Lec 9 General pathology

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Diseases of the Immune System

The classic definition of immunity is protection from infectious pathogens.

immunity in its broader sense includes host reactions against

1. cancers (tumor immunity).
2. tissue transplants.
3. self-antigens (autoimmunity).

The mechanisms of immunity fall into two broad categories:

1. **Innate immunity** (also called natural, or native, immunity) is always present, ready to provide immediate defense against microbes and to eliminate damaged cells.

   Components of Innate Immunity

   1. Epithelia of the skin and gastrointestinal and respiratory tracts act as mechanical barriers to the entry of microbes from the external environment.
   2. Monocytes and neutrophils are phagocytes in the blood that can be rapidly recruited to any site of infection; monocytes that enter the tissues and mature are called macrophages.
   3. Dendritic cells (DCs) are specialized cells present in epithelia, lymphoid organs, and most tissues. They capture protein antigens and display peptides for recognition by T lymphocytes.
   4. Innate lymphoid cells (ILCs) are tissue-resident lymphocytes that lack T-cell antigen receptors and cannot respond to antigens, but instead are activated by cytokines and other mediators produced at sites of tissue damage.

5. **Other cell types. Several other cell types can sense and react to microbes, these include mast cells.**
6. **Plasma proteins.**

2. **Adaptive Immunity:**

The adaptive immune system consists of lymphocytes and their products, including antibodies.

There are two types of adaptive immunity:

1. **humoral immunity, which protects against extracellular microbes and their toxins. It is mediated by B (bone marrow–derived) lymphocytes and their secreted products, antibodies (also called immunoglobulins, Ig)**
2. **cell-mediated (or cellular) immunity, which is responsible for defense against intracellular**

microbes and against cancers. It is mediated by T (thymus-derived) lymphocytes.

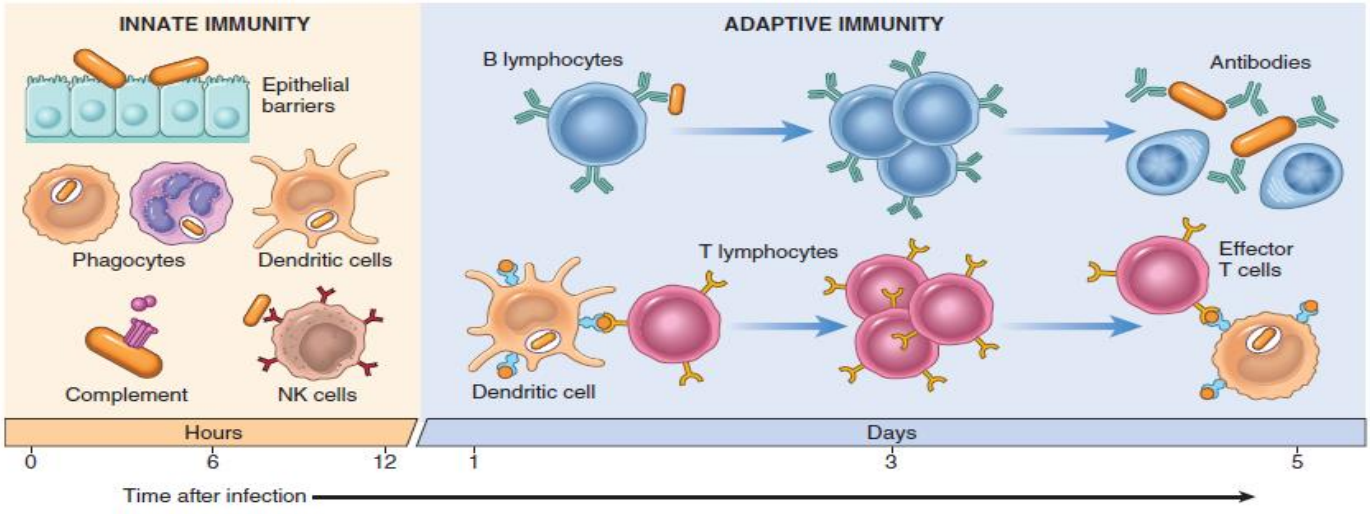

Figure 6.1 The principal components of innate and adaptive immunity. *NK*, Natural killer.

Major Histocompatibility Complex Molecules:

The Peptide Display System of Adaptive Immunity

The function of MHC molecules is to display peptide fragments of protein antigens for recognition by antigen specific T cells. Because MHC molecules are fundamental to antigen recognition by T cells and are linked to many autoimmune diseases. MHC molecules are called human leukocyte antigens (HLA) because they were initially detected on leukocytes.

On the basis of their structure, cellular distribution, and function, MHC gene products are divided into two major classes:

1. **Class I MHC molecules are expressed on all nucleated cells and platelets. Class I MHC molecules display peptides that are derived from cytoplasmic proteins, including normal proteins and virus- and tumor-specific antigens, which are all recognized bound to class I MHC molecules by CD8+ T cells. the peptide-class I complexes are recognized by CD8+ T cells, which function as CTLs. Because important functions of CD8+ CTLs include the *elimination of viruses*, which may infect any nucleated cell, and killing of *tumor cells*, which may arise from any nucleated cell, it makes good sense that all nucleated cells express class I MHC molecules and can be surveyed by CD8+ T cells.**
2. **Class II MHC molecules present antigens derived from extracellular microbes and proteins following their internalization into endosomes or lysosomes. the class II-peptide complex is recognized by CD4+ T cells, which function as helper cells. Because CD4+ T cells can recognize antigens only in the context of self-class II molecules, they are referred to as class II MHC restricted. In contrast to class I molecules, class II molecules are mainly expressed on cells that present ingested antigens and respond to T-cell help (macrophages, B lymphocytes, and DCs).**

Clinical significant of MHC

It is believed that this degree of polymorphism evolved to ensure that at least some individuals in a species would be able to display any microbial peptide and thus provide protection against any infection. This polymorphism also means that no two individuals (other than identical twins)

are likely to express the same MHC molecules, and therefore grafts exchanged between these individuals are recognize as foreign and attacked by the immune system.

The diseases of the immune system:

1. **hypersensitivity reactions**
2. **disorders caused by the failure of tolerance to self-antigens, called autoimmune disorders.**
3. **rejection of transplants.**
4. **immunodeficiency diseases.**

Hypersensitivity: Immunologically Mediated Tissue Injury:

Injurious immune reactions, called hypersensitivity, are responsible for the pathology associated with immunologic diseases. Hypersensitivity implies an excessive or harmful reaction to an antigen.

There are several important general features of hypersensitivity disorders.

- **Hypersensitivity reactions can be elicited by exogenous environmental antigens (microbial and nonmicrobial) or endogenous self –antigens. EX dust, pollen, food, drugs, microbes, and various chemicals. ranging effect from itching of the skin, to potentially fatal diseases, such as anaphylaxis. the most common reactions to environmental antigens cause the group of diseases known as allergy. Immune responses against self-antigens, cause autoimmune diseases.**

- **Hypersensitivity usually results from an imbalance between the effector mechanisms of immune responses and the control mechanisms that serve to limit such responses.**
- **The development of hypersensitivity diseases (both allergic and autoimmune) is often associated with the inheritance of particular susceptibility genes.**
- **The mechanisms of tissue injury in hypersensitivity reactions are the same as the effector mechanisms of defense against infectious pathogens. The problem in hypersensitivity is that these reactions are poorly controlled, excessive, or misdirected (e.g., against normally harmless environmental and self-antigens).**

Classification of Hypersensitivity Reactions:

1. **immediate hypersensitivity (type I hypersensitivity)**
2. **antibody-mediated disorders (type II hypersensitivity)**
3. **immune complex–mediated disorders (type III hypersensitivity)**
4. **cell-mediated immune disorders (type IV hypersensitivity).**

Immediate (Type I) Hypersensitivity:

Immediate, or type I, hypersensitivity is a rapid immunologic reaction occurring in a previously sensitized individual that is triggered by the binding of an antigen to IgE antibody on the surface of mast cells. These reactions are often called *allergy,* and the antigens that elicit them are *allergens.*

Phases of type I hypersensitivity:

1. **The immediate reaction is characterized by vasodilation, vascular leakage, and, depending on the tissue, smooth muscle spasm or glandular secretions. These changes usually become evident within minutes after exposure to an allergen and tend to subside in a few hours. In many instances (e.g., allergic rhinitis and bronchial asthma).**
2. **late-phase reaction sets in 2 to 24 hours later without additional exposure to antigen and may last for several days. This late-phase reaction is characterized by infiltration**

of tissues with eosinophils, neutrophils, basophils, monocytes, and CD4+ T cells, as well as tissue destruction, typically in the form of mucosal epithelial cell damage.

Sensitization and Activation of Mast Cells

Because mast cells are central to the development of immediate hypersensitivity, we first review some of their salient characteristics. Mast cells are bone marrow–derived cells that are widely distributed in the tissues. They are abundant near small blood vessels and nerves and in subepithelial tissues, which explains why local immediate hypersensitivity reactions often occur at these sites.

Basophils are similar to mast cells in many respects, including the presence of cell surface IgE Fc receptors as well as cytoplasmic granules. In contrast to mast cells, however, basophils are not normally present in

tissues but rather circulate in the blood in small numbers. Similar to other granulocytes, basophils can be recruited to inflammatory sites.

Mediators of Immediate Hypersensitivity

Granule contents. Mediators contained within mast cell granules are the first to be released and can be divided into three categories.

- **Vasoactive amines. The most important mast cell–derived amine is histamine. Histamine causes intense smooth muscle contraction, increases vascular permeability, and stimulates mucus secretion by nasal, bronchial, and gastric glands.**

• Enzymes. The enzymes cause tissue damage and lead to the generation of kinins and activated components of complement (e.g., C3a) by acting on their precursor proteins.

• Proteoglycans. These include heparin, a well-known anticoagulant, and chondroitin sulfate. The proteoglycans serve to package and store the amines in the granules.

Lipid mediators. The major lipid mediators are arachidonic acid–derived products

- **Leukotrienes. they are several thousand times more active than histamine in increasing vascular permeability and causing bronchial smooth muscle contraction also is highly chemotactic for neutrophils, eosinophils, and monocytes.**
- **Prostaglandin. This is the most abundant mediator produced in mast cells. It causes intense bronchospasm and increases mucus secretion.**
- **Platelet-activating factor (PAF). PAF is a lipid mediator produced by some mast cell populations that is not derived from arachidonic acid. It causes platelet aggregation, histamine release, bronchospasm, increased vascular permeability, and vasodilation. Its role in immediate hypersensitivity reactions is not well established.**
- **Cytokines. Mast cells are sources of many cytokines, which may play an important role at several stages of immediate hypersensitivity reactions. The cytokines include: TNF, IL-1, and chemokines, which promote leukocyte recruitment.**

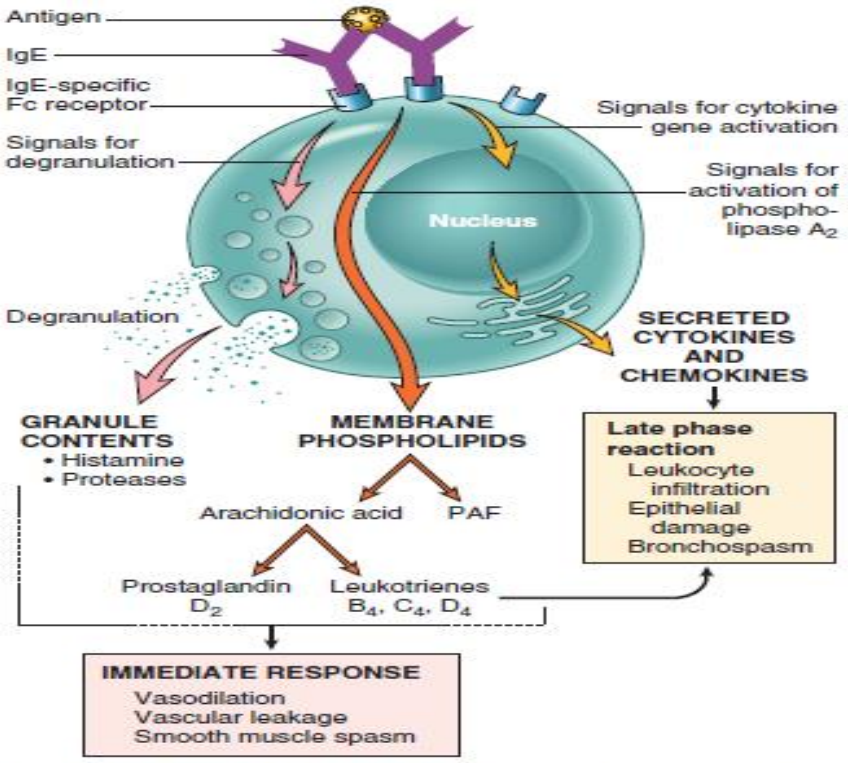

Figure 6.15 Mast cell mediators. On activation, mast cells release various classes of mediators that are responsible for the immediate and late-phase reactions. *PAF*, Platelet-activating factor.

<u>Immediate hypersensitivity may occur as a systemic disorder or as a local reaction:</u>

Systemic Anaphylaxis: is characterized by vascular shock, widespread edema, and difficulty in breathing. Within minutes after exposure to allergens, itching, hives, and skin erythema appear, followed shortly thereafter by a striking contraction of pulmonary bronchioles and respiratory distress. Laryngeal edema results in hoarseness and further compromises breathing. Vomiting, abdominal cramps, diarrhea, and laryngeal obstruction follow, and the patient may go into shock and even die within the hour.

Causes

1. **individuals in hospital settings after administration of foreign proteins.**
2. **Hormones**
3. **enzymes**
4. **polysaccharides**
5. **drugs (e.g., the antibiotic penicillin)**
6. **food allergens (e.g., peanuts, shellfish) or insect toxins (e.g., those in bee venom).**

Local Immediate Hypersensitivity Reactions About 10% to 20% of the population suffers from allergies

involving localized reactions to common environmental allergens, such as pollen, animal dander, house dust, foods, and the like. Specific diseases include urticaria, allergic rhinitis (hay fever), bronchial asthma, atopic dermatitis, and food allergies.

Antibody-Mediated (Type II) Hypersensitivity

Antibodies that react with antigens present on cell surfaces or in the extracellular matrix cause disease by destroying these cells, triggering inflammation, or interfering with normal functions.

The antibodies may be specific for normal cell or tissue antigens (autoantibodies) or for exogenous

antigens, such as chemical or microbial proteins, that bind to a cell surface or tissue matrix. The antibody-dependent mechanisms that cause tissue injury and disease.

***Clinically,* antibody-mediated cell destruction and phagocytosis occur in the following situations:**

(1) transfusion reactions, in which cells from a blood group mismatched donor react with and are opsonized by preformed antibody in the host

(2) hemolytic disease of the fetus and newborn (erythroblastosis fetalis), in which there is an antigenic difference between the mother and the fetus, and IgG anti-erythrocyte antibodies from the mother cross the
placenta and cause destruction of fetal red cells.
(3) autoimmune hemolytic anemia, agranulocytosis, and thrombocytopenia, in which individuals produce antibodies to their own blood cells, which are then destroyed.
(4) certain drug reactions. In some cases of drug induced antibody-mediated destruction of blood cells, the
drug binds to plasma membrane proteins on host cells, and antibodies are produced against the drug-protein complex.

Immune Complex–Mediated (Type III) Hypersensitivity:

Antigen-antibody complexes produce tissue damage mainly by eliciting inflammation at the sites of deposition.

The pathologic reaction is usually initiated when antigen combines with antibody in the circulation, creating immune complexes that typically deposit in vessel walls.

The antigens that form immune complexes may be

1.exogenous, such as a foreign protein that is injected or produced by an infectious microbe.
2. endogenous, if the individual produces antibody against self-antigens (autoimmunity).

Immune complex–mediated diseases tend be systemic, but often preferentially involve the kidney (glomerulonephritis), joints (arthritis), and small blood vessels (vasculitis), all of which are common sites of
immune complex deposition.

Systemic Immune Complex Disease

Serum sickness is the prototype of a systemic immune complex disease; it was once a frequent sequela to the administration of large amounts of foreign serum (e.g., serum from immunized horses used for protection against diphtheria). In modern times, the disease is infrequent and usually seen in individuals who receive antibodies from other individuals or species.

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

1. **Formation of immune complexes. The introduction of a protein antigen triggers an immune response that results in the formation of antibodies, typically about 1 week after the injection of the protein. These antibodies are secreted into the blood, where they react with the antigen still present in the circulation and form antigen-antibody complexes.**
2. **Deposition of immune complexes. In the next phase, the circulating antigen-antibody complexes are deposited in vessels. Organs where blood is filtered at high pressure to form other fluids, like urine and synovial fluid, are sites where immune complexes become concentrated and tend to deposit; hence, immune complex disease often affects glomeruli and joints.**
3. **Inflammation and tissue injury. Once immune complexes are deposited in the tissues, they initiate an acute inflammatory reaction. During this phase (approximately 10 days after antigen administration).**

clinical features

1.fever

2.urticaria

3.joint pain

4. lymph node enlargement

5.proteinuria appear

In acute serum sickness, caused by a single exposure to a large amount of antigen, the lesions tend to resolve as a result of catabolism of the immune complexes.

A form of chronic serum sickness results from repeated or prolonged exposure to an antigen. This occurs in several diseases, such as *systemic lupus erythematosus (SLE),* which is associated with persistent antibody responses to autoantigens. In many diseases, the morphologic changes and other findings suggest immune complex deposition, but the inciting antigens are unknown. Included in this category are membranous glomerulonephritis and several vasculitides.

Local Immune Complex Disease

The Arthus reaction is a localized area of tissue necrosis resulting from acute immune complex vasculitis, usually elicited in the skin. The reaction can be produced experimentally by intracutaneous injection of antigen in a previously immunized animal that contains circulating antibodies against the antigen. As the antigen diffuses into the vascular wall, it binds the preformed antibody, and large immune complexes are formed locally. These complexes precipitate in the vessel walls and cause fibrinoid necrosis, and superimposed thrombosis worsens the ischemic injury.

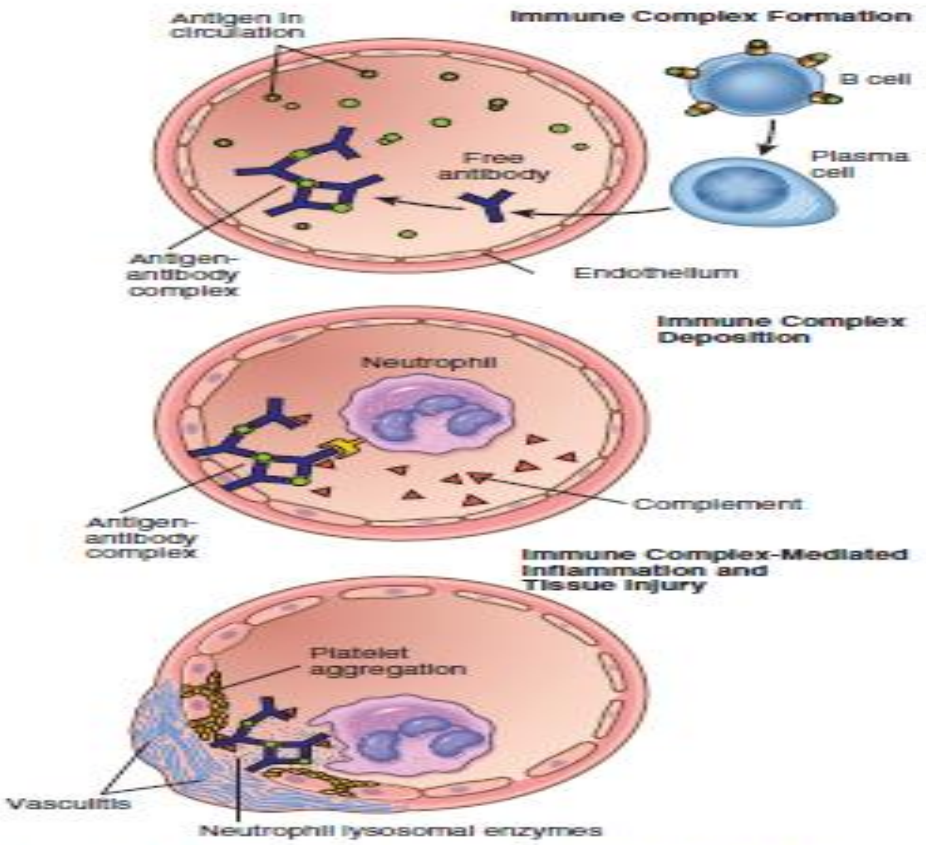

Figure 6.17 Immune complex disease. The sequential phases in the induction of systemic immune complex–mediated diseases (type III hypersensitivity).

T Cell–Mediated (Type IV) Hypersensitivity

Cell-mediated hypersensitivity is caused mainly by inflammation resulting from cytokines produced by CD4+ T cells.

CD4+ T cell–mediated hypersensitivity induced by environmental and self- antigens is the cause of many

autoimmune and other chronic inflammatory diseases.

Cell killing by CD8+ cells may also be involved in some autoimmune diseases and may be the dominant mechanism of tissue injury in certain reactions, especially those that follow viral infections.

CD4+ T cell–mediated hypersensitivity reactions, cytokines produced by T cells induce inflammation that

may be chronic and destructive. The prototype of T cell–mediated inflammation is delayed-type hypersensitivity (DTH), a tissue reaction to antigens given to immune individuals. In this reaction, an antigen administered into the skin of a previously immunized individual results in a detectable

cutaneous reaction within 24 to 48 hours.

The classic example of DTH is the tuberculin reaction, which is produced by the intracutaneous injection of purified protein derivative (PPD, also called tuberculin), a protein-containing antigen of the tubercle bacillus. In a previously sensitized individual, reddening and induration of the site appear in 8 to 12 hours, reach a peak in 24 to 72 hours, and thereafter slowly subside.

Morphologically, delayed-type hypersensitivity is characterized by the accumulation of mononuclear cells,

mainly CD4+ T cells and macrophages, around venules, producing perivascular "cuffing.

With sustained activation, macrophages often undergo a morphologic transformation into epithelioid cells,

large cells with abundant cytoplasm. Aggregates of epithelioid cells, usually surrounded by lymphocytes, form grossly visible small nodules called *granulomas*. This pattern of chronic inflammation, called *granulomatous inflammation.*

***Contact dermatitis* is a common example of tissue injury resulting from DTH reactions and presents as an itchy, vesicular (blistering) dermatitis.**

CD4+ T cell–mediated inflammation is the basis of tissue injury in many organ-specific and systemic autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis, as well

as diseases linked to uncontrolled reactions to bacterial commensals, such as inflammatory bowel disease.

CD8+ T Cell–Mediated Cytotoxicity

In this type of T cell–mediated reaction, CD8+ CTLs kill antigen-expressing target cells. Tissue destruction by CTLs may be a component of some T cell–mediated diseases, such as *type 1 diabetes*.

Table 6.1 Mechanisms of Hypersensitivity Reactions

Type	Immune Mechanisms	Histopathologic Lesions	Prototypical Disorders
Immediate (type I) hypersensitivity	Production of IgE antibody → immediate release of vasoactive amines and other mediators from mast cells; later recruitment of inflammatory cells	Vascular dilation, edema, smooth muscle contraction, mucus production, tissue injury, inflammation	Anaphylaxis; allergies; bronchial asthma (atopic forms)
Antibody-mediated (type II) hypersensitivity	Production of IgG, IgM → binds to antigen on target cell or tissue → phagocytosis or lysis of target cell by activated complement or Fc receptors; recruitment of leukocytes	Phagocytosis and lysis of cells; inflammation; in some diseases, functional derangements without cell or tissue injury	Autoimmune hemolytic anemia; Goodpasture syndrome
Immune complex–mediated (type III) hypersensitivity	Deposition of antigen-antibody complexes → complement activation → recruitment of leukocytes by complement products and Fc receptors → release of enzymes and other toxic molecules	Inflammation, necrotizing vasculitis (fibrinoid necrosis)	Systemic lupus erythematosus; some forms of glomerulonephritis; serum sickness; Arthus reaction
Cell-mediated (type IV) hypersensitivity	Activated T lymphocytes → (1) release of cytokines, inflammation and macrophage activation; (2) T cell–mediated cytotoxicity	Perivascular cellular infiltrates; edema; granuloma formation; cell destruction	Contact dermatitis; multiple sclerosis; type 1 diabetes; tuberculosis

Ig, Immunoglobulin.

CTLs directed against cell surface histocompatibility antigens play an important role in *graft rejection*. They also play a role in reactions against viruses (e.g., in viral hepatitis). Tumor

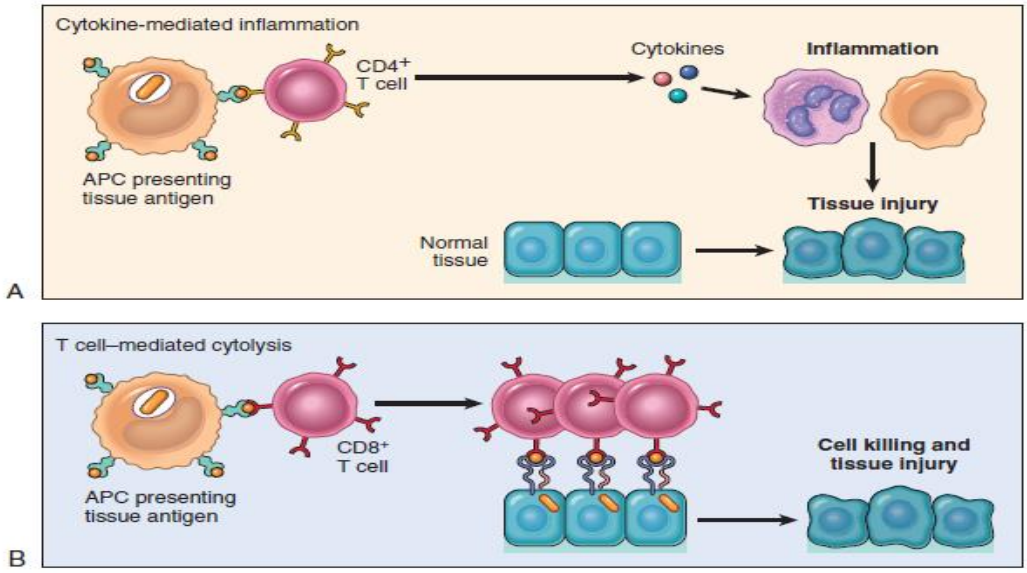

Figure 6.18 Mechanisms of T-cell–mediated (type IV) hypersensitivity reactions. (A) CD4+ Th1 cells (and sometimes CD8+ T cells, *not shown*) respond to tissue antigens by secreting cytokines that stimulate inflammation and activate phagocytes, leading to tissue injury. CD4+ Th17 cells contribute to inflammation by recruiting neutrophils (and, to a lesser extent, monocytes). (B) In some diseases, CD8+ cytotoxic T lymphocytes directly kill tissue cells. *APC*, Antigen-presenting cell.

antigens are also presented on the surface of tumor cells.