Hypersensitivity

- Chapter 25
- Types of Hypersensitivity
- Immunological mechanisms of Hypersensitivity
- Factors that predispose to Hypersensitivity
- Clinical manifestations of Hypersensitivity

### Cells in Hypersensitivity Reactions

- **A** - in skin and mucosal tissues
- **B** - Granulocytes: circulate in the blood and extravasate into tissues
- **C** - Mononuclear cells: monocytes (macrophage) and lymphocytes

### 3 Types of Hypersensitivity

<table>
<thead>
<tr>
<th>Immediate</th>
<th>Intermediate</th>
<th>Delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start within seconds, resolve within 2 hours.</td>
<td>Start within hours, may resolve within 24 hours.</td>
<td>Start ~48 hours after antigen exposure.</td>
</tr>
<tr>
<td>Ag cross-linking of IgE on surface of mast cells induces release of vasoactive mediators.</td>
<td>Both involve IgE immune complex formation and cell damage through complement activation and other NK cells (type I) or neutrophils (type III).</td>
<td>T cells release cytokines that activate macrophages, resulting in cell damage.</td>
</tr>
</tbody>
</table>

**Table 25.1** Trends in allergy

<table>
<thead>
<tr>
<th>Burden of asthma in the United States</th>
</tr>
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<tbody>
<tr>
<td>6.8 million cases in 1980; 17.3 million in 2000</td>
</tr>
<tr>
<td>Prevalence increasing 5% per yr</td>
</tr>
<tr>
<td>500/000 new cases every yr</td>
</tr>
<tr>
<td>No. 1 reason for hospitalization of children</td>
</tr>
<tr>
<td>No. 1 reason for days lost from school</td>
</tr>
</tbody>
</table>

Estimated direct and indirect costs in 1998: $12.7 billion

3,850 deaths among persons aged 0–24 yr from 1980 through 1993

*The prevalence of atopic diseases, primarily bronchial asthma, atopic dermatitis (eczema), and allergic rhinoconjunctivitis (hay fever) is increasing.*
Type I Immediate Hypersensitivity

- Example: Mosquito bites: the swelling and redness
- 1st bite generates immune response to mosquito salivary protein antigens =
  - IgE antibodies are produced.
- IgE abs are immobilized on surface of Mast cells by high affinity IgE FcR
- 2nd bite: salivary Ag bind IgE.
  - Signal transduction to Mast cells to release histamine and serotonin into tissues
- Capillary endothelial cells pull apart and fluids seep into tissues bringing in Complement and cytokines

<table>
<thead>
<tr>
<th>Table 25.3 Type I hypersensitivity responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
</tr>
<tr>
<td>Wheezing</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Chest tightness</td>
</tr>
<tr>
<td>Atopic rhinoconjunctivitis (hay fever)</td>
</tr>
<tr>
<td>Runny, itchy nose and eyes</td>
</tr>
<tr>
<td>Atopic urticaria (hives)</td>
</tr>
<tr>
<td>Atopic dermatitis (eczema)</td>
</tr>
<tr>
<td>Dry, itchy skin</td>
</tr>
<tr>
<td>Acute</td>
</tr>
<tr>
<td>Hives</td>
</tr>
<tr>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Flushing</td>
</tr>
<tr>
<td>Angioedema</td>
</tr>
<tr>
<td>Oral itching</td>
</tr>
<tr>
<td>Chronic (not all are type I responses)</td>
</tr>
<tr>
<td>Eczema</td>
</tr>
<tr>
<td>Asthma</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
</tbody>
</table>

Type I Immediate Hypersensitivity

- Example: Mosquito bites: itching sensation
- Histamine binds to type c nerve fibers that sense pain and initiate the itching sensation
- A “wheat” or fluid-filled itchy bump is formed.
- Further induction of capillary dilation and “flare” reaction develops - increased redness
- More scratching results in more extensive dilation of capillaries
Type I Immediate Hypersensitivity

- After the wheal and flare response subsides,
- Second wave of immune mediators are made by the mast cells
- The arachidonic acid derivatives (fatty acid derivatives):
  - Cysteinyl leukotrienes
- Recruit cells into the injured area and form a bump or papule that lasts hours or days
  - Caused by PMNs and eosinophils during first 2 hours
  - Then the mononuclear cells arrive...
  - All fight any infectious agent injected by the mosquito bite...

Table 21.2: Mediators of type I hypersensitivity reaction

<table>
<thead>
<tr>
<th>Reactogen</th>
<th>Correlation with reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine</td>
<td>Increased vascular permeability; smooth muscle contraction</td>
</tr>
<tr>
<td>Eosinophil chemoattractant factor</td>
<td>Eosinophil chemotaxis</td>
</tr>
<tr>
<td>Leukotriene</td>
<td>Increased vascular permeability, constriction of pulmonary smooth muscle</td>
</tr>
<tr>
<td>Platelet activating factor</td>
<td>Platelet aggregation and degranulation, constriction of pulmonary smooth muscle</td>
</tr>
<tr>
<td>Endothelin</td>
<td>Increased vascular permeability, smooth muscle contraction</td>
</tr>
</tbody>
</table>

IgE FcR

Type I Immediate Hypersensitivity

Inflammatory response

- LTs are all cysteine leukotrienes
  - Zileuton = Zyflo
  - Montelukast = Singulair
  - Zafirlukast = Accolate
- PGs are all prostaglandins
  - NSAIDS = ibuprofen etc
  - Rofecoxib = Vioxx
  - Celecoxib = Celebrex
- TX are thromboxanes
• Origins of Allergic Responses

Dendritic cells, macrophage, and eosinophils likely bring allergens to the lymph nodes for B cell activation and Switching to IgE.

IgE FcR Activation

Cross-linking of IgE FcR results in signal transduction and subsequent mast cell degranulation.

Common Allergens

Exposure to allergens varies based on season and location.

Mast Cell Activation and Degranulation

Cross linking of IgE FcR leads to signal transduction events:
- cAMP production
- Activated PKC
- Elevated intracellular calcium levels
Mast Cell Activation and Degranulation

- Active PKC phosphorylates granule membrane proteins
- Permeability to water and calcium changes
- Granules swell, migrate, fuse with the membrane and release their granules

Asthma

- Inflammatory disease of the small bronchioles of the lung
- Lungs of asthmatics have significant inflammation affecting all layers of the bronchiolar tissue
- Involves multiple cell types
- Surface is coated with a thicker layer of mucus
- Underlying tissues are packed with eosinophils and activated lymphocytes
- Smooth muscle of airways is thickened and hyperreactive
- Bronchioles contain high densities of mast cells that are armed with allergen specific IgE

Mast Cell Activation and Degranulation

- Cross linking of IgE FcR leads to signal transduction events:
  - Production of Arachidonic acid
  - Production of PG, TX, and LT
  - Acute inflammation

Asthma Attack

- Initiation occurs when a sensitized individual is exposed to the allergen that binds IgE on mast cells
- Bronchiolar restrictive response begins in minutes
- Caused by release of histamines from mast cells
  - Smooth muscle response to histamines causes constriction
- Release of Arachidonic acid and derivatives (PG, LT, TX) from mast cells triggers second wave of airway constriction
  - Neutrophils and eosinophils move into airways
  - Severe compromise of oxygen and carbon dioxide exchange
Type II Intermediate Hypersensitivity

- IgG Mediated Hypersensitivity
- Reactions occur when antibodies to self proteins or carbohydrates binds to self tissues
- 4 classic types
  - Maternal antibodies that cross the placenta bind to child’s tissues and cause damage
  - Antibodies against blood transfusion or organ transplant
  - Antibody response to foreign substances that has adhered to own cells
  - Antibodies to own tissues

- Example:
  - Autoantibodies to pancreatic beta cells may cause insulin-dependent diabetes (type II diabetes)
  - Cells are destroyed through ADCC or classical complement cascade and MAC activation
Type II Hypersensitivity

- Erythroblastosis fetalis or
- hemolytic disease of the newborn

Goodpasture Disease

- Autoantibodies against Type IV collagen in the lungs and kidneys
- Results in complement activation and neutrophil influx
- Tissue damage