Hypersensitivities

• Hypersensitivity
  • Any immune response against a foreign antigen exaggerated beyond the norm

• Four types
  • Type I (immediate)
  • Type II (cytotoxic)
  • Type III (immune complex-mediated)
  • Type IV (delayed or cell-mediated)
Hypersensitivities

• **Type I (Immediate) Hypersensitivity**
  • Localized or systemic reaction that results from the release of inflammatory molecules in response to an antigen
  • Develops within seconds or minutes following exposure to an antigen
  • Commonly called **allergies**
  • The antigens that stimulate it are called **allergens**
Hypersensitivities

- **Type I (Immediate) Hypersensitivity**
  - Reactions occur via a two-step process
    - Sensitization upon initial exposure to an allergen
    - Degranulation of sensitized cells
Figure 18.1a The mechanisms of a type I hypersensitivity reaction.

1. Antigen-presenting cell (APC) phagocytizes and processes antigen.
2. APC presents epitope (carried by MHC-II) to Th2 cell
3. IL-4 from Th2 cell stimulates selected B cell clone.
4. B cells become plasma cells that secrete IgE.
5. IgE binds to mast cells, basophils, and eosinophils.

(a) Sensitization
Figure 18.1b  The mechanisms of a type I hypersensitivity reaction.

Sensitized mast cell, basophil, or eosinophil

Histamines, kinins, proteases, leukotrienes, prostaglandins, and other inflammatory molecules

(b) Degranulation
Hypersensitivities

- **Type I (Immediate) Hypersensitivity**
  - Roles of degranulating cells in an allergic reaction
    - Mast cells
      - Distributed throughout the body in connective tissue
      - Have granules that contain inflammatory chemicals
        - Degranulation releases histamine, kinins, proteases, leukotrienes, and prostaglandins
Table 18.1 Inflammatory Molecules Released from Mast Cells

<table>
<thead>
<tr>
<th>Molecules</th>
<th>Role in Hypersensitivity Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Released During Degranulation</strong></td>
<td></td>
</tr>
<tr>
<td>Histamine</td>
<td>Causes smooth muscle contraction, increased vascular permeability, and irritation</td>
</tr>
<tr>
<td>Kinins</td>
<td>Cause smooth muscle contraction, inflammation, and irritation</td>
</tr>
<tr>
<td>Proteases</td>
<td>Damage tissues and activate complement</td>
</tr>
<tr>
<td><strong>Synthesized in Response to Inflammation</strong></td>
<td></td>
</tr>
<tr>
<td>Leukotrienes</td>
<td>Cause slow, prolonged smooth muscle contraction, inflammation, and increased vascular permeability</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>Some contract smooth muscle; others relax it</td>
</tr>
</tbody>
</table>
Hypersensitivities

• **Type I (Immediate) Hypersensitivity**
  • Roles of degranulating cells in an allergic reaction
    • Basophils
      • Least numerous leukocyte in the blood
      • Have granules that contain inflammatory chemicals
      • Degranulate like mast cells when allergens are encountered
Hypersensitivities

• Type I (Immediate) Hypersensitivity
  • Roles of degranulating cells in an allergic reaction
    • Eosinophils
      • *Eosinophilia* is the accumulation of eosinophils in blood
      • Mast cell degranulation can trigger the release of eosinophils from the bone marrow
      • Eosinophils in the bloodstream can degranulate
        • Release large amounts of leukotrienes
        • Increases severity of a hypersensitivity response
Hypersensitivities

• **Type I (Immediate) Hypersensitivity**
  • Clinical signs of localized allergic reactions
    • Usually mild and localized
    • Site of reaction depends on portal of entry
    • Inhaled allergens may cause **hay fever**
    • Small inhaled allergens may reach lungs and cause **asthma**
    • Some allergens may cause inflammation of the skin called hives, or **urticaria**
Figure 18.2 Some common allergens.
Figure 18.3 Urticaria.
Hypersensitivities

• **Type I (Immediate) Hypersensitivity**
  • Clinical signs of systemic allergic reactions
    • Many mast cells may degranulate at once
      • Release large amounts of histamine and inflammatory mediators
    • **Acute anaphylaxis** or **anaphylactic shock** can result
    • Clinical signs are those of suffocation
    • Must be treated promptly with *epinephrine*
    • Common causes include bee stings and certain foods
Hypersensitivities

• **Type I (Immediate) Hypersensitivity**
  
  • Diagnosis of type I hypersensitivity
    
    • Based on detection of high levels of allergen-specific immunoglobulin E (IgE)
    
    • Test referred to as ImmunoCAP Specific IgE blood test, CAP RAST, or Pharmacia CAP
    
    • Can also diagnose using skin tests
Figure 18.4 Skin tests for diagnosing type I hypersensitivity.
Hypersensitivities

• Type I (Immediate) Hypersensitivity
  • Prevention of type I hypersensitivity
    • Identification and avoidance of allergens
    • Food allergens identified using an elimination diet
    • Immunotherapy ("allergy shots") can help prevent allergic reactions
      • Administration of a series of injections of dilute allergen
      • Must be repeated every two to three years
      • Not effective in treating asthma
Hypersensitivities

• **Type I (Immediate) Hypersensitivity**
  • Treatment of type I hypersensitivity
    • Administer drugs that counteract inflammatory mediators
      • **Antihistamines** neutralize histamine
    • Treat asthma with a glucocorticoid and a bronchodilator
      • *Epinephrine* neutralizes many mechanisms of anaphylaxis
        • Relaxes smooth muscle
        • Reduces vascular permeability
        • Used in emergency treatment of severe asthma and anaphylactic shock
Hypersensitivities

- **Type II (Cytotoxic) Hypersensitivity**
  - Results when cells are destroyed by an immune response
    - Often the combined activities of complement and antibodies
  - A component of many autoimmune diseases
  - Two significant examples
    - Destruction of blood cells following an incompatible blood transfusion
    - Destruction of fetal red blood cells
Hypersensitivities

• **Type II (Cytotoxic) Hypersensitivity**
  • The ABO system and transfusion reactions
    • *Blood group antigens* are surface molecules of red blood cells
    • Each person’s red blood cells have A antigen, B antigen, both antigens, or neither antigen
    • *Transfusion reaction* can result if an individual receives different blood type
    • Donor’s blood group antigens may stimulate the production of antibodies in the recipient, destroying the transfused cells
Hypersensitivities

• **Type II (Cytotoxic) Hypersensitivity**
  • The ABO system and transfusion reactions
    • Recipient has preexisting antibodies to foreign blood group antigens
      • Immediate destruction of donated blood cells can occur
    • Recipient has no preexisting antibodies to foreign blood group antigens
      • Transfused cells initially circulate and function normally
      • Eventually recipient’s immune system mounts a primary response against the foreign antigens and destroys them
Figure 18.5 Events leading to hemolysis.
Table 18.2 ABO Blood Group Characteristics and Donor-Recipient Matches

<table>
<thead>
<tr>
<th>ABO Blood Group</th>
<th>ABO Antigen(s) Present</th>
<th>Antibodies Present</th>
<th>Can Donate To</th>
<th>Can Receive From</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A</td>
<td>Anti-B</td>
<td>A or AB</td>
<td>A or O</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
<td>Anti-A</td>
<td>B or AB</td>
<td>B or O</td>
</tr>
<tr>
<td>AB</td>
<td>A and B</td>
<td>None</td>
<td>AB</td>
<td>A, B, AB, or O (universal recipient)</td>
</tr>
<tr>
<td>O</td>
<td>None</td>
<td>Both anti-A and anti-B</td>
<td>A, B, AB, or O (universal donor)</td>
<td>O</td>
</tr>
</tbody>
</table>
Hypersensitivities

• **Type II (Cytotoxic) Hypersensitivity**
  • The Rh system and hemolytic disease of the newborn
    • Rh antigen
      • Common to red blood cells of humans and rhesus monkeys
    • About 85% of humans are Rh positive (Rh+)
    • If Rh-negative (Rh−) woman is carrying an Rh+ fetus, antibody immune response may be initiated against the fetal cells
    • In subsequent pregnancy, the fetus may be at risk for hemolytic disease
    • Administration of anti-Rh immunoglobulin, called RhoGAM, has reduced cases of hemolytic disease of the newborn
Figure 18.6 Events in the development of hemolytic disease of the newborn.

(a) First pregnancy

During delivery, Rh antigens enter mother's circulation through breaks in the placenta.

Mother makes anti-Rh antibodies, which have no effect on this baby, who has been born.

(b) Subsequent pregnancy

Mother's anti-Rh antibodies still circulate.

Mother's anti-Rh antibodies cross the placenta and destroy fetal blood cells.
Hypersensitivities

• **Type III (Immune Complex–Mediated) Hypersensitivity**
  • Caused by formation of **immune complexes**
    • Triggers release of inflammatory chemicals
  • Can cause localized reactions
    • Hypersensitivity pneumonitis
    • Glomerulonephritis
  • Can cause systemic reactions
    • Systemic lupus erythematosus (SLE)
    • Rheumatoid arthritis (RA)
Figure 18.7 The mechanism of type III (immune complex–mediated) hypersensitivity.

1. Antigens combine with antibodies to form antigen-antibody complexes.
   - Antigen
   - Antibody (IgG)
   - Antigen-antibody complex

2. Phagocytes remove most of the complexes, but some lodge in the walls of blood vessels.

3. There, the complexes activate complement.
   - Inactive complement
   - Active complement

4. Antigen-antibody complexes and activated complement attract and activate neutrophils, which release enzymes.
   - Neutrophil
   - Enzymes

5. Enzymes and inflammatory chemicals damage underlying tissues.
Hypersensitivities

• **Type III (Immune Complex–Mediated) Hypersensitivity**
  
  • Hypersensitivity pneumonitis
    
    • Inhalation of antigens deep in the lungs stimulates the production of antibodies
    
    • Subsequent inhalation of the same antigen stimulates the formation of immune complexes
      
      • Activates complement
Hypersensitivities

• Type III (Immune Complex–Mediated) Hypersensitivity
  • Glomerulonephritis
    • Immune complexes circulating in the bloodstream are deposited in the walls of glomeruli
    • Damage to the glomerular cells impedes blood filtration
    • Kidney failure and ultimately death result
Hypersensitivities

- **Type III (Immune Complex–Mediated) Hypersensitivity**
  - Rheumatoid arthritis (RA)
    - Immune complexes deposited in the joint
    - Results in release of inflammatory chemicals
    - The joints begin to break down and become distorted
      - Damage is progressively more severe
    - Trigger not well understood
  - Treated with anti-inflammatory drugs
Figure 18.8  The crippling distortion of joints characteristic of rheumatoid arthritis.
Hypersensitivities

• **Type III (Immune Complex–Mediated) Hypersensitivity**
  - Systemic lupus erythematosus (SLE)
    - Autoantibodies against DNA result in immune complex formation
    - Many other autoantibodies can also occur
      - Against red blood cells, platelets, lymphocytes, and muscle cells
    - Trigger unknown
  - Treatment with immunosuppressive drugs reduces autoantibody formation
  - Treatment with corticosteroids reduces inflammation
Figure 18.9 The characteristic facial rash of systemic lupus erythematosus.
Hypersensitivities

• **Type IV (Delayed or Cell-Mediated) Hypersensitivity**
  - Inflammation 12–24 hours after contact with certain antigens
  - Results from the actions of antigen, antigen-presenting cells, and T cells
  - Delay reflects the time it takes for macrophages and T cells to migrate to and proliferate at the site of the antigen
Hypersensitivities

• **Type IV (Delayed or Cell-Mediated) Hypersensitivity**
  • Tuberculin response
    • Skin exposed to tuberculosis or tuberculosis vaccine reacts to an injection of tuberculin beneath the skin
    • Used to diagnose contact with antigens of *M. tuberculosis*
      • No response when individual has not been infected or vaccinated
      • Red, hard swelling develops in individuals previously infected or immunized
    • Response mediated by memory T cells that cause a slowly developing inflammation
Figure 18.10  A positive tuberculin test, a type IV hypersensitivity response.
Hypersensitivities

- **Type IV (Delayed or Cell-Mediated) Hypersensitivity**
  - Allergic contact dermatitis
    - Cell-mediated immune response resulting in an intensely irritating skin rash
    - Triggered by chemically modified skin proteins that the body regards as foreign
    - In severe cases, acellular, fluid-filled blisters develop
    - Can be caused by poison ivy, formaldehyde, cosmetics, and chemicals used to produce latex
    - Treated with corticosteroids
Figure 18.11 Allergic contact dermatitis, a type IV hypersensitivity response.
Hypersensitivities

- **Type IV (Delayed or Cell-Mediated) Hypersensitivity**
  - Graft rejection
    - Rejection of tissues or organs that have been transplanted
    - Grafts perceived as foreign by a recipient undergo rejection
    - Normal immune response against foreign major histocompatibility complex (MHC) proteins present on graft cells
    - Likelihood of rejection depends on the degree to which the graft is foreign to the recipient
      - Based on the type of graft
Figure 18.12 Types of grafts.

- **Autograft**: genetically identical sibling or clone
- **Isograft**: genetically identical sibling or clone
- **Allograft**: genetically different member of same species
- **Xenograft**: genetically different species

© 2018 Pearson Education, Inc.
Hypersensitivities

• **Type IV (Delayed or Cell-Mediated) Hypersensitivity**
  • Graft-versus-host disease
    • Donated bone marrow cells regard the patient’s cells as foreign
    • Donor and recipient differ in MHC class I molecules
      • Grafted T cells attack all of the recipient’s tissues
    • Donor and recipient differ in MHC class II molecules
      • Grafted T cells attack the host’s antigen-presenting cells
    • Immunosuppressive drugs can stop graft-versus-host disease
Hypersensitivities

- **Type IV (Delayed or Cell-Mediated) Hypersensitivity**
  - Donor-recipient matching and tissue typing
    - MHC compatibility between donor and recipient is difficult due to a high degree of variability
      - The more closely the donor and recipient are related, the smaller the difference in their MHC
    - Preferable that grafts are donated by a parent or sibling
    - Tissue typing used to match donor and recipient
Table 18.3  The Characteristics of the Four Types of Hypersensitivity Reactions

<table>
<thead>
<tr>
<th>Descriptive</th>
<th>Name</th>
<th>Cause</th>
<th>Time Course</th>
<th>Characteristic Cells Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Immediate hypersensitivity</td>
<td>Antibody (such as IgE) on sensitized cells’ membranes binds antigen, causing degranulation</td>
<td>After initial sensitization, seconds to minutes</td>
<td>Previously sensitized mast cells, basophils, or eosinophils</td>
</tr>
<tr>
<td>Type II</td>
<td>Cytotoxic hypersensitivity</td>
<td>Antibodies and complement lyse target cells</td>
<td>Minutes to hours</td>
<td>Plasma cells secrete antibodies that act against other body cells</td>
</tr>
<tr>
<td>Type III</td>
<td>Immune complex-mediated hypersensitivity</td>
<td>Nonphagocytized complexes of antibodies and antigens trigger complement activation, leading to inflammation, and cause neutrophils to release damaging enzymes</td>
<td>Several hours</td>
<td>Neutrophils</td>
</tr>
<tr>
<td>Type IV</td>
<td>Delayed (cell-mediated) hypersensitivity</td>
<td>T cells attack the body’s cells</td>
<td>Several days</td>
<td>Activated T cells</td>
</tr>
</tbody>
</table>
Hypersensitivities

- **Type IV (Delayed or Cell-Mediated) Hypersensitivity**
  - Actions of immunosuppressive drugs
    - Immunosuppressive drugs important to success of modern transplantation
    - Important classes of immunosuppressive drugs
      - Glucocorticoids
      - Cytotoxic drugs
      - Cyclosporine
      - Lymphocyte-depleting therapies
### Table 18.4 The Four Classes of Immunosuppressive Drugs

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids</td>
<td>Prednisone, methylprednisolone</td>
<td>Anti-inflammatory; kill T cells</td>
</tr>
<tr>
<td>Cytotoxic drugs</td>
<td>Cyclophosphamide, azathioprine, mycophenolate mofetil, brequinar sodium, leflunomide</td>
<td>Block cell division nonspecifically</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Cyclosporine</td>
<td>Blocks T cell responses</td>
</tr>
<tr>
<td>Lymphocyte-depleting therapies</td>
<td>Antilymphocyte globulin, monoclonal antibodies</td>
<td>Kill T cells nonspecifically, or kill activated T cells, or inhibit IL-2 reception</td>
</tr>
</tbody>
</table>
Hypersensitivities

• **Tell Me Why**
  
  • During the war in Afghanistan in 2012, an army corporal with type AB blood received a life-saving transfusion from his sergeant, who had type O blood. Later, the sergeant was involved in a traumatic accident and needed blood desperately. The corporal wanted to help but was told his blood was incompatible. Explain why the corporal could receive blood from but could not give blood to the sergeant.
Autoimmune Diseases

• Causes of Autoimmune Diseases
  • Occur more often in the elderly
  • Are more common in men than in women
  • May result when an individual begins to make antibodies or cytotoxic T cells against normal body cells
Autoimmune Diseases

- **Causes of Autoimmune Diseases**
  - Estrogen may stimulate destruction of tissue by cytotoxic T cells
  - Some maternal cells may cross the placenta, colonize the fetus, and trigger autoimmune disease later in life
  - Fetal cells may cross the placenta and trigger autoimmunity in the mother
  - Environmental factors such as viral infections
  - Genetic factors such as certain MHC genes
  - T cells may encounter self-antigens that are normally “hidden”
  - Microorganisms may trigger autoimmunity due to **molecular mimicry**
  - Failure of the normal control mechanisms of the immune system
Autoimmune Diseases

- Examples of Autoimmune Diseases
  - Two major categories
    - Systemic autoimmune diseases
    - Single-organ autoimmune diseases
      - Can affect many different organs
        - Blood cells
        - Endocrine glands
        - Nervous tissue
        - Connective tissue
Autoimmune Diseases

- **Examples of Autoimmune Diseases**
  - Autoimmunity affecting blood cells
    - Autoimmune hemolytic anemia
      - Individuals produce antibodies against red blood cells
      - Causes severe anemia
      - Precise cause is unknown
        - Some cases follow viral infection or treatment with certain drugs
Autoimmune Diseases

• **Examples of Autoimmune Diseases**
  
  • Autoimmunity affecting endocrine organs
    
    • Autoimmune responses can develop against cells in the pancreas or thyroid gland
    
    • Can cause destruction of the gland and hormone deficiencies
  
  • Type 1 diabetes mellitus
    
    • Can result from damage to the islets of Langerhans
    
    • Treatment with immunosuppressive drugs delays the onset in some individuals
Autoimmune Diseases

- **Examples of Autoimmune Diseases**
  - Autoimmunity affecting endocrine organs
    - Graves’ disease
      - Autoimmune response against the thyroid gland
      - Triggers excessive production of thyroid hormone and growth of the thyroid gland (goiter)
      - Treated with antithyroid medication or radioactive iodine
    - Surgical removal of the thyroid is sometimes required
Autoimmune Diseases

• Examples of Autoimmune Diseases
  • Autoimmunity affecting nervous tissue
    • Multiple sclerosis (MS)
      • Cytotoxic T cells destroy the myelin sheaths that insulate brain and spinal cord neurons
      • Impairs vision, speech, and neuromuscular function
  • Autoimmunity affecting connective tissue
    • Rheumatoid arthritis
Autoimmune Diseases

• **Tell Me Why**
  
  • Why can’t scientists use the postulates of Robert Koch to determine the specific cause of Graves’ disease?
Immunodeficiency Diseases

• Conditions resulting from defective immune mechanisms
• Two general types
  • Primary immunodeficiency diseases
    • Result from some genetic or developmental defect
    • Develop in infants and young children
  • Acquired immunodeficiency diseases
    • Develop as a direct consequence of some other recognized cause
    • Develop in later life
Table 18.5 Some Primary Immunodeficiency Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Defect</th>
<th>Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic granulomatous disease</td>
<td>Ineffective phagocytes</td>
<td>Uncontrolled infections</td>
</tr>
<tr>
<td>Severe combined immunodeficiency disease (SCID)</td>
<td>Lack of T cells and B cells</td>
<td>No resistance to any type of infection, leading to rapid death</td>
</tr>
<tr>
<td>DiGeorge syndrome</td>
<td>Lack of T cells and thus no cell-mediated immunity</td>
<td>Overwhelming viral infections</td>
</tr>
<tr>
<td>Bruton-type agammaglobulinemia</td>
<td>Lack of B cells and thus lack of immunoglobulins</td>
<td>Overwhelming bacterial infections</td>
</tr>
</tbody>
</table>
Immunodeficiency Diseases

• Acquired Immunodeficiency Diseases
  • Result from a number of causes
    • Severe stress
      • Suppression of cell-mediated immunity results from an excess production of corticosteroids
    • Malnutrition and environmental factors
      • Inhibit production of B cells and T cells
    • Acquired immunodeficiency syndrome (AIDS)
      • Opportunistic infections, low CD4 cells, and presence of human immunodeficiency syndrome (HIV)
Immunodeficiency Diseases

• Acquired Immunodeficiency Diseases
  • Signs and symptoms of AIDS
    • Not a disease but a syndrome
    • Defined as certain opportunistic or rare infections along with infection by HIV or a severe decrease in the number of helper T cells and a positive test for HIV
  • Several infections and diseases define AIDS
Figure 18.13 Diseases associated with AIDS.
# Table 18.6 Opportunistic Infections Associated with AIDS

<table>
<thead>
<tr>
<th>Disease</th>
<th>Causative Agent</th>
<th>Organ Primarily Affected</th>
<th>(Chapter Where Covered)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coccidioidomycosis</td>
<td>Coccidioides (fungus)</td>
<td>Lung (22)</td>
<td></td>
</tr>
<tr>
<td><em>Cytomegalovirus</em> disease</td>
<td><em>Cytomegalovirus</em></td>
<td>Brain (20), liver (23)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea (severe and prolonged)</td>
<td>Various bacteria, <em>Cryptosporidium</em> (protozoan)</td>
<td>Intestines (23)</td>
<td></td>
</tr>
<tr>
<td>Herpes</td>
<td><em>HerpesvirusSimplexvirus</em></td>
<td>Skin (19)</td>
<td></td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td><em>Histoplasma</em> (fungus)</td>
<td>Lung (22)</td>
<td></td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td><em>Human herpesvirus 8</em></td>
<td>Blood vessels (21)</td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td><em>Cryptococcus</em> (yeast), <em>Listeria</em> (bacterium)</td>
<td>Brain and meninges (20)</td>
<td></td>
</tr>
<tr>
<td>Oral hairy leukoplakia</td>
<td><em>Lymphocryptovirus</em> (Epstein-Barr virus)</td>
<td>Tongue (23)</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td><em>Pneumocystis</em> (fungus)</td>
<td>Lung (22)</td>
<td></td>
</tr>
<tr>
<td>Shingles</td>
<td><em>Varicellovirus</em></td>
<td>Skin (19)</td>
<td></td>
</tr>
<tr>
<td>Thrush</td>
<td><em>Candida</em> (yeast)</td>
<td>Mouth and tongue (23), vagina (24)</td>
<td></td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td><em>Toxoplasma</em> (protozoan)</td>
<td>Lungs, liver, heart (21)</td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td><em>Mycobacterium</em></td>
<td>Lung (22)</td>
<td></td>
</tr>
</tbody>
</table>
Immunodeficiency Diseases

• Acquired Immunodeficiency Diseases
  • AIDS pathogen and its virulence factors
    • HIV
      • Enveloped, +ssRNA virus
      • Retrovirus—uses reverse transcriptase to make DNA copy of genome
  • Two major types of HIV
    • HIV-1 is prevalent in the United States and Europe
    • HIV-2 is prevalent in West Africa
Immunodeficiency Diseases

- Acquired Immunodeficiency Diseases
  - AIDS pathogen and its virulence factors
    - Structure of HIV
      - Viral envelope has two antigenic glycoproteins
        - gp120
          - Primary attachment molecule of HIV
          - Antigenic variability during prolonged infection
        - gp41
          - Promotes fusion of viral envelope to target cell
      - Viral characteristics impede immune clearance of HIV
Figure 18.14 Artist’s conception of HIV.
Immunodeficiency Diseases

• Acquired Immunodeficiency Diseases
  • AIDS pathogen and its virulence factors
    • Origin of HIV
      • Likely arose from mutation of simian immunodeficiency virus
      • May have emerged in the human population around 1930
      • Whether the two HIV types are derived from the same or different SIV strains is unknown
Figure 18.15  The replication cycle of HIV.

1. Attachment

2. Entry by endocytosis

3. Uncoating

4. Synthesis of DNA

5. Integration

6. Synthesis of RNA and polypeptides

7. Release

8. Assembly and maturation (protease function)

HIV

CD4

Endosome

gp 41

Virus enters cytosol and capsid uncoats

dsDNA is transcribed from ssRNA by reverse transcriptase

Cytoplasmic membrane

gp 120

Translation of mRNA into viral proteins

Genome RNA

mRNA

Transcription

dsDNA

Integrate

Provirus

Virus inserted into human DNA

Human DNA

Nucleus

© 2018 Pearson Education, Inc.
Figure 18.16  The process by which HIV attaches to and enters a host cell.

1. gp120 binds to CD4 receptor on target cell.
2. CD4-gp120 complex attaches to fusin (CXCR4), which triggers endocytosis.
3. The virus is now in an endosome.
4. Glycoprotein 41 facilitates fusion of the viral envelope with the endosome membrane.
5. The viral capsid is now in the cytosol.
6. The capsid breaks down, releasing viral RNA and proteins.
Immunodeficiency Diseases

- **Acquired Immunodeficiency Diseases**
  - Details of synthesis and latency
    - Reverse transcriptase transcribes dsDNA from ssRNA
    - Antigenic variants of HIV result from errors introduced in the genome during transcription
  - dsDNA *provirus* enters the nucleus
    - Viral *integrase* inserts provirus into a human chromosome
    - Integrated DNA is passed to progeny cells during replication
    - Provirus can remain dormant for years
  - Macrophages and monocytes are major reservoirs of HIV
Immunodeficiency Diseases

• **Acquired Immunodeficiency Diseases**
  • Details of release, assembly, and maturation
    • HIV exits cell at *lipid rafts* in the cytoplasmic membrane
      • Lipid raft components become the viral envelope
    • Capsomeres form immature capsid outside the cell
    • Viral *protease* releases proteins that produce a mature virus
      • *Protease inhibitors* are used to treat HIV
Figure 18.17 Action of reverse transcriptase, depicted here as three distinct steps.
### Table 18.7 Characteristics of HIV That Challenge the Immune System

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Effect(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrovirus with a genome that consists of two copies of +ssRNA</td>
<td>Reassortment of viral genes possible; reverse transcription produces much mutation and thus genetic variation; genome integrates into host’s chromosome</td>
</tr>
<tr>
<td>Targets helper T cells especially, but also macrophages, dendritic cells, and muscle cells, and possibly liver, nerve, and epithelial cells</td>
<td>Permanently infects key cells of host’s immune system</td>
</tr>
<tr>
<td>Antigenic variability</td>
<td>Numerous antigenic variations due to mutations help virus evade host’s immune response</td>
</tr>
<tr>
<td>Induces fusion of infected cells with neighboring cells</td>
<td>Increases routes of infection; intracellular site helps virus evade immune detection</td>
</tr>
</tbody>
</table>
Immunodeficiency Diseases

• Acquired Immunodeficiency Diseases
  • Pathogenesis of AIDS
    • Only humans replicate HIV
    • HIV destroys the immune system
      • Destruction of helper T cells relates to course of AIDS
Figure 18.18 The course of AIDS follows the course of helper T cell destruction.
Immunodeficiency Diseases

• **Acquired Immunodeficiency Diseases**
  
  • Epidemiology of AIDS
    • AIDS was first recognized in young male homosexuals in the United States
    • AIDS is now found worldwide
    • HIV found in blood, semen, saliva, vaginal secretions, and breast milk can cause infections
      • Blood and semen are more infective than other secretions
      • Infected fluid must be injected or encounter a tear or lesion in the skin or mucous membranes
Figure 18.19 The global distribution of HIV/AIDS.
Figure 18.20  Modes of HIV transmission in people over 12 years of age in the United States during 2011.

**Adult Males**
- Male homosexual contact plus use of injected drugs 3.6%
- High-risk heterosexual contact 11.8%
- Other 0.1%
- Use of injected drugs 5.7%
- Other 0.1%
- Male homosexual contact 78.7%

**Adult Females**
- Use of injected drugs
- Other 0.15%
- High-risk heterosexual contact 14%
- Other 0.15%
- High-risk heterosexual contact 86%
Immunodeficiency Diseases

• Acquired Immunodeficiency Diseases
  • Epidemiology of AIDS
    • Some behaviors increase the risk of HIV infection
      • Anal intercourse
      • Sexual promiscuity
      • Intravenous drug use
      • Intercourse with someone in these categories
    • A few cases of casual HIV spread have been documented
Immunodeficiency Diseases

• **Acquired Immunodeficiency Diseases**
  • Diagnosis, treatment, and prevention
    • Diagnosis
      • AIDS diagnosis is based on symptoms, low levels of CD4 lymphocytes, and presence of antibodies against HIV
      • Antibodies against HIV are detected by ELISA or western blot
        • Positive test does not indicate presence of AIDS
      • Long-term nonprogressors
        • Do not develop AIDS
        • Possible reasons: defective virions, poor binding of HIV to cells, or well-developed immune systems
Immunodeficiency Diseases

• Acquired Immunodeficiency Diseases
  • Diagnosis, treatment, and prevention
    • Treatment
      • Antiretroviral therapy (ART) currently used to reduce viral replication
        • Cocktail of antiviral drugs
        • Does not cure the infection
        • Inhibits HIV replication
        • Patient can live relatively normal life while on treatment
Immunodeficiency Diseases

• Acquired Immunodeficiency Diseases
  • Diagnosis, treatment, and prevention
    • Treatment
      • Various problems must be overcome to develop vaccine
        • Vaccine must generate antibodies and cytotoxic T cells
        • Induction of IgG can be detrimental to patient
        • Numerous HIV variants within an individual
        • HIV can spread directly from cell to cell
        • HIV infects cells important to combating infections
        • Vaccine testing involves ethical and medical concerns
Immunodeficiency Diseases

- **Acquired Immunodeficiency Diseases**
  - Diagnosis, treatment, and prevention
    - Prevention
      - Behavioral changes can slow the AIDS epidemic
        - Abstinence and safe sex
        - Use of clean needles
        - Providing antiviral drugs to infected pregnant women
        - Screening of blood products
        - Use of protective wear to prevent contact with blood
        - Circumcision reduces infection through sexual activity
        - Pre-exposure prophylaxis (oral tenofovir)
        - Vaginal application of tenofovir before and after intercourse reduces the chance of infection
Immunodeficiency Diseases

• **Tell Me Why**
  
  • Why is it difficult for a medical treatment to rid the body’s cells of HIV?
Micro Matters

• In the Micro Matters video in Chapter 18, Mark has meningococcal meningitis. Mark’s classmates research this disease to learn more about it.
  • Meningococcal meningitis is an infection that causes inflammation of the meninges.
  • Meningococcal meningitis is caused by the bacterium *Neisseria meningitidis*.
  • Rapid treatment of meningococcal meningitis with antibiotics is critical to prevent permanent damage to the CNS or death.