**Immunology 2011**  
**Lecture 23**  
**Immediate Hypersensitivity**  
26 October

### Allergic Reactions

**"Immediate Hypersensitivity"**

Hay fever, food, drug & animal allergies, reactions to bee stings, etc.

Symptoms may include discomfort, rash & itching, diarrhea, asthma, systemic anaphylaxis/shock.

**Rapid, potentially lethal**

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### Outline

- Gell & Coombs Classification
- IgE, allergic reaction, mediators
- Immediate vs. Late Phase Response
- 2 Models of cutaneous anaphylaxis
  - Passive Cutaneous Anaphylaxis
    - Prausnitz-Küstner Reaction
- Evaluation, treatment, heterogeneity
- Mast cell degranulation, drug & food allergies
- **Poison Oak: CMI/DTH**

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### Gell and Coombs Classification of Immune Reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Description</th>
<th>Antibody</th>
<th>Skin Reaction (Cellular Infiltrate)</th>
<th>Time to Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>TYPE I</td>
<td>Immediate hypersensitivity</td>
<td>IgE</td>
<td>Allergy skin test (eosinophils &amp; PMNs, late phase only)</td>
<td>1-20 min</td>
</tr>
<tr>
<td>TYPE II*</td>
<td>membrane/matrix-associated Ag</td>
<td>IgG/IgM</td>
<td>(+ C)</td>
<td></td>
</tr>
<tr>
<td>TYPE III</td>
<td>Immune complexes</td>
<td>IgG(IgM) (+ C)</td>
<td>Arthus reaction (PMNs)</td>
<td>7-10 hrs</td>
</tr>
<tr>
<td>TYPE IV</td>
<td>Delayed-type hypersensitivity (DTH)</td>
<td>-</td>
<td>TB skin test (mononuclear cells)</td>
<td>1-3 days</td>
</tr>
</tbody>
</table>

\[ *has been suggested to define "TYPE V", anti-receptor autoantibodies/\]

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### IgE: Reaginic Antibody

**Low Serum Levels - nanograms/ml**  
(more commonly quantitated in "International Units", or "IU")

**Heat Labile - 30 min @ 56°C**

**“Homocytotropic” - binds to mast cells**

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### Two Steps for Initiation of Allergic Reactions

**Sensitization** (weeks) - Antigen is introduced, processed, presented, etc.; stimulates IgE humoral response. IgE binds to tissue mast cells.

**Reaction** (minutes) - Antigen binds to IgE on the surface of mast cells, triggers degranulation and mediator release.
**Immediate versus Late-Phase Responses**

**Immediate Phase:** Release of histamine, prostaglandins, leukotrienes etc.; minutes

**Late Phase:** Induction and continuing synthesis of prostaglandins, leukotrienes, cytokines and chemokines, resulting in cell infiltrate & inflammation hours to days later, smooth muscle contraction, edema. May lead to chronic inflammatory reaction.

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**Mediators Released by Mast Cells**

- **Histamine**: Contraction of smooth muscle of the bronchi, gut and venules; arteriole & capillary dilation (blood “pooling”); increased mucus secretion.
- **Prostaglandins & Leukotrienes** (SRSA et al.) – Bronchoconstriction; increase mucus secretion and vascular permeability.
- **Chemotactic Factors**: - ECFA (eosinophils); also neutrophil chemotactic factors (recruit PMNs)
- **Kinin**: (newly synthesized) - Vasodilation, histamine-like.

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**Effects of Mediator Release**

**Airways:** Constriction and blockage; asthma.

**GI Tract:** Increased fluid secretion & peristalsis; expulsion.

**Blood Vessels:** Increased local blood flow and capillary permeability (inflammation, rash); peripheral “pooling”, anaphylaxis.

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**Immediate vs. Late Phase Response in Skin (above) and Lung (below)**

**Immediate**: Mast cell mediators

**Chronic**: Recruitment of cells by chemotactic factors; production of Th1 cytokines, destructive activities of eosinophils, macrophages & PMNs.
Three experimental and clinical models of allergic reactions

1) Vascular anaphylaxis in the guinea pig
2) Passive cutaneous anaphylaxis
3) Prausnitz-Küstner reaction

Evaluation of the Allergic State

- Determination of IgE levels
  - RIST - total serum IgE
  - RAST - specific serum IgE antibody
- Skin Testing
- Test Diets - pragmatic approach
  (but note that not all food sensitivities are allergic)
- Significant inherited component, HLA et al.
  - Variable organ sensitivity

Managing the Allergic State

1) Avoidance of (all) allergen(s)
2) Desensitization (deliberate immunization to induce IgG)
3) Drugs
   - Antihistamines & decongestants
   - Corticosteroids
   - Leukotriene antagonists
   - Cromolyn sodium
   - Epinephrine, prednisone/albuterol...
Effect of Anti-IgE Therapy in Patients with Peanut Allergy.

Anti-IgE (ClI3), prevents binding to the high-affinity FcR on mast cells; 3 months’ treatment increases threshold for reaction to peanut ingestion by ~10-fold.

(mAb TNX-901, “humanized” IgG1 αIgE)

Leung et al., NEJM 348:986, 2003

Heterogeneity of Allergic Reactions

- Variable sensitization, genetic component (including HLA) ...“atopy”
- Allergy vs. non-specific inflammation
- Variable target organ sensitivity

Triggers of Mast Cell Degranulation

- IgE/FceR1 crosslinking by antigen
- C3a/C5a (“anaphylotoxins”)
- Hyperosmotic conditions (...cold, dry air)
- Mechanical stimuli

1) Mechanical Triggering of Mast Cell Degranulation

(Visualize rise in intracellular Ca++)

RBL cells (rat basophilic leukemia) in culture.

2) Spread of degranulation via soluble factor(s)...

...i.e., release of ATP, activation via P2 receptors

Osipchuk & Cahalan, 1992
Penicillin Allergy

- β-lactam ring is reactive and can bind to self-proteins
- IgE response can trigger allergy - rash, anaphylaxis etc.
- Importance of skin-testing

Note: Penicillin and other drugs may also trigger other forms of hypersensitivity, e.g. Hemolytic Anemia (Type II), or Serum Sickness (Type III)

Surgical Transfer of Allergic State
France, 1997

- 22-year-old man accidentally ate peanuts and died of an anaphylactic reaction
- Liver & right kidney transplanted to 35 year old man, pancreas and left kidney to 27 year old woman
- Three months later, man had a rash and asthmatic reaction to eating peanuts. Woman was tested and found to be negative
- Man was advised to avoid peanuts and sent home

Some organs (e.g. liver, lung, gut) may contain significant amounts of lymphoid tissue (also significant for GvH)

Popsicle-induced anaphylaxis due to carmine dye allergy
Baldwin, Chou & Solomon, 1997

27-year-old woman with anaphylaxis required emergency treatment following ingestion of a Good Humor SnoFruit popsicle colored with carmine. She experienced nausea within minutes, and pruritis, urticaria and hypotension with tachycardia within 3 hours. Patient responded to intravenous fluids, epinephrine and diphenhydramine, discharged on loratidine 18 hours after presentation.

(Illustration of allergy skin test & Prausnitz-Küstner Rx...)

Poison Oak/Ivy Sensitivity

- CMI/DTH, not immediate hypersensitivity reaction
- Urushiol, long-chain fatty acids on leaves
- Degraded in mitochondria
- Final product is highly reactive, binds to proteins in cytosol
- Modified self-peptides presented with MHC Class I
- Generation of CD8^+ effector T_C cells
  * Not transferred by serum
  * Develops over 24-72 hours