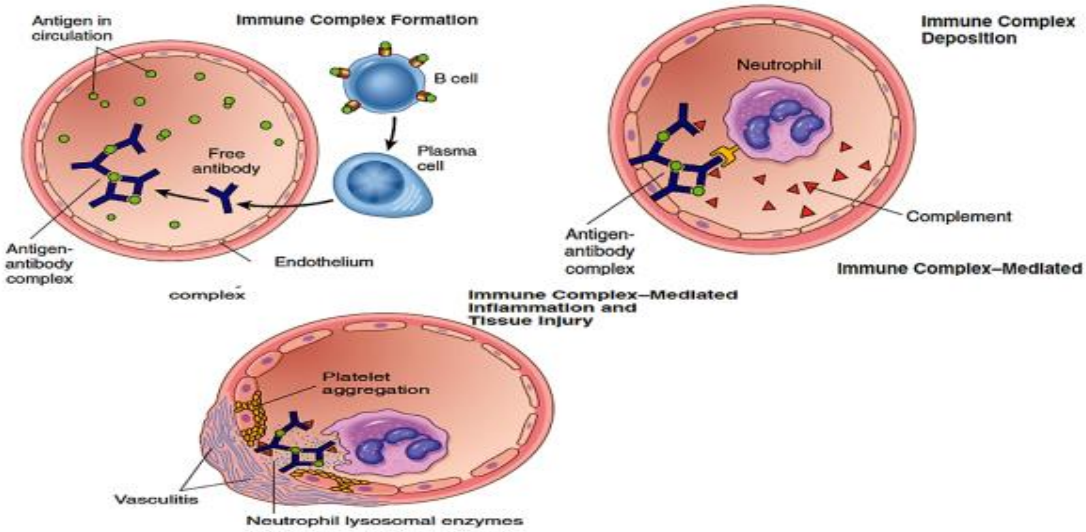
-Endogenous antigens, if the individual produces antibody against self antigens (autoimmunity).

Immune complex mediated injury is: either

1- systemic immune complex disease: when the complexes are formed in the circulation and are deposited in several organs

The pathogenesis of systemic immune complex disease can be divided into three phases:

(1) formation of antigen-antibody complexes in the circulation and
(2) deposition of the immune complexes in various tissues, thus initiating
(3) an inflammatory reaction in various sites throughout the body



The resultant inflammatory lesion is termed:

Vasculitis** if it occurs in **blood vessels.

***Glomerulonephritis** if it occurs in **renal glomeruli**.*

***Arthritis** if it occurs in the **joints**.*

Acute serum sickness: is the prototype of systemic immune complex when large amount of foreign serum administrated for passive immunization.

2-Local Immune Complex Disease (Arthus Reaction): A model of local immune complex diseases is the Arthus reaction, in which an area of tissue necrosis appears as a result of acute immune complex vasculitis.

The reaction is produced experimentally by injecting an antigen into the skin of a previously immunized animal with preformed antibody.

Immune complexes form as the antigen diffuses into the vascular wall at the site of injection, triggering the same inflammatory reaction and histologic appearance as in systemic immune complex disease

lesions evolve over a few hours and reach a peak 4 to 10 hours after injection, when the injection site develops edema and hemorrhage, occasionally followed by ulceration.

4-T cell-mediated (Type 4) hypersensitivity:

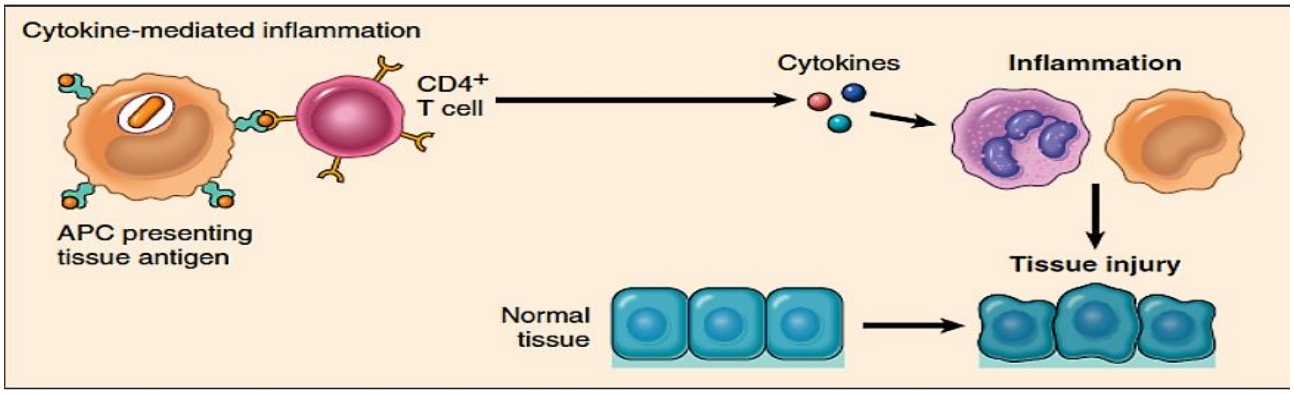
Two types of reaction mediated by T- lymphocytes:

1. Cytokine-mediated inflammation that produce by CD4+ T- cells e.g. tuberculin reaction (Delayed type Hypersensitivity reaction (DTH))

2. Direct cell cytotoxicity mediated by CD8+ T cells (T cell mediated cytotoxicity)

1- DTH reaction: In DTH CD4+ T cells are activated by exposure to antigens and differentiate into TH1 effectors cells.

Subsequent exposure to the antigen result in the secretion of cytokines IFN-gamma which activated macrophages to produce substances that caused tissue damage and promote inflammation.



Tuberculin reaction: it classic example of DTH, it elicited by Ag challenge in an individual already sensitized to the tuberculous bacilli by previous injection, the reaction starts 8- 12 hours after intracutaneous injection of tuberculin, a local area of erythema and induration appears, reaching a peak (typically 1-2cm in diameter) in 24- 72hours (so called delayed) then subside slowly.

Prolonged DTH reactions against persistent microbes or other stimuli may result in a special pattern of reaction called **granulomatous inflammation**

The initial perivascular CD4+ T cell infiltrate is progressively replaced by macrophages over a period of 2 to 3 weeks, these accumulated macrophages become activated and become large, flat, and eosinophilic, and are called epithelioid cells, the epithelioid cells occasionally fuse under the influence of cytokines (e.g., IFN-γ) to form multinucleate giant cells. An aggregate of epithelioid cells, typically surrounded by a collar of lymphocytes, is called a granuloma.

2-T- cell Mediated Cytotoxicity: In this type the CD8+ cytotoxic T lymphocytes (CTLs) specific for an antigen recognize cells expressing the target antigen and kill these cells, CTLs play an important role in the rejection of solid organs transplant and contribute in many immunological diseases such as type I diabetes.