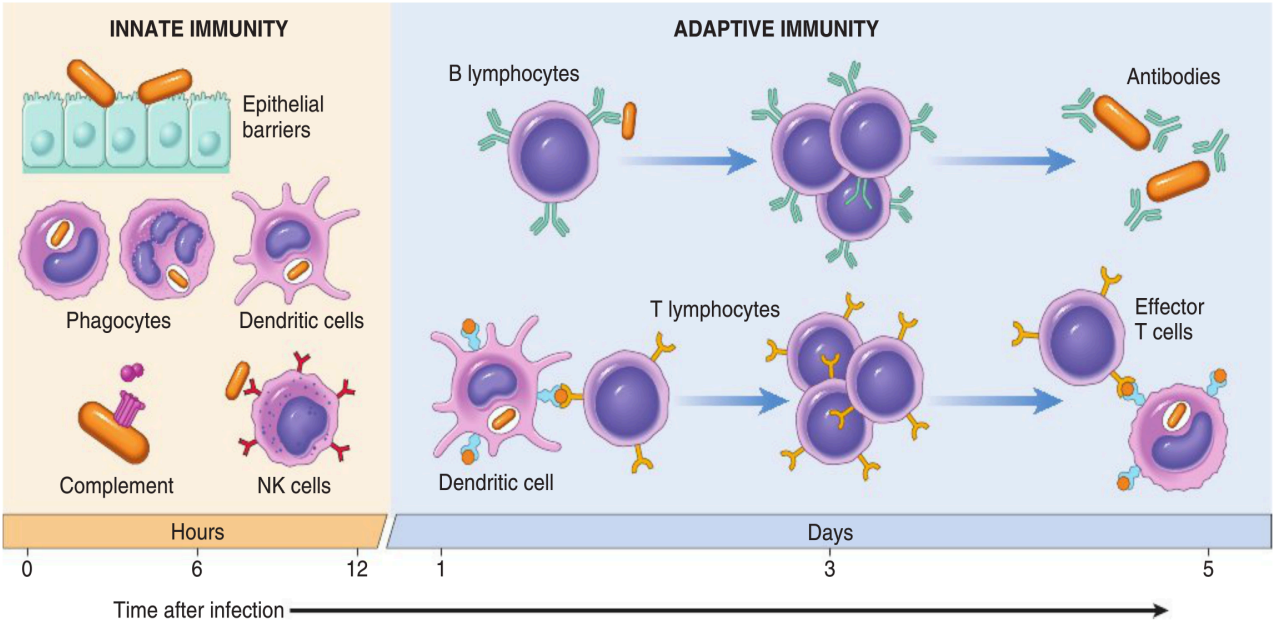
Pathology

DISEASES OF IMMUNITY

1. **5.1 General features of the immune system**
2. **5.2 Hypersensitivity reactions**
3. **5.3 Immunologic tolerance and causative mechanisms of auto immune disease**
4. **5.4 Acquired immunodeficiency syndrome (AIDS)**

What is the difference between innate and adaptive immunity?

Innate immunity (also called natural, or native, immunity) refers to the mechanisms that are ready to react to infections even before they occur, and that have evolved to specifically recognize and combat microbes. Adaptive immunity (also called acquired, or specific, immunity) consists of mechanisms that are stimulated by (“ adapt to”) microbes and are capable of recognizing microbial and nonmicrobial substances.



What is humoral and cell mediated immunity?

There are two types of adaptive immunity: humoral immunity, which protects against extracellular microbes and their toxins, and cell-mediated (or cellular) immunity, which is responsible for defense against intracellular microbes. Humoral immunity is mediated by B (bone marrow‑derived) lymphocytes and their secreted products, antibodies (also called immunoglobulins, Ig), and cellular immunity is mediated by T (thymus-derived) lymphocytes. Both classes of lymphocytes express highly specific receptors or a wide variety of substances, which are called antigens.

What is Type 1 hypersensitivity reaction?

These are also called allergic reactions, or allergies. They are induced by environmental antigens (allergens) that stimulate strong TH2 responses and IgE production in genetically susceptible individuals. IgE coats mast cells by binding to Fcε receptors; reexposure to the allergen leads to cross-linking of the IgE and FcεRI, activation of mast cells, and release of mediators. The principal mediators are histamine, proteases, and other granule contents, prostaglandins and leukotrienes, and cytokines. The mediators are responsible for the immediate vascular and smooth muscle reactions and the late-phase reaction (inflammation). The clinical manifestations may be local or systemic, and range from mildly annoying rhinitis to fatal anaphylaxis.

What is Type 2 hypersensitivity reaction?

In antibody-mediated disorders (type II hypersensitivity), secreted IgG and IgM antibodies injure cells by promoting their phagocytosis or lysis and injure tissues by inducing inflammation. Antibodies may also interfere with cellular functions and cause disease without tissue injury.

Table 6-3 Examples of Antibody-Mediated Diseases (Type II Hypersensitivity)

Disease	Target Antigen	Mechanisms of Disease	Clinicopathologic Manifestations
Autoimmune hemolytic anemia	Red cell membrane proteins (Rh blood group antigens, I antigen)	Opsonization and phagocytosis of red cells	Hemolysis, anemia
Autoimmune thrombocytopenic purpura	Platelet membrane proteins (GpIIb:IIIa integrin)	Opsonization and phagocytosis of platelets	Bleeding
Pemphigus vulgaris	Proteins in intercellular junctions of epidermal cells (epidermal cadherin)	Antibody-mediated activation of proteases, disruption of intercellular adhesions	Skin vesicles (bullae)
Vasculitis caused by ANCA	Neutrophil granule proteins, presumably released from activated neutrophils	Neutrophil degranulation and inflammation	Vasculitis
Goodpasture syndrome	Noncollagenous protein in basement membranes of kidney glomeruli and lung alveoli	Complement- and Fc receptor–mediated inflammation	Nephritis, lung hemorrhage
Acute rheumatic fever	Streptococcal cell wall antigen; antibody cross-reacts with myocardial antigen	Inflammation, macrophage activation	Myocarditis, arthritis
Myasthenia gravis	Acetylcholine receptor	Antibody inhibits acetylcholine binding, down-modulates receptors	Muscle weakness, paralysis
Graves disease (hyperthyroidism)	TSH receptor	Antibody-mediated stimulation of TSH receptors	Hyperthyroidism
Insulin-resistant diabetes	Insulin receptor	Antibody inhibits binding of insulin	Hyperglycemia, ketoacidosis
Pernicious anemia	Intrinsic factor of gastric parietal cells	Neutralization of intrinsic factor, decreased absorption of vitamin B_{12}	Abnormal erythropoiesis, anemia

ANCA, Antineutrophil cytoplasmic antibodies; TSH, thyroid-stimulating hormone.

What is Type 3 hypersensitivity?

In immune complex‐mediated disorders (type III hypersensitivity), IgG and IgM antibodies bind anti-gens usually in the circulation, and the antigen-antibody complexes deposit in tissues and induce inflammation. The leukocytes that are recruited (neutrophils and mono-cytes) produce tissue damage by release of lysosomal enzymes and generation of toxic free radicals.

What is Type 4 hypersensitivity?

In cell-mediated immune disorders (type IV hypersensitivity), sensitized T lymphocytes (TH1 and TH17 cells and CTLs) are the cause of the tissue injury. TH2 cells induce lesions that are part of immediate hypersensitivity reactions and are not considered a form of type IV hypersensitivity.

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.

What is the pathogenesis of autoimmune disease?

Autoimmunity arises from a combination of the inheritance of susceptibility genes, which may contribute to the breakdown of self-tolerance, and environmental triggers, such as infections and tissue damage, which promote the activation of self-reactive lymphocytes.

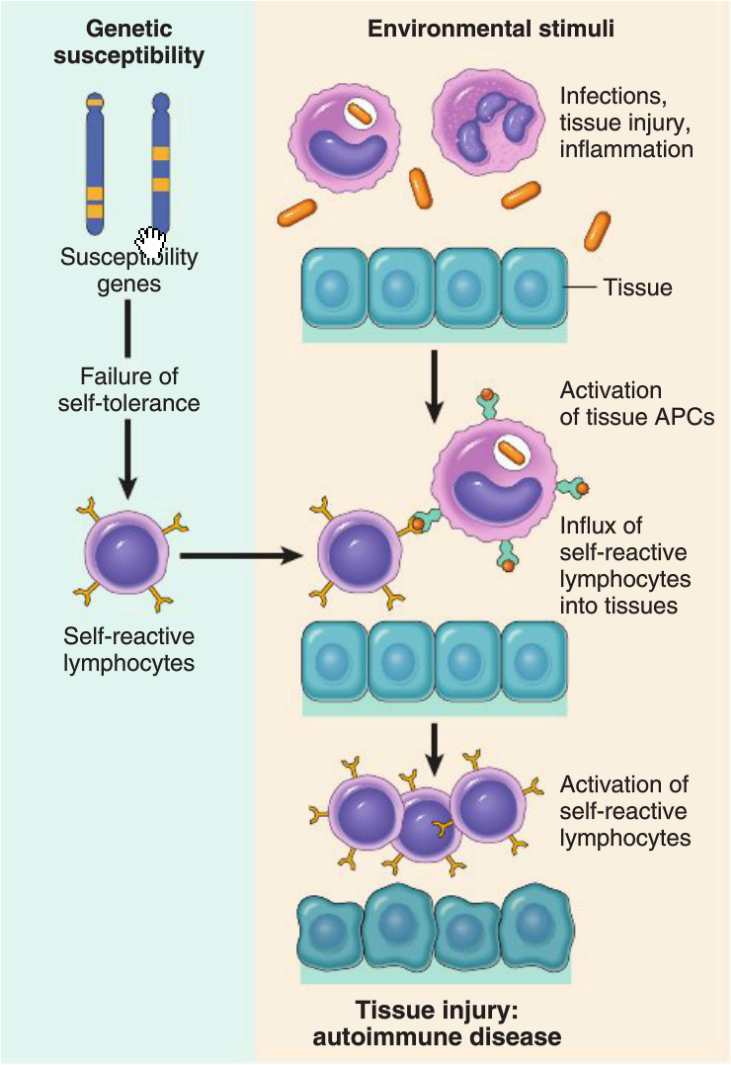


Figure 6-22 Pathogenesis of autoimmunity. Autoimmunity results from multiple factors, including susceptibility genes that may interfere with self-tolerance and environmental triggers (such as infections, tissue injury, and inflammation) that promote lymphocyte entry into tissues, activation of self-reactive lymphocytes, and tissue damage.

What is SLE (systemic lupus erythematosis)?

SLE is an autoimmune disease involving multiple organs, characterized by a vast array of autoantibodies, particularly antinuclear antibodies (ANAs), in which injury is caused mainly by deposition of immune complexes and binding of antibodies to various cells and tissues. The disease may be acute or insidious in its onset, and is typically a chronic, remitting and relapsing, often febrile, illness. Injury to the skin, joints, kidney, and serosal membranes is prominent. Virtually every other organ in the body, however, may also be affected.

What is Sjogren's syndrome?

Sjögren syndrome is a chronic disease characterized by dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia) resulting from immunologically mediated destruction of the lacrimal and salivary glands. It occurs as an isolated disorder (primary form), also known as the sicca syndrome, or more often in association with another autoimmune disease (secondary form). Among the associated disorders, rheumatoid arthritis is the most common, but some patients have SLE, polymyositis, scleroderma, vasculitis, mixed connective tissue disease, or thyroiditis.

What is systemic sclerosis?

Systemic sclerosis is characterized by:
(1) chronic inflammation thought to be the result of autoimmunity
(2) widespread damage to small blood vessels
(3) progressive interstitial and perivascular fibrosis in the skin and multiple organs.
Although the term scleroderma is ingrained in clinical medicine, this disease is better named systemic sclerosis because it is characterized by excessive fibrosis throughout the body. The skin is most commonly affected, but the gastrointestinal tract, kidneys, heart, muscles, and lungs also are frequently involved. In some patients the disease seems to remain confined to the skin for many years, but in the majority it progresses to visceral involvement with death from renal failure, cardiac failure, pulmonary insufficiency, or intestinal malabsorption.

What is Acquired Immune Deficiency Syndrome?

AIDS is a disease caused by the retrovirus human immunodeficiency virus (HIV) and characterized by profound immunosuppression that leads to opportunistic infections, secondary neoplasms, and neurologic manifestations.

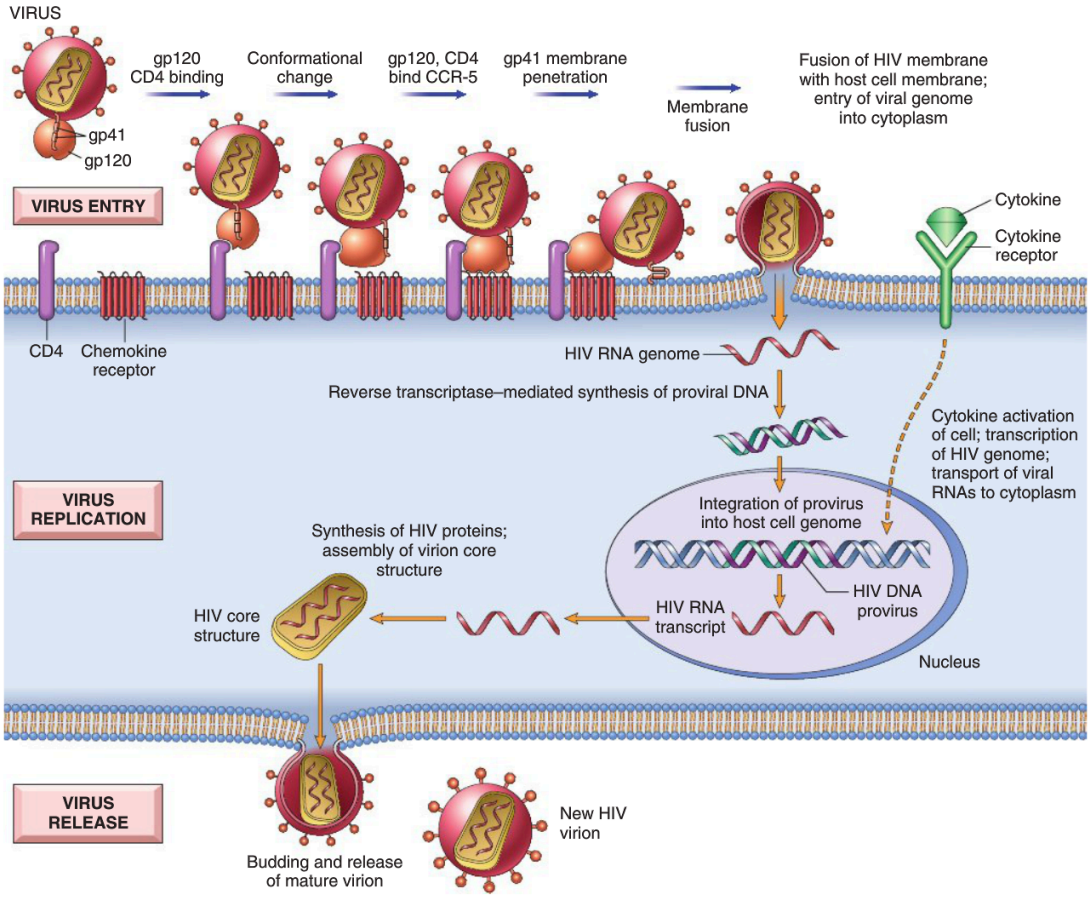


Figure 6-40 The life cycle of HIV showing the steps from viral entry to production of infectious virions. (Adapted with permission from Wain-Hobson S: HIV. One on one meets two. Nature 1996;384:117. Copyright 1996, Macmillan Magazines Limited.)

The life cycle of HIV consists of infection of cells, integration of the provirus into the host cell genome, activation of viral replication, and production and release of infectious virus. HIV infects cells by using the CD4 molecule as receptor and various chemokine receptors as coreceptors.

Table 6-16 AIDS-Defining Opportunistic Infections and Neoplasms Found in Patients with HIV Infection

Infections
Protozoal and Helminthic Infections
Cryptosporidiosis or isosporidiosis (enteritis)
Pneumocystosis (pneumonia or disseminated infection)
Toxoplasmosis (pneumonia or CNS infection)
Fungal Infections
Candidiasis (esophageal, tracheal, or pulmonary)
Cryptococcosis (CNS infection)
Coccidioidomycosis (disseminated)
Histoplasmosis (disseminated)
Bacterial Infections
Mycobacteriosis ("atypical," e.g., *Mycobacterium avium-intracellulare,* disseminated or extrapulmonary; *Mycobacterium tuberculosis,* pulmonary or extrapulmonary)
Nocardiosis (pneumonia, meningitis, disseminated)
Salmonella infections, disseminated
Viral Infections
Cytomegalovirus (pulmonary, intestinal, retinitis, or CNS infections)
Herpes simplex virus (localized or disseminated infection)
Varicella-zoster virus (localized or disseminated infection)
Progressive multifocal leukoencephalopathy
Neoplasms
Kaposi sarcoma
Primary lymphoma of brain
Invasive cancer of uterine cervix