Chapter 18
Hypersensitivities
Hypersensitivity

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

• 4 types
  • Type I (immediate)
  • Type II (cytotoxic)
  • Type III (immune-complex mediated)
  • Type IV (delayed or cell-mediated)
Type I (Immediate) Hypersensitivity

• Localized or systemic reactions

• Result from the release of inflammatory molecules in response to an antigen

• Develop within seconds or minutes following exposure to an antigen

• Commonly called allergies and the antigens that stimulate them are called allergens
Type I (Anaphylactic) Reactions

- Involve IgE, mast cells, basophiles, & eosinophiles
- Localized: Hives or asthma from contact or inhaled antigens
- Systemic: Shock from ingested or injected antigens

Figure 19.1a
Type I (Anaphylactic) Reactions

- Skin testing
- Desensitization

Figure 19.3
Figure 18.1

1. Antigen-presenting cell (APC) phagocytizes and processes antigen.

2. APC presents antigenic determinant to $T_H^2$ cell.

3. IL-4 from $T_H^2$ cell stimulates B cell.

4. B cell becomes plasma cell, which secretes IgE.

5. IgE binds to mast cells, basophils, and eosinophils.

**(a) Sensitization**

- Sensitized mast cell, basophil, or eosinophil
- Histamines, kinins, proteases, leukotrienes, prostaglandins, and other inflammatory molecules

**Subsequent exposure to allergen**
Mast Cells

- Found in sites close to body surfaces
  - skin
  - walls of the intestines
  - airways
- Characteristic feature is a cytoplasm filled with large granules
  - Granules contain a mixture of potent inflammatory chemicals
<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</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>Some contract smooth muscle; others relax it</td>
</tr>
</tbody>
</table>
Basophils and Eosinophils

• Basophils
  • Leukocytes that contain granules that stain with basophilic dyes
  • Granules filled with inflammatory chemicals similar to those in the mast cells
  • Sensitized basophils bind IgE and degranulate in the same way as mast cells
Basophils and Eosinophils

- Eosinophils
  - Leukocytes that contain granules that stain with the dye eosin
  - Granules contain inflammatory mediators and leukotrienes that contribute to the severity of a hypersensitivity response
  - Mast cell degranulation stimulates the release of eosinophils that migrate to the site of mast cell degranulation where they then degranulate
Clinical Signs of Localized Allergic Reactions

• Type I hypersensitivity reactions are usually mild and localized

• Site of the reaction depends on the portal of entry
  • Inhaled allergens may cause hay fever, an upper respiratory tract response
    • Marked by watery nasal discharge, sneezing, itchy throat and eyes, and excessive tear production
    • Commonly caused by mold spores, pollens, flowering plants, some trees, and dust mites
Clinical Signs of Localized Allergic Reactions

- Inhaled allergens that are small may reach the lungs
  - Causes asthma
  - Characterized by wheezing, coughing, excessive production of mucus, and constriction of the smooth muscles of the bronchi
- Some foods may contain allergens
  - Cause diarrhea and other gastrointestinal signs and symptoms
- Local dermatitis
  - Produces hives, or urticaria, due to release of histamine and other mediators into nearby skin tissue and the leakage of serum from local blood vessels
Clinical Signs of Systemic Allergic Reactions

- Degranulation of many mast cells at once causes the release of large amounts of histamine and inflammatory mediators

- Acute anaphylaxis or anaphylactic shock can result

- Clinical signs are those of suffocation
  - Bronchial smooth muscle contracts violently
  - Leakage of fluid from blood vessels causes swelling of the larynx and other tissues
  - Contraction of the smooth muscle of the intestines and bladder

- Must be treated promptly with epinephrine
Type II (Cytotoxic) Hypersensitivity

- Involve IgG or IgM antibodies and complement
- Results when cells are destroyed by an immune response
- Is a component of many autoimmune diseases
- 2 significant examples
  - Destruction of blood cells following an incompatible blood transfusion
  - Destruction of fetal red blood cells in hemolytic disease of the newborn
ABO System and Transfusion Reactions

• Blood group antigens = surface glycoproteins

• The ABO blood group
  • two antigens
    • A antigen
    • B antigen
  • Each person’s red blood cells have either A antigen, B antigen, both antigens, or neither
## ABO Blood Group System

<table>
<thead>
<tr>
<th>Blood Group</th>
<th>Erythrocyte or Red Blood Cell Antigens</th>
<th>Illustration</th>
<th>Plasma Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB</td>
<td>A and B</td>
<td></td>
<td>Neither anti-A nor anti-B antibodies</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
<td></td>
<td>Anti-A</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
<td></td>
<td>Anti-B</td>
</tr>
<tr>
<td>O</td>
<td>None</td>
<td></td>
<td>Anti-A and Anti-B</td>
</tr>
</tbody>
</table>
Transfusion Reactions

• If recipient has **preexisting antibodies** to foreign blood group antigens
  
  • **Immediate destruction** of donated blood cells can occur by two mechanisms
    
    • Antibody-bound cells may be phagocytized by macrophages and neutrophils
    
    • Hemolysis- antibodies agglutinate cells, and complement ruptures them
    
    • Can result in kidney damage, blood clotting and stress on the liver
Transfusion Reactions

• If recipient has no preexisting antibodies to foreign blood group antigens
  • Transfused cells circulate and function normally for a while
  • Eventually recipient’s immune system mounts a primary response against the foreign antigens that destroys them
    • Happens over a extended period such that severe symptoms and signs don’t occur
# 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</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(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</td>
<td>O</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(universal donor)</td>
</tr>
</tbody>
</table>
RH System and Hemolytic Disease of the Newborn

- Based on the rhesus, or Rh, antigen
  - Antigen that is common to the red blood cells of humans and rhesus monkeys
  - Transports anions and glucose across the cytoplasmic membrane
- Rh positive (Rh+) individuals have the Rh antigen on their red blood cells while Rh- individuals do not
- Preexisting antibodies against Rh antigen do not occur
- Risk of hemolytic disease of the newborn
Hemolytic Disease of the Newborn

Figure 19.4
During delivery, Rh antigens enter mother's circulation through breaks in the placenta. Rh-negative mother.

Mother makes anti-Rh antibodies.

Anti-Rh antibodies.

(a) First pregnancy

Mother has anti-Rh antibodies.

Anti-Rh antibodies cross the placenta and destroy fetal blood cells.

(b) Subsequent pregnancy

Maternal circulation.

Fetal red blood cells destroyed.
Preventions of Hemolytic Disease of the Newborn

- Administer anti-Rh serum, called Rhogam, to Rh-negative pregnant women
  - Destroys any fetal red blood cells that may have entered the body
  - Sensitization of the mother does not occur and subsequent pregnancies are safer
Drug-Induced Cytotoxic Reactions

- Some drug molecules can form haptens
  - Spontaneously bind to blood cells or platelets and stimulate the production of antibodies
- Can produce various diseases
  - Immune thrombocytopenic purpura
  - Agranulocytosis
  - Hemolytic anemia
1. Drug molecules bind to platelets forming drug-platelet complex

2. Complexes are antigenic, triggering a humoral immune response

3. Antibodies bind to drug molecules; complement binds to antibodies

4. Complement’s membrane attack complexes lyse platelet
Type III (Immune-Complex Mediated) Hypersensitivity

• Due to the formation of antigen-antibody complexes, also called immune-complexes

• Can cause systemic or localized reactions
  • Systemic
    • Systemic lupus erythematosus
    • Rheumatoid arthritis
  • Localized
    • Hypersensitivity pneumonitis
    • Glomerulonephritis
Type III (Immune Complex) Reactions

- IgG antibodies and antigens form complexes that lodge in basement membranes.
1. Antigens combine with antibodies to form antigen-antibody complexes.
   - Antigen
   - Antibody
   - Antigen-antibody complex

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

3. The complexes activate complement.
   - Inactive complement
   - Active complement

4. Antigen-antibody complexes and activated complement attract and activate neutrophils, which release inflammatory chemicals.
   - Neutrophil
   - Inflammatory chemicals

5. Inflammatory chemicals damage underlying blood vessel wall.
Localized Type III Hypersensitivity Reactions

- Hypersensitivity pneumonitis

- Individuals become sensitized when antigens are inhaled deep into the lungs, stimulating the production of antibodies

- Subsequent inhalation of the same antigen stimulates the formation of immune complexes that activate complement
Localized Type III Hypersensitivity Reactions

- Glomerulonephritis
  - Immune complexes circulating in the bloodstream are deposited on the walls of glomeruli (small blood vessels in the kidney’s)
  - Damage to the glomerular cells impedes blood filtration
  - Result is kidney failure and ultimately death
Type IV (Delayed or Cell-Mediated) Hypersensitivity

• Inflammation due to contact with certain antigens occurs after 12-24 hours

• Result from the interactions of antigen, antigen-presenting cells, and T cells

• Delay in this response reflects the time it takes for macrophages and T cells to migrate to and proliferate at the site of the antigen
Type IV (Cell-Mediated) Reactions

- Delayed-type hypersensitivities due to $T_D$ cells
- Cytokines attract macrophages and initiate tissue damage
Type IV (Delayed or Cell-Mediated) Hypersensitivity

- 4 examples
  - Tuberculin response
  - Allergic contact dermatitis
  - Graft rejection
  - Graft versus host disease
Tuberculin Response

• Skin of an individual exposed to tuberculosis or tuberculosis vaccine reacts to an injection beneath the skin of tuberculin.

• Used to diagnose contact with antigens of *M. tuberculosis*.
  
  • No response when tuberculin injected into the skin of a never infected or vaccinated individual.
  
  • A red hard swelling develops when tuberculin is injected into a previously infected or immunized individual.
The tuberculin response is mediated by memory T cells.

- When first infected with M. tuberculosis, the resulting cell-mediated response generates memory T cells that persist in the body.
- When sensitized individual is injected with tuberculin, dendritic cells migrate to the site and attract memory T cells.
- T cells secrete cytokines that attract more T cells and macrophages to produce a slowly developing inflammatory response.
- Macrophages ingest and destroy the tuberculin, allowing the tissue to return to normal.
Allergic Contact Dermatitis

- A cell-mediated immune response resulting in an intensely irritating skin rash

- Response triggered by chemically modified skin proteins that the body regards as foreign
  - Can happen when a hapten, such as the oil from poison ivy and related plants, binds to proteins on the skin

- In severe cases, $T_C$ cells destroy so many skin cells that acellular, fluid-filled blisters develop

- Other haptens include formaldehyde, cosmetics, and chemicals used to produce latex

- Can be treated with corticosteroids
## 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 1</td>
<td>Immediate hypersensitivity</td>
<td>IgE on sensitized cells' membranes binds antigen, causing degranulation</td>
<td>Seconds to minutes</td>
<td>Mast cells, basophils, and 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>Red blood cells</td>
</tr>
<tr>
<td>Type III</td>
<td>Immune-complex mediated hypersensitivity</td>
<td>Nonphagocytized immune complexes trigger mast cell degranulation</td>
<td>Several hours</td>
<td>Neutrophils</td>
</tr>
<tr>
<td>Type IV</td>
<td>Delayed hypersensitivity</td>
<td>T&lt;sub&gt;C&lt;/sub&gt; cells attack the body's cells</td>
<td>Several days</td>
<td>Activated T cells</td>
</tr>
</tbody>
</table>