Topic 9 (Ch16_18)
Immune Disorders

Topics
- Allergies
- Autoimmunity
- Immunodeficiency

Allergies

• Allergens (antigens) cause an exaggerated immune response or hypersensitivity – 4 types:
  – Type I
  – Type II
  – Type III
  – Type IV

4 Hypersensitivity Types
Type I Hypersensitivity

- Epidemiology
- Allergens
- Mechanisms
- Syndromes

Epidemiology

- 10% - 30% of population suffer from allergies
- Hereditary – generalized susceptibility to allergies
- Allergic antibody (IgE) production
- Increased reactivity of mast cells
- Age, infection, and geographic locale can also determine risk for allergies

Allergens

- Protein
- Hapten
- (must combine with a larger carrier molecule)
- Entry
  - Respiratory tract
    - Inhalants (pollen, mold spores)
  - Gastrointestinal tract
    - Ingestants (food, water)
  - Skin
    - Injectants (bites)
Type I- Urticaria

Hives: a vascular reaction of the upper dermis marked by transient appearance of slightly elevated patches.

Some Common allergens:

<table>
<thead>
<tr>
<th>TABLE 16.2 Common Allergens, Classified by Portal of Entry</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhalants</strong></td>
</tr>
<tr>
<td>Pollen</td>
</tr>
<tr>
<td>Dust</td>
</tr>
<tr>
<td>Molds spores</td>
</tr>
<tr>
<td>Dander</td>
</tr>
<tr>
<td>Animal hair</td>
</tr>
<tr>
<td>Insect parts</td>
</tr>
<tr>
<td>Formalin</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>Enzymes</td>
</tr>
</tbody>
</table>

Mechanisms

• First exposure
  – Sensitizing dose - elicits no symptoms
  – Memory B cells are produced
  – Small amount of IgE antibodies are produced
  – Mast cells and basophils
• Re-exposure (Second exposure) → fast, increased rxn
Mast Cells and Basophils

- Contain receptors that bind IgE antibodies
- Ubiquitous location (connective tissue for most organs)
- Secrete chemical mediators from cytoplasmic granules
- Release contents of granules by degranulation

Second Exposure

- Allergens bind to memory B cells
- B cells produce large amounts of IgE antibodies (high titer)
- IgE bind to mast and basophils
- Release chemical mediators
- Degranulation

Chemical Mediators

- Responsible for allergic symptoms
  - Histamine
  - Serotonin
  - Leukotriene
  - Platelet-activating factor
  - Prostaglandins
  - Bradykinin
Histamine
- Fast-acting allergic mediator
- Constricts smooth muscle layers – small bronchi, intestine
- Relaxes vascular smooth muscle, dilates arterioles and venules
- Stimulator of glands and eosinophils
- Wheal and flare reactions in the skin
- Pruritis (itching)
- Headache
- Anaphylaxis

Serotonin
- Complements histamine
- Increases vascular permeability, capillary dilation, smooth muscle contraction, intestinal peristalsis, respiratory rate
- Diminishes central nervous system activity

Leukotriene
- Different types
- Prolonged bronchospasm
- Vascular permeability
- Mucous secretions
- Stimulate polymorphonuclear leukocyte (PML) activity
Platelet-activating Factor (PAF)

- Lipid
- Produced by basophils, neutrophils, monocytes, and macrophages
- Response similar to histamine

Prostaglandins

- Vasodilation
- Increase vascular permeability
- Increase sensitivity to pain
- Bronchoconstriction

Bradykinin

- Prolonged smooth muscle contractions of the bronchioles
- Dilatation of peripheral arterioles
- Increase capillary permeability
- Increase mucous secretion
Type I Syndromes

- Atopic diseases
- Food allergy
- Drug allergy
- Anaphylaxis
- Treatment
Atopic Diseases

- Atopy – chronic local allergy
  - Hay fever (allergic rhinitis)
  - Asthma
  - Dermatitis

Hay Fever

- Reaction to pollen or molds
- Targets respiratory membranes
- Symptoms
  - Nasal congestion
  - Sneezing
  - Coughing
  - Mucous secretions
  - Itchy, red and teary eyes
  - Mild bronchoconstriction

Asthma

- Severe bronchoconstriction
- Symptoms
  - Shortness of breath to suffocation
  - Wheezing
  - Cough
  - Inflamed respiratory tract
Atopic Dermatitis

- Intense itchy inflammatory condition of the skin (eczema)
- Can begin in infancy and progress to adulthood
- Symptoms
  - Dry, scaly, thickened skin
  - Face, scalp, neck, inner surface of limbs and trunk

Anaphylaxis

- Cutaneous
  - Wheal and flare inflammatory reaction to the local injection of an allergen
- Systemic
  - Rapid immune response that can disrupt respiratory and circulatory systems
  - Can result in death
Treatment

• Diagnosis
  – Skin testing
• Drug
  – Antiallergy medications
• Desensitization
  – IgG antibodies block/compete for IgE sites and block function

Example skin test

Blocking antibody for allergic desensitization
Type I Hypersensitivity Treatment

- Administer drugs that counteract inflammatory mediators
  - Antihistamines neutralize histamine
- Treat asthma with a corticosteroid and a bronchodilator
- Epinephrine neutralizes many mechanisms of anaphylaxis
  - Relaxes smooth muscle
  - Reduces vascular permeability
  - Emergency Rx severe asthma and anaphylactic shock

Type II

- Interaction of antibodies, foreign cells, and complement, → foreign cell lysis
- ABO blood groups:
  - RBC markers (glycoproteins)
  - Rh factor
  - other RBC antigens
  - Drug induced cytotoxicity (hapten formation)

Immune Thrombocytopenic Purpura

Low platelet count due to immune destruction → purple coloration in skin and mucosa due to decreased clotting...
Blood types

- Each individual develops antibodies against other antigenic types (environmental sensitization).
  - Type A → anti-B antibodies
  - Type B → anti-A antibodies
  - Type O → anti-B & anti-A antibodies
    - Universal donor
  - Type AB → no anti-B or anti-A antibodies
    - Universal recipient

Major characteristics of the four blood types.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Blood Type</th>
<th>Antigen Present on Erythrocyte Membrane</th>
<th>Antibody in Plasma</th>
<th>Incidence of Type in United States</th>
<th>Incidence of Other Ancestral Groups in United States</th>
<th>Incidence of Other Ancestral Groups in United States</th>
</tr>
</thead>
<tbody>
<tr>
<td>A, AB</td>
<td>A</td>
<td>Ant-A</td>
<td>-</td>
<td>40%</td>
<td>28%</td>
<td>27%</td>
</tr>
<tr>
<td>B, BO</td>
<td>B</td>
<td>Ant-B</td>
<td>-</td>
<td>10%</td>
<td>27%</td>
<td>23%</td>
</tr>
<tr>
<td>AI, AI</td>
<td>A</td>
<td>Ant-A</td>
<td>-</td>
<td>4%</td>
<td>3%</td>
<td>7%</td>
</tr>
<tr>
<td>OO</td>
<td>O</td>
<td>Neither A nor B</td>
<td>-</td>
<td>65%</td>
<td>40%</td>
<td>46%</td>
</tr>
</tbody>
</table>
Mixing incompatible blood types results in:
- agglutination
- complement activation
- cell lysis

**Rh factor**
- Another RBC antigen
  - At least one dominant allele = Rh⁺
  - Two recessive alleles = Rh⁻
- Placental sensitization
- Hemolytic disease
- Prevention

**Hemolysis**
- Rh⁻ mother and Rh⁺ fetus
- First birth
  - Little anti-Rh antibody produced
  - Memory cells
- Second birth
  - Larger immune response
  - Hemolysis
Hemolytic Disease of Newborn

Prevention

- Passive immunity using anti-Rh factor immunoglobulin
  - 28-38 weeks
  - Immediately after delivery
- Administer for each pregnancy that involves Rh+ fetus
- Ineffective if mother is already sensitized

Type III

- Mechanism
- Immune complex reactions
- Diseases
Type III Mechanisms

- Similar to Type II, except antibodies react with free-antigens, no fixed antigens
- Ab-Ag complexes deposit in tissue causing immune complex reactions

Pathogenic immune complex formation

Diseases

- Arthus reaction
- Serum sickness
Arthus reaction

- Injected antigen (for example, vaccine, drug)
- Localized dermal injury due to inflamed blood vessels, neutrophil infiltration
- Acute response to a second similar antigen injection
- Severe cases result in necrosis and loss of tissue

Arthus Rxn (Type III) Study From: J New Zealand Medical Assn, 22-October-2004, Vol 117 No 1204

- A 67-year-old woman with chronic atrial fibrillation on warfarin was admitted with infected leg hematoma (farm accident). She had no other significant past medical history.
- Warfarin was withheld and her hematoma was evacuated under general anesthesia.
- On day 1 postoperatively, she was started on subcutaneous enoxaparin 40 mg (low molecular weight heparin marketed).
- Following second dose of enoxaparin, she developed a painful round erythematous skin lesion with a central necrotic area at the lower abdominal injection site.

Arthus - Type III (cont.)

- Skin reactions to heparin have been described as eczema-type reactions (delayed hypersensitivity reaction) or as tender, erythematous plaques with necrotic patches (type III Arthus reaction)
Type III Mechanism

Arthus Rxn (cont.)

Arthus Rxn- Close-up
Serum sickness

- Injection of serum, hormones, drugs
- Systemic Arthus injury
- Ag-Ab complexes circulate in the blood and eventually settle into membranes (kidney, heart, skin)
- Chronic – enlarged lymph nodes, rashes, painful joints, swelling, fever, and renal dysfunction

Type IV- Delayed type

- Cell-mediated (delayed) reactions
  - Primary a T cell response
- Delayed-type hypersensitivity
- Infectious allergy
- Contact dermatitis
- Tissue rejection

Sensitization from TB infection (example of infectious allergy)

Sensitivity to watchband material (example of contact dermatitis)
Contact dermatitis (example - poison oak)

Allergic Contact Dermatitis

Tissue rejection

- T cell mediated recognition of foreign MHC receptors
  - Cytotoxic T cells
  - Host rejection of graft
  - Graft rejection of host

- Classes of grafts
- Types of transplants
Two possible reactions that can occur due to transplantation.

Transplantation Classes

- **Autograft**
  (Tissue transplanted from one part of the body to another in the same individual)
- **Isograft**
  (Tissue transplanted between two genetically identical individuals)
- **Allograft**
  (Tissue or organ transplanted from one species donor, but different genetic makeup)

Types of transplants

- Live donors – skin, liver, kidney, bone marrow
- Fetal donors – pancreas, brain tissue
- Cadaver donors – heart, kidney, cornea
- Stem cells – bone marrow, blood, umbilical cord
Autoimmunity

- Antibodies, T cells or both, mount an immune response against self antigens
  - Systemic or organ-specific
  - Type II or III reactions

- Occurrence
  - Genetic – more common in men
  - Age – more common in the elderly

- Origins
- Diseases

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Some autoimmune disease examples:

<table>
<thead>
<tr>
<th>Disease</th>
<th>Target</th>
<th>Type of Hypersensitivity</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus (SLE)</td>
<td>Systemic</td>
<td>III and IV</td>
<td>Inflammation of many organs, antibodies against red and white blood cells, platelets, clotting factors, nuclear DNA.</td>
</tr>
<tr>
<td>Rheumatoid arthritis and ankylosing spondylitis</td>
<td>Systemic</td>
<td>II</td>
<td>Tendons, ligaments, and joints. Anti-collagen antibodies in organs.</td>
</tr>
<tr>
<td>IDIOPATHIC DISEASES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graves’ disease</td>
<td>Thyroid</td>
<td>II</td>
<td>Autoimmune disease resulting from hyperactive thyroid.</td>
</tr>
<tr>
<td>Porphyria cutanea</td>
<td>Skin</td>
<td>II</td>
<td>Autoimmune disease resulting from porphyrin.</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Muscles</td>
<td>II</td>
<td>Autoimmune disease resulting from antibodies to acetylcholine receptors.</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>Pancreas</td>
<td>II</td>
<td>Autoimmune disease resulting from insulin.</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Nervous system</td>
<td>II and IV</td>
<td>Autoimmune disease resulting from neurotransmitters and neural receptors.</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Kidney</td>
<td>II</td>
<td>Autoimmune disease resulting from antibodies to basement membrane of the glomerulus.</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Joint</td>
<td>II</td>
<td>Autoimmune disease resulting from antibodies to joint tissues.</td>
</tr>
</tbody>
</table>

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Autoimmunity Origins

- Sequestered antigen theory
- Clonal selection theory
- Theory of immune deficiency
- Inappropriate expression of MHC II
- Molecular mimicry
- Viral infections
Why do Autoimmune Diseases Occur?

Some hypothetical possibilities:

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

2 Major Types of Disease

- Systemic
- Single-organ:
  - RBCs → hemolytic anemia
  - Endocrine organs → Type I Diabetes Mellitus, Grave’s Disease
  - Nervous → Multiple Sclerosis
  - Connective Tissue → Rheumatoid Arthritis

Diseases

- Systemic autoimmunities
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
- Endocrine
  - Graves disease
  - Hashimoto thyroiditis
  - Diabetes mellitus
- Neuromuscular
  - Myasthenia gravis
  - Multiple sclerosis
Systemic lupus

Rheumatoid arthritis

The autoimmune response in Type I diabetes mellitus.

Myasthenia gravis – autoantibodies block attachment of acetylcholine.
Immunodeficiency

• A person can be born with or develop a weakened immune system
  – Primary
  – Secondary (Acquired)

Primary

• Affects antibody production and phagocytosis
• Inherited abnormality
  – Deficiencies in B-cell or T-cell and development and expression
  – Combined B- and T-cell deficiency
DiGeorge syndrome, a T cell development deficiency disease:

- Immunodeficiency due to hypoplasia of the thymus
- Hypocalcemia due to hypoplasia of the parathyroid glands
- Congenital heart disease with defects of the heart outflow tracts - pulmonary artery and aorta.
- Next to Down’s syndrome, DiGeorge syndrome is most common genetic cause of congenital heart disease.

Secondary Immunodeficiency diseases

Caused by:
- Infection
- Organic disease
- Chemotherapy
- Radiation

Categories of Primary and Secondary immunodeficiency diseases

<table>
<thead>
<tr>
<th>TABLE 14.5</th>
<th>General Categories of Immunodeficiency Diseases with Selective Examples</th>
<th>Secondary Immune Deficiencies (Acquired)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B Cell Defects (due to cells and antibodies)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Aplastic anemia (Caused by Idiopathic, non-autoimmune) 
Monoclonal gammopathies 
Verocay infections (e.g., influenza) 
Chronic granulomatous disease | 
From Natural Causes 
Infections: AIDs, hepatitis, tuberculosis 
Stress: systemic lupus, atopic dermatitis 
Genetic: chronic granulomatous disease 
Aging 
Aplastic anemia |
| T Cell Defects (Lack of All Cells of T Cells) | 
Classic ataxia-telangiectasia 
Chronic granulomatous disease 
Unrelated Infections (usually caused by Leuk or nonneutrophil granulocytes) 
Shiga toxin-mediated immune deficiency (STIMI) 
X-linked agammaglobulinemia (XLA) 
Wiskott-Aldrich syndrome | 
Booster: organ transplantation 
Infections: cytomegalovirus, varicella-zoster, alphaherpesvirus, other |