Hypersensitivity Reactions Outline

- Introduction
Introduction

- Normal immune reactions do their job without hurting the host.
- Sometimes, immune reactions can be excessive, resulting in disease.
- People who mount normal immune responses are sensitized to that antigen.
- People who have excessive responses are hypersensitive.
What antigens initiate these reactions?

- Bugs
- Environmental antigens
- Self antigens
What happens in these reactions?

- The immune response is triggered and maintained inappropriately.
- Hard to eliminate stimulus!
- Hard to stop response once it starts!
- ...so hypersensitivity diseases are often chronic, debilitating, hard to treat.
Four types of hypersensitivity reactions

- Type I Hypersensitivity
- Type II Hypersensitivity
- Type III Hypersensitivity
- Type IV Hypersensitivity
Hypersensitivity Reactions Outline

- Introduction
- Type I Hypersensitivity
Type I Hypersensitivity

- **ALLERGY**
- “Immediate” hypersensitivity
- Antigen (allergen) binds to IgE antibodies on surface of mast cell
- Mast cell releases nasty mediators
- End result: vessels dilate, smooth muscle contracts, inflammation persists
Sequence of Events

- Allergen is inhaled/eaten/injected
- Allergen stimulates $T_{H2}$ production
- $T_{H2}$ cell secretes cytokines:
  - IL-4 stimulates B cells to make IgE
  - IL-5 recruits eosinophils
  - IL-13 stimulates mucous secretion
- Mast cell binds IgE
- Allergen bridges IgE on mast cell
- Mast cell degranulates
Exposure to allergen

Allergen (e.g., pollen)

Mucosal lining

Activation of TH2 cells and IgE class switching in B cells

Production of IgE

B cell

TH2 cell

IgE-secreting B cell

IgE

Binding of IgE to FcεRI on mast cells

Mast cell

FcεRI

Repeat exposure to allergen

Mediators

Vasoactive amines, lipid mediators

Immediate hypersensitivity reaction (minutes after repeat exposure to allergen)

Late phase reaction (2-8 hours after repeat exposure to allergen)
Mast cells: Normal (left) and degranulated (right)
What nasty stuff do mast cells release?

- Granule contents
  - histamine
  - some chemotactic factors
- Membrane phospholipid metabolites
  - prostaglandin D$_2$
  - leukotrienes
- Cytokines
  - TNF
  - interleukins
  - IL-13
What do these nasty substances do?

- Act on blood vessels, smooth muscle, and WBCs.
- Immediate response (minutes)
  - vasodilation, vascular leakage, smooth muscle spasm
  - granule contents, prostaglandin, leukotrienes
- Late phase reaction (hours)
  - inflammation, tissue destruction
  - cytokines
What happens to the patient?

- Local reactions
  - skin: itching, hives
  - GI: diarrhea
  - lung: bronchoconstriction

- Anaphylaxis
  - itching, hives, erythema
  - constriction of bronchioles, wheezing
  - laryngeal edema, hoarseness, obstruction
  - vomiting, cramps, diarrhea
  - shock
  - DEATH
Hypersensitivity Reactions Outline

• Introduction
• Type I Hypersensitivity
• Type II Hypersensitivity
Type II Hypersensitivity

- ANTIBODIES
- “Antibody-mediated” hypersensitivity
- Antibodies bind to antigens on cell surface
- Macrophages eat up cells, complement gets activated, inflammation comes in
- End result: cells die, inflammation harms tissue
<table>
<thead>
<tr>
<th>Disease</th>
<th>Antigen</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>RBC antigens, drugs</td>
<td>Hemolysis</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>Proteins between epithelial cells</td>
<td>Bullae</td>
</tr>
<tr>
<td>Goodpasture syndrome</td>
<td>Proteins in glomeruli and alveoli</td>
<td>Nephritis, lung hemorrhage</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Acetylcholine receptor</td>
<td>Muscle weakness</td>
</tr>
<tr>
<td>Graves disease</td>
<td>TSH receptor</td>
<td>Hyperthyroidism</td>
</tr>
</tbody>
</table>
Sequence of Events

- Antibodies bind to cell-surface antigens
- One of three things happens:
  - Opsonization and phagocytosis
  - Inflammation
  - Cellular dysfunction
Opsonization and phagocytosis
Inflammation

- Fc receptor
- Complement activation
- Complement by-products (C5a, C3a)
- Neutrophil enzymes, reactive oxygen intermediates

Inflammation and tissue injury
Cellular dysfunction

Graves disease

Myasthenia gravis
Hypersensitivity Reactions Outline

- Introduction
- Type I Hypersensitivity
- Type II Hypersensitivity
- Type III Hypersensitivity
Type III Hypersensitivity

- IMMUNE COMPLEXES
- “Immune complex-mediated” hypersensitivity
- Antibodies bind to antigens, forming complexes
- Complexes circulate, get stuck in vessels, stimulate inflammation
- End result: bad inflammation, necrotizing vasculitis
Which diseases involve type III hypersensitivity?

<table>
<thead>
<tr>
<th>Disease</th>
<th>Antigen</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Nuclear antigens</td>
<td>Nephritis, skin lesions, arthritis...</td>
</tr>
<tr>
<td>Post-streptococcal glomerulonephritis</td>
<td>Streptococcal antigen</td>
<td>Nephritis</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>Hepatitis B antigen</td>
<td>Systemic vasculitis</td>
</tr>
<tr>
<td>Serum sickness</td>
<td>Foreign proteins</td>
<td>Arthritis, vasculitis, nephritis</td>
</tr>
<tr>
<td>Arthus reaction</td>
<td>Foreign proteins</td>
<td>Cutaneous vasculitis</td>
</tr>
</tbody>
</table>
Two Kinds of Type III Hypersensitivity Reactions

- **Systemic immune complex disease**
  - complexes formed in circulation
  - deposited in several organs
  - example: serum sickness

- **Local immune complex disease**
  - complexes formed at site of antigen injection
  - precipitated at injection site
  - example: Arthus reaction
Serum Sickness

• In olden days: used horse serum for immunization
• Inject foreign protein (antigen)
• Antibodies are made; they form complexes with antigens
• Complexes lodge in kidney, joints, small vessels
• Inflammation causes fever, joint pain, proteinuria
Arthus Reaction

- “Arthus reaction” = localized area of skin necrosis resulting from immune complex vasculitis
- Inject antigen into skin of previously-immunized person
- Pre-existing antibodies form complexes with antigen
- Complexes precipitate at site of infection
- Inflammation causes edema, hemorrhage, ulceration
How do the complexes cause inflammation?

- Immune complexes activate complement, which:
  - attracts and activates neutrophils and monocytes
  - makes vessels leaky
- Neutrophils and monocytes release bad stuff (PG, tissue-dissolving enzymes, etc.)
- Immune complexes also activate clotting, causing microthrombi
- Outcomes: vasculitis, glomerulonephritis, arthritis, other -itises
Immune-complex-mediated vasculitis
What complement fractions are important to know?

- C3b: promotes phagocytosis of complexes (and bugs!)
- C3a, C5a (anaphylatoxins): increase permeability
- C5a: chemotactic for neutrophils, monocytes
- C5-9: membrane damage or cytolysis
C5a is chemotactic
Hypersensitivity Reactions Outline

• Introduction
• Type I Hypersensitivity
• Type II Hypersensitivity
• Type III Hypersensitivity
• Type IV Hypersensitivity
Type IV Hypersensitivity

- **T CELLS**
- “T-cell-mediated” hypersensitivity
- Activated T cells do one of two things:
  - release cytokines that activate macrophages, or
  - kill cells directly
- This process is normally useful against intracellular organisms (viruses, fungi, parasites)
- Here, it causes bad stuff: inflammation, cell destruction, granuloma formation
Two Kinds of Type IV Hypersensitivity

- Delayed-type hypersensitivity (DTH)
  - CD4+ T cells secrete cytokines
  - macrophages come and kill cells
- Direct cell cytotoxicity
  - CD8+ T cells kill targeted cells
Delayed-Type Hypersensitivity

- Patient exposed to antigen
  - APC presents antigen to CD4+ T cell
  - T cells differentiate into effector and memory $T_H1$ cells
- Patient exposed to antigen again
  - $T_H1$ cells come to site of antigen exposure
  - Release cytokines that activate macrophages, increase inflammation
- Results
  - Macrophages eat antigen (good)
  - Lots of inflammation and tissue damage (bad)
Delayed-Type Hypersensitivity (DTH)
Perivascular cuffing by CD4+ cells
Delayed-Type Hypersensitivity

- Good example of DTH: positive Mantoux test
- Patient previously exposed to TB
- Inject (inactive) TB antigen into skin
- See reddening, induration. Peaks in 1-3 days
T-Cell Mediated Cytotoxicity

- CD8+ T cells recognize antigens on the surface of cells
- T cells differentiate into cytotoxic T lymphocytes (CTLs) which kill antigen-bearing cells
- CTLs normally kill viruses and tumor cells
- In T-cell mediated cytotoxicity, CTLs kill other things:
  - Transplanted organ cells
  - Pancreatic islet cells (Type I diabetes)
T-Cell-Mediated Cytotoxicity
Summary

Type I
- Allergy
- \( T_H^2 \) cells, IgE on mast cells, nasty mediators

Type II
- Antibodies
- Opsonization, complement activation, or cell dysfunction

Type III
- Immune complexes
- Lodge, cause inflammation, tissue injury

Type IV
- CD4+ or CD8+ T cells
- DTH or T-cell-mediated cytotoxicity