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Outline

• Self and non-self
• Introduction to hypersensitivity and autoimmune diseases
• Type I hypersensitivity mechanism of disease
• Type II hypersensitivity mechanism of disease
• Type III hypersensitivity mechanism of disease
• Type IV hypersensitivity mechanism of disease

Self and non-self

• The immune system is continually exposed and responding to foreign antigens from potentially disease and also innocuous agents.
• Complex mechanisms exist for distinguishing self antigens (e.g. normal proteins expressed in our bodies) from foreign antigens (components of potentially disease causing agents).
• Derangement of these mechanisms can lead to aberrant immune and immune-mediated diseases
How is self-tolerance generated in the immune system?

- **Central tolerance** – autoreactive B and T lymphocytes are destroyed or rendered harmless during development in bone marrow and thymus.
  - T-lymphocytes: deletion of autoreactive clones in thymus.
  - Not all self-antigens are expressed in thymus.
  - B-lymphocytes: modification of autoreactive receptors.
    - Process is called receptor editing.
- **Peripheral tolerance** –
  - Anergy (literally = no energy) – autoreactive lymphocytes are rendered non-responsive
  - Deletion – activation-induced cell death

Excessive immune responses result in hypersensitivity and autoimmune diseases

- **Hypersensitivity diseases** are characterized by excessive immune responses to antigens that are typically on innocuous materials (allergens)
  - Pollens, pet dander, mold spores
  - Drugs
  - Food components e.g. wheat gluten
- **Autoimmune diseases** are characterized by immune response to self ‘antigens’
- **Hypersensitivity disease** are responsible for considerable morbidity e.g. allergic rhinitis
- Some autoimmune diseases cause severe medical problems and are life shortening e.g. multiple sclerosis.

Examples of hypersensitivity diseases

- **Allergic rhinitis** e.g. pollen, house dust mite
  - Runny nose and eyes, sneezing
- **Allergic bronchitis** [Asthma] e.g. molds, pet dander, smoke
  - Difficulty breathing, coughing, cyanosis
- **Drug reaction** e.g. skin eruptions due to some antibiotics
- **Anaphylaxis** – systemic hypersensitivity
  - Frequently fatal
Examples of hypersensitivity diseases II

- Narrowing of airways due to swelling and muscle constriction
- Swelling and reddening of soft tissue in nasal cavity

Anaphylaxis
- Acute systemic immune hypersensitivity
- History of prior immune hypersensitivity (e.g., to bee sting venom)
- Life threatening

Peracute — Acute — Chronic

Examples of autoimmune disease I

- Immune-response against DNA and / or phospholipids
  - Systemic lupus erythematosus (‘lupus’)
    - diverse symptoms and signs
- Immune-responses against cell surface proteins
  - Pemphigus foliaceus — disease of skin / epidermis
  - Myasthenia gravis — nicotinic acetylcholine receptor on nerve endings
  - Autoimmune hemolytic anemia
  - Immune-mediated thrombocytopenia

Examples of autoimmune disease II

- Pemphigus foliaceus
  - Desmoglein I is expressed in upper epidermis
  - Blisters / pustules form within upper epidermis
  - Pustular skin disease most severe on the head

Systemic lupus erythematosus
- Immune complex deposition in various organs
- Promotes multi-organ inflammatory disease — highly variable between patients
What are the cellular mechanisms of hypersensitivity and autoimmune diseases?

- **Type 1 hypersensitivity (immediate-type)**
  - Allergic rhinitis
  - Allergic bronchitis
  - Anaphylaxis
- **Type 2 hypersensitivity (antibody-mediated)**
  - Autoimmune hemolytic anemia (AIHA)
  - Pemphigus foliaceus
- **Type 3 hypersensitivity (immune complex-mediated)**
  - Systemic lupus erythematosus
- **Type 4 hypersensitivity (delayed-type hypersensitivity)**
  - Diabetes mellitus type I
  - Contact dermatitis e.g. poison ivy
  - Tuberculosis skin (PPD) test

Principles of hypersensitivity responses

- Exposure to antigen results in sensitization
- Subsequent exposure to antigen results in excessive [hypersensitivity] immune response
  - Antigens involved can be exogenous or endogenous
  - Development of hypersensitivity responses (allergic and autoimmune) is associated with inheritance of susceptibility genes

Type 1 hypersensitivity. I. Overview

- Rapid immune response to antigen (allergen) that binds to IgE and activates mast cells.
- Can be localized or systemic reaction
- Immediate and late-phase responses
Type 1 hypersensitivity. II. 
The mast cell

Normal mast cell in tissue

Neoplastic mast cells in blood

Normal functions
• Wound healing
• Protection against pathogens e.g. metazoan parasites
• Present in low numbers in tissues e.g. skin, airways
• Not normally present in blood

Pathologic roles
• Key role in type 1 hypersensitivity
• Occasionally become neoplastic

Type 1 hypersensitivity. III. Immediate reactions are mediated mainly by granule contents

• Allergen specific IgE
• Allergen binds to IgE
• IgE binds to mast cell via FcE receptor
• FcE binding activates mast cell
• Degranulation releases histamine, the main mediator of immediate response
  • Vasodilation
  • Increased vascular permeability (edema)

Type 1 hypersensitivity. IV. 
Activities of histamine

Structure of histamine

Many drugs used to treat allergies are H1 receptor antagonists e.g. diphenhydramine

Histamine receptor I
Histamine receptor I (H1) is present in airways and blood vessels.

Binding of H1 receptor by histamine mediates bronchoconstriction, vasodilation and increased vascular permeability
Type 1 hypersensitivity. V. Delayed reactions are mediated by granules, lipid mediators and cytokines

- Granule contents e.g. eosinophil chemotactic factor (ECF)
- Proinflammatory lipids released from plasma membrane e.g. leukotrienes
  - Amplify vasodilation and bronchoconstriction effects of histamine
- Protein inflammatory mediators secreted and released (cytokines)

Type 1 hypersensitivity. VI. Anaphylaxis

- What do you think would be the response to systemic and massive mast cell degranulation?

Type 2 hypersensitivity. I.

- Antibody generated to cell surface molecule
- Typically a protein or glycoprotein
- This type of hypersensitivity is typically involved in autoimmune disease
- The consequence of antibody – antigen interaction depend on the specific disease
  - Opsonization and phagocytosis
  - Complement and Fc receptor-mediated phagocytosis
  - Antibody-mediated cell dysfunction
Mechanisms of antibody-mediated cell injury and dysfunction

<table>
<thead>
<tr>
<th>Type of Antibody-Mediated Injury</th>
<th>Diagram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune-mediated thrombocytopenia</td>
<td>![Diagram of thrombocytopenia]</td>
</tr>
<tr>
<td>Pemphigus foliaceus</td>
<td>![Diagram of Pemphigus foliaceus]</td>
</tr>
<tr>
<td>C. myasthenia gravis</td>
<td>![Diagram of myasthenia gravis]</td>
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</tbody>
</table>

Type 3 hypersensitivity. I.

- Circulating antibodies react with autoantigens in blood
- Antigen-antibody complexes deposit in vessel walls in various tissues and organs
- Antigen-antibody complexes promote inflammatory responses through Fc receptor and complement-mediated pathways
- Vasculitis [i.e. inflammation of blood vessels] is often a feature of diseases caused by this mechanism
- Systemic lupus erythematosus is an important disease in this group

Type 3 hypersensitivity. II.

Skin, kidneys and blood vessels are the primary targets for immune complex disease

- Severe vasculitis
- Stain for IgG in kidney glomerulus
- Direct visualization of immune complexes in kidney by electron microscopy
Type 4 hypersensitivity (delayed). 1. Cell-mediated CD4 hypersensitivity

A. Delayed-type hypersensitivity and immune inflammation

- Sensitized CD4+ T cells are exposed to antigen. They become activated and produce excessive amounts of cytokines that promote inflammatory responses.
- The specific form of the hypersensitivity response depends on the type of CD4+ lymphocyte that is activated (Th1 versus Th17).

PPD skin test: skin test for tuberculosis

Diagnostic use of type 4 hypersensitivity

Intra-dermal injection of antigen

Analysis of induration

2-3 days

What does a positive test result tell us? Is the person infected?

What response would you expect in someone with tuberculosis who is also HIV positive?

Type 4 hypersensitivity. III. Cell-mediated CD8 hypersensitivity

B. T cell-mediated cytosis

- Sensitized CD8+ T cells are exposed to antigen. They become activated and directly destroy target cells.
### Diseases in which type 4 hypersensitivity is important

<table>
<thead>
<tr>
<th>Disease</th>
<th>Antigen</th>
<th>Consequences</th>
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</thead>
<tbody>
<tr>
<td>Diabetes mellitus type 1</td>
<td>Pancreatic beta cell proteins</td>
<td>Inflammation Beta cell destruction</td>
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<tr>
<td>Multiple sclerosis</td>
<td>Oligodendrocyte proteins</td>
<td>Demyelinating disease</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td>Antigen in synovial membrane</td>
<td>Chronic arthritis</td>
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<tr>
<td>Neuropathies</td>
<td>Schwann cell antigen</td>
<td>Paralysis</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>Environmental chemicals, e.g. poison ivy</td>
<td>Dermatitis</td>
</tr>
</tbody>
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### Example / study questions

- Name a cell-type critical for the immediate response in type I hypersensitivity
- Name one disease caused by a type III hypersensitivity immune response
- What are the immediate life-threatening signs in a person or animal with anaphylaxis?
- How do you think a toxic drug reaction differs from a drug hypersensitivity reaction?