Biological Basis of the Allergic Response

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Allergic reactions

- Also known as type I hypersensitivity reactions
- Requires prior exposure and sensitization (IgE)
- Atopy: familial disposition towards allergy
  - “He comes from an atopic family”
- Allergic sensitization
  - Production of IgE and arming of FcεRI-bearing cells but does not necessarily mean clinical disease
Sequence of Events (Priming)

1) Ag Presented
2) TH2 Response
   - (IL4, IL5 and IL-13)
3) IL-4 -> IgE Production
4) IgE loads mast cells

A.B. Kay, NEJM 2001, 344:1, 30-37

Antigen Uptake and Presentation

Antigen Presentation Leads to T cell Differentiation

- Surface ligands
  - OX40L
  - CD40L
  - Jagged
  - ICOSL
  - Dim CD69
  - Dim CD80

- Secreted cytokines
  - IL-4
  - IL-13
  - IL-8
  - IL-10
  - TGFβ
  - IFNγ
  - TNFα
  - CCL7

- T cell subsets
  - Th0
  - Th1
  - Th2
  - Th17
  - Treg
  - IL-2
  - IL-17

IL-4 and IL-13 cytokine receptors

- IL-4 receptor
  - IL-4Rα
  - IL-13Rα1

- Jak-3
- Jak-1
- STAT-6
- Nucleus

- IL-13 receptor
  - IL-4Rα
  - Tyk-2
  - Jak-1
- STAT-6

Th2 cells influence B cells to make IgE through isotype switching

What Makes an Antigen IgE-Promoting?

- Protein, not lipid; can rarely be carbohydrate
- Mucosal exposure
- Low concentration but must be multivalent
- Stable, water soluble
- Many have protease activity
  - e.g., grass pollens, dust mite
- Some resemble helminthic parasite antigens
  - Filarial tropomyosin is similar to house dust mite, shellfish and cockroach proteins
Unique Characteristics of IgE

IgE-FcεRI interactions

## Consequences of FcεRI triggering

![Diagram](Consequences_of_FcεRI_triggering.png)


## Mast cells and Basophils

<table>
<thead>
<tr>
<th>Mediator</th>
<th>MC</th>
<th>Baso</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Tryptase</td>
<td>+++</td>
<td>+/-</td>
</tr>
<tr>
<td>LTs</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>PG’s</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>IL-4</td>
<td>+/-</td>
<td>+++</td>
</tr>
<tr>
<td>IL-13</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Other cytokines</td>
<td>+++</td>
<td>+</td>
</tr>
</tbody>
</table>

![Images](Mast_cells_and_Basophils.png)

Dvorak AM, J. Histochem Cytochem 53:1043, 2005

Courtesy of John Schroeder
Skin Testing: wheal and flare responses

Laboratory measurement of serum specific IgE levels, more recently including component testing
Biophysiologic Effects of Histamine

- Nerve activation (itch)
- Vasodilation & edema
- Gland secretion
- Smooth muscle contraction

Various Mediators of Allergic Diseases and their Receptors

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine</td>
<td>H1 – H4</td>
</tr>
<tr>
<td>PGD$_2$</td>
<td>DP1, DP2</td>
</tr>
<tr>
<td>PGE$_2$</td>
<td>EP1 – EP4</td>
</tr>
<tr>
<td>PGF$_{2a}$</td>
<td>FP, IP, TP</td>
</tr>
<tr>
<td>Sulfidopeptide LT</td>
<td>CysLT1, CysLT2</td>
</tr>
<tr>
<td>Sphingosine-1-P</td>
<td>$S_1P_1 – S_1P_5$</td>
</tr>
</tbody>
</table>
Definition and Diagnosis of Anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Sudden onset of an illness (minutes to several hours), with involvement of the skin, mucous tissues, or both (e.g., generalized hives, itching or flushing, swollen lips/tongue/neck)

   AND AT LEAST ONE OF THE FOLLOWING:

   - Sudden respiratory symptoms and signs (e.g., shortness of breath, wheezes, cough, stridor, hyperventilation)
   - Sudden reduced BP or symptoms of end-organ dysfunction (e.g., hypotension, syncope, hypoglycemia)

2. Two or more of the following that occur suddenly after exposure to a likely allergen or other trigger for that patient (minutes to several hours):

   - Sudden skin or mucosal symptoms and signs (e.g., generalized hives, itching or flushing, swollen lips/tongue/neck)
   - Sudden respiratory symptoms and signs (e.g., shortness of breath, wheezes, cough, stridor, hyperventilation)
   - Sudden reduced BP or symptoms of end-organ dysfunction (e.g., hypotension, syncope, hypoglycemia)
   - Sudden gastrointestinal symptoms (e.g., diarrhea, abdominal pain, vomiting)

3. Reduced blood pressure (BP) after exposure to a known allergen for that patient (minutes to several hours):

   - Infants and children: low systolic BP (age-specific) or greater than 30% decrease in systolic BP
   - Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline


Allergic responses are not just immediate

![Immediate and Late-Phase Reaction graph]

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Chemokine receptors


TABLE 7-3  Cellular Expression of Chemokine Receptors*

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Chemokine Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naïve T cells</td>
<td>CXC4, CCR7</td>
</tr>
<tr>
<td>Th1 cells</td>
<td>CCR5, CXC3</td>
</tr>
<tr>
<td>Th2 cells</td>
<td>CCR4, CCR8</td>
</tr>
<tr>
<td>Th17 cells</td>
<td>CCR6</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>CCR3</td>
</tr>
<tr>
<td>Basophils</td>
<td>CCR3</td>
</tr>
</tbody>
</table>

Chemokines in Asthma


Role of Eosinophils in Asthma

Key concepts

- Can’t have allergies without IgE or FcεRI
- Mediators released during allergic reactions cause a characteristic pattern of signs and symptoms
- A myriad of preformed and newly synthesized biochemical and protein mediators, and their respective receptors, provide a range of therapeutic targets