**Immune Diseases**  
Lecture 23 - Chapter 16

- Allergies
- Autoimmunity
- Immunodeficiency

**Allergies**

- **Allergens** (antigens, immunogens) can cause an exaggerated immune response, also called: “Hypersensitivity”
  - Type I (IgE-dependent hypersensitivity)
  - Type II (fixed non-self antigen-based hypersensitivity)
  - Type III (soluble non-self antigen-based hypersensitivity)
  - Type IV (cell-mediated ‘delayed-type’ hypersensitivity)

**Type I - Etiology**

- 10% - 30% of population suffer from **allergies** - this is considered medium prevalence
- Involves production of the allergic antibody (IgE) - mediated via increased reactivity of mast cells (bind Fc end if IgE)
- Other risk determinants for allergies are:
  - Hereditary pedigree,
  - Age,
  - Infection
  - Geographic location

**Type I - Allergens**

- Type I allergens are **protein** antigens or **haptens**
- Main portals of Entry for Type I allergens:
  - Respiratory tract
    - Inhalants (pollen, mold spores)
  - Gastrointestinal tract
    - Ingestants (food, drugs, water)
  - Skin
    - Injectants (bites, stabs)
    - Contactants (drugs, chemicals)
- => See Table 16.2

<table>
<thead>
<tr>
<th>Inhalants</th>
<th>Ingestants</th>
<th>Injectants</th>
<th>Contactants</th>
</tr>
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<tbody>
<tr>
<td>Pollen</td>
<td>Food</td>
<td>Hymenoptera</td>
<td>Drugs</td>
</tr>
<tr>
<td>Dust</td>
<td>(milk, peanuts, wheat, shellfish)</td>
<td>venom (bee, wasp)</td>
<td>Cosmetics</td>
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<tr>
<td>Mold spores</td>
<td>soybeans, nuts, eggs</td>
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<td>Heavy metals</td>
</tr>
<tr>
<td>Dander</td>
<td></td>
<td>Drugs</td>
<td>Detergents</td>
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<tr>
<td>Animal hair</td>
<td></td>
<td>Vaccines</td>
<td>Formalin</td>
</tr>
<tr>
<td>Insect parts</td>
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<td>Serum</td>
<td>Rubber</td>
</tr>
<tr>
<td>Formalin</td>
<td>Food additives</td>
<td>Enzymes</td>
<td>Glue</td>
</tr>
<tr>
<td>Drugs</td>
<td>Drugs (aspirin, penicillin)</td>
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<tr>
<td>Enzymes</td>
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</tbody>
</table>

**Type I - Mechanisms**

**First exposure**

- **Sensitizing dose** - elicits normal IR, in which memory B cells are produced
- In addition to other lgs (IgM and IgG), a small amount of IgE antibodies is produced
- No allergy symptoms !!!!

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**Table 16.2 Common Allergens, Classified by Portal of Entry**

<table>
<thead>
<tr>
<th>Inhalants</th>
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<td>Enzymes</td>
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</table>
Type I Mechanisms

Second exposure
- Allergens bind to memory B cells (IgM receptor)
- B cells derived from memory B cells produce large amounts (high titer) of IgE antibodies
- IgE-allergen complex binds to mast cell and basophil receptors
  - > Degranulation and release chemical mediators

Mast cells and basophils
- Contain receptors that bind IgE-Fc
- Ubiquitous location with regard to portals of entry (connective tissue for most organs)
- Secrete chemical mediators derived from cytoplasmic granules by degranulation

Type I - chemical mediators
- Degranulation will release these mediators that are responsible for allergic symptoms
  - Histamine
  - Serotonin
  - Leukotriene
  - Platelet-activating factor (PAF)
  - Prostaglandins
  - Bradykinin

Histamine
- Fast-acting allergic mediator
- Constricts bronchial and intestinal smooth muscle layers
- Relaxes vascular smooth muscle, dilates arterioles and venules
- Wheal and flare reactions in the skin
- Pruritis (itching)
- Headache
- Anaphylaxis
- Stimulator of glands and eosinophils

Serotonin
- Complements histamine
- Increases vascular permeability, capillary dilation, smooth muscle contraction, intestinal peristalsis, respiratory rate
- Diminishes central nervous system activity by leading to a serotonin/dopamine imbalance (serotonin plays an important role in the regulation of mood, sleep, vomiting, sexuality and appetite. Low levels of Serotonin have been associated with several disorders, notably depression, migraine, bipolar disorder and anxiety).

Leukotriene
- Causes prolonged bronchio-spasms
- Increases vascular permeability
- Activates mucous secretions
- Stimulates polymorphonuclear leukocyte (granulocyte) activity
**Platelet-activating factor**

- Lipid-like chemical nature
- Produced by basophils, neutrophils, monocytes and macrophages
- Response is similar to histamine

**Prostaglandins**

- Cause vasodilation
  - Increase in vascular permeability
- Increase sensitivity to pain
- Bronchio-constriction

**Bradykinin**

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

**Allergic Syndromes**

- Atopic (non-systemic) diseases
- Anaphylaxis
- Treatment

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Fig. 16.4 The spectrum of reactions to inflammatory cytokines

Fig. 16.3 A schematic view of cellular reactions during the Type I hypersensitive (allergic) response.
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 bronchio-constriction

Asthma

• Severe bronchio-constriction
• Symptoms
  – Shortness of breath to suffocation
  – Wheezing
  – Cough
  – Inflamed respiratory tract

Atopic dermatitis (eczema)

• Intense itchy inflammatory condition of the skin
• 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 of atopic symptoms

- Diagnosis
  - Skin testing
- Drug
  - Anti-allergy medications
- Desensitizing (neutralization)
  - IgG antibodies that block IgE function

**Type II**

- Interaction of antibodies with **antigen on foreign cells**, and complement, which then leads to foreign cell lysis
  - ABO blood group antigens (IgM-type Ab)
  - Rh factor antigen (IgG-type Ab)

**ABO blood groups**

- Landsteiner blood types - genetically determined
- RBC markers (glyco/lipo-proteins)
- Alleles – A, B, O

**ABO blood groups**

- Specific genes that encode for enzymes that add a unique sugar to the RBC receptor are the basis for the A and B antigens.
Blood types

Each individual will have antibodies against another antigenic type (environmental sensitization).
- Type A will have anti-B antibodies
- Type B will have anti-A antibodies
- Type O will have anti-B and anti-A antibodies
  - Universal (cell) donor (RBC have no "A" & "B" antigens)
- Type AB has no anti-B or anti-A antibodies
  - Universal (cell) recipient (RBC have "A" & "B" antigens)

Incompatible blood will result in agglutination, complement activation, and cell lysis.

ABO blood groups

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<th>B+</th>
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<td>2</td>
<td>8</td>
<td>5</td>
<td>2</td>
<td>1</td>
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</tbody>
</table>

Rh factor

- Another RBC antigen
  - At least one dominant allele = Rh⁺
  - Two recessive alleles = Rh⁻
- => IgG-type Rh(D) antibody is “culprit”
- Hemolytic disease

Hemolysis

- Rh⁻ mother and Rh⁺ fetus
- First birth
  - Little anti-Rh antibody produced (B-cells)
  - But B Memory cells
- Second birth (= second exposure)
  - strong immune response
  - Hemolysis
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

Fig. 16.13 Pathogenesis of immune complex disease.

Type III diseases: Arthus reaction

- Injected antigen (eg. Vaccine, drug)
- Localized dermal injury due to inflamed blood vessels
- Acute response to a second similar antigen injection
- Severe cases result in necrosis and loss of tissue

Type III diseases: Serum sickness

- Injection of serum, hormones, drugs
- Systemic 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

- Cell-mediated delayed-type hypersensitivity
  (Primarily a T cell response)
  - Infectious allergy
  - Contact dermatitis
  - Tissue rejection
An example of an infectious allergy would be an individual that is sensitized by a tuberculosis infection.

Contact dermatitis can result from poison oak.

Two possible reactions that can occur due to transplantation.

Tissue rejection

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

Autoimmunity

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

An example some major autoimmune diseases.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Target</th>
<th>Type of Hypersensitivity</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>Synovial</td>
<td>Type II</td>
<td>Anti-cyclic citrullinated peptide antibodies against joint synovial tissue</td>
</tr>
<tr>
<td>Systemic lupus</td>
<td>Nucleus</td>
<td>Type III</td>
<td>Antibodies against DNA and histones</td>
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<td>Sjogren’s syndrome</td>
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<td>Type IV</td>
<td>Antibodies against salivary gland and lacrimal gland epithelial cells</td>
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<td>Type II</td>
<td>Antibodies against pancreatic beta cells</td>
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<td>Encephalomyelitis</td>
<td>Nervous system</td>
<td>Type III</td>
<td>Antibodies against myelin basic protein</td>
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<td>Myasthenia</td>
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<td>Type IV</td>
<td>Antibodies against acetylcholine receptor</td>
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<tr>
<td>Antibodies to complement receptor</td>
<td>Actin</td>
<td>Type III</td>
<td>Antibodies against muscle actin</td>
</tr>
</tbody>
</table>

Table 16.4 Selected autoimmune diseases.
Origins of autoimmunity

• Sequestered antigens
• Clonal selection against self
• Immune deficiency
• Inappropriate expression of MHC II
• Molecular mimicry
• Viral infections

Diseases

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

Immunodeficiency

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

- Antibody production and phagocytosis
- Inherited abnormality
  - Deficiencies in B-cell or T-cell and development and expression
  - Combined B- and T-cell deficiency

Secondary

- Caused by
  - Infection
  - Chemotherapy
  - Radiation

Summary of the primary and secondary immunodeficiency diseases.

<table>
<thead>
<tr>
<th>Primary Immunodeficiencies (Genetic)</th>
<th>Secondary Immunodeficiencies (Acquired)</th>
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</thead>
<tbody>
<tr>
<td>B-Cell Defects (Low Levels of B Cells and Antibodies)</td>
<td>Infectious Agents (e.g., infections, vaccines)</td>
</tr>
<tr>
<td>Agammaglobulinemia (lack of antibody production)</td>
<td>Other Disease Conditions:</td>
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<tr>
<td>T-Cell Defects (Deficiencies in T Cells)</td>
<td>Severe dysfunction (e.g., SLE, lupus)</td>
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<td>Severe combined immunodeficiency (SCID)</td>
<td>Pregnancy</td>
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<td>Combined B and T-Cell Defects (Usually Caused by Lack of One or Abnormality of Spleen Tissue)</td>
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<tr>
<td>Severe combined immunodeficiency (SCID)</td>
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<td>Hypergammaglobulinemia</td>
<td>Rheumatoid arthritis</td>
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<tr>
<td>Chronic granulomatous disease of children (CGD)</td>
<td>Renal failure</td>
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<td>Deficiency of natural killer cells</td>
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<td>Frequent infections</td>
<td>Cancer</td>
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<td>Table 16.5 General categories of immunodeficiency diseases</td>
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