Hypersensitivity Reactions

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Hypersensitivity Reactions Outline

- 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 $T_H^2$ production
- $T_H^2$ 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 T_{H2} cells and IgE class switching in B cells

B cell -> T_{H2} cell

Production of IgE

IgE-secreting B cell -> IgE

Binding of IgE to FcεRI on mast cells

Mast cell

Repeat exposure to allergen

Activation of mast cell; release of mediators

Mast cell

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)

Cytoxines
Antigen
IgE
IgE Fc receptor
Signals for cytokine gene activation
Signals for degranulation
Signals for activation of phospholipase A$_2$
Nucleus
Degranulation
SECRETED CYTOKINES
GRANULE CONTENTS
- Histamine
- Proteases
- Chemotactic factors (ECF, NCF)
MEBRANE PHOSPHOLIPIDS
- Arachidonic acid
- Prostaglandin D$_2$
- Leukotrienes B$_4$, C$_4$, D$_4$
PAF
IMMEDIATE RESPONSE
- Vasodilation
- Vascular leakage
- Smooth muscle spasm
Late phase reaction
- Leukocyte infiltration
- Epithelial damage
- Bronchospasm
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
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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
### Which diseases involve type II hypersensitivity?

<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
Cellular dysfunction

Graves disease

Myasthenia gravis
Hypersensitivity Reactions Outline

- Introduction
- Type I Hypersensitivity
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- 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
PHASE I
Immune Complex Formation

Antigen in circulation

Endothelium

B cell

Plasma cell

Antigen-antibody complex

Free antibody
PHASE III
Immune Complex-Mediated Inflammation

- Complement
- Neutrophil
- Platelet aggregation
- Fibrinoid necrosis
- Neutrophil lysosomal enzymes
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
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- 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
- Th2 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