Hypersensitivity Disorders

**Immune Response**

<table>
<thead>
<tr>
<th>Type of Hypersensitivity</th>
<th>Pathologic immune response</th>
<th>Mechanisms of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate</td>
<td>IgE antibodies released from mast cells and basophils</td>
<td>Mast cell degranulation, smooth muscle constriction, vasodilation, hypotension, diarrhea, urticaria</td>
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<tr>
<td>Anaphylactoid</td>
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**Disease Example**

- **IgE**
  - Ragweed hay fever
- **IgG**
  - Cytotoxic: Hemolytic anemia
  - Immune complex: Serum sickness
- **T Cell**
  - Poison ivy

IgE-mediated Diseases

- Allergic rhinitis (Hay fever)
- Asthma
- Anaphylaxis
- Urticaria
- Atopic dermatitis

Definitions

- **Allergy**
  - Abnormal IgE response to innocuous environmental allergens
- **Atopic Diseases**
  - Allergic diseases; includes diseases such as atopic dermatitis in which allergens cannot always be demonstrated
- **Allergen**
  - Antigen that causes an allergic immune response

Overall View of IgE Response

**IgE-mediated Inflammation**

**Early Phase**

- **Time course:** Minutes after antigen challenge
- **Example:** Acute asthma
- **Cause:** Mediators released by cells attracted to area of inflammation
- **Cells involved:** Mast cells, basophils
**IgE-mediated Inflammation**

**Late Phase**

- **Time course:** Hours after antigen challenge
- **Example:** Chronic asthma
- **Cause:** Mediators released by cells attracted to area of inflammation during and after the early phase
- **Cells involved:** Eosinophils, Basophils, Neutrophils, Lymphocytes

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**IgE Production**

Dependent on a TH-2 immune response

- Presence of IL-4, IL-5, IL-9, IL-13 favor a TH-2 response
- IL-10 suppresses a TH-1 response, high levels also suppress a TH-2 response

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**Control of IgE Production**

1. Genetic predisposition
2. Availability of antigen (“allergen”)
3. Method of immunization

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**Control of IgE Production (Candidate Genes)**

I. Localization to specific chromosomes
   a. Chromosome 5q - Promoter variants for IL-4 (IL-3, 5, 9, 13 and GM-CSF)
   b. Chromosome 11q β Subunit of FcεRI (High affinity IgE receptor)
   c. Others

II. HLA linkage to specific antigen responses

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**Control of IgE (Environmental Factors)**

1. Presence of and nature of antigen
2. Possible enhancement by agents such as respiratory syncytial virus (RSV)
3. Possible suppression by agents such as measles, hepatitis A, and *M. tuberculosis*
4. Paradoxical low incidence of allergy in helminth infected patients with high IgE levels (? Very high IL-10 levels suppress both Th1 and Th2)

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**“Hygiene Hypothesis”**

- Observation (one of a number of examples) – Children raised in rural areas close to animals and exposed to endotoxin in dust have a lower incidence of atopic disease
- Theory – Endotoxin acting on Toll-like receptors influences the cytokines that APC’s secrete as they present antigen so as to favor a Th1 instead of a Th2 response
Control of IgE Production (Method of immunization)

Experimental Animals

Antigen + Freund’s adjuvant yields an IgG response (Th1)

Antigen + Pertussis bacilli yields an IgE response (Th2)

IgE Receptors - FcεRI (High Affinity)

- Mast cells
- Basophils
- Activated eosinophils
- Langerhan’s cells

Effect of IgE Level on Numbers of IgE Receptors on Mast Cells

High serum levels of IgE causes higher levels of high affinity IgE receptors on mast cells

If you can lower the serum IgE level, you will lower the number of these IgE receptors on the mast cell and make the cells less susceptible to mediator release

IgE Receptors - FcεRII (CD23) (Low Affinity)

- B cells (down regulates B cells)
- Activated T cells
- Monocytes, macrophages
- Eosinophils
- Follicular dendritic cells
- Platelets
- Thymic epithelial cells

IgE Receptor Cross-linking on Mast Cell

Activation of Mast Cells

Step 1 – Cluster of two or more IgE-bound FcεRI by multivalent antigen
Step 2 - Activation of protein tyrosine kinases
  - First - Lyn
  - Second - Syk
Step 3 - Transmission of signal further into cell
Step 4 – Mediator release (newly synthesized or from storage granules)
Stem Cell

SCF

Mast cell progenitor

Myeloid lineage

(SCF)

(Mast cell)

SCF = Stem Cell Factor

Acts on mast cell receptor called “Kit”

(SCF) (IL-3)

Basophil

Mast cell

Mast Cell Progenitor Lineage

SCF = Stem Cell Factor

Acts on mast cell receptor called “Kit”

Mast Cells

Require SCF

Basophils

Require IL-3

Sessile

Sessile

Circulate

Present in Early Response

Both

IgE receptors

Release of inflammatory mediators

Present in Late response

Mast Cells and Basophils

• Arachidonic acid metabolites

  Leukotrienes (e.g. LTC₄)

  Prostaglandins (e.g. PGD₂)

Mediators Released from Mast Cells and Basophils

Arachadonic Acid Metabolism

Arachadonic Acid

5-Lipoxygenase

Cyclooxygenase

LTB₄

Cysteinyl-LTs

Prostaglandins

Thromboxanes

e.g., LTC₄

e.g., PDG₂

Effect of ASA on Cyclooxygenase

• Acetylsalicylic acid (ASA, aspirin) inhibits cyclooxygenase

• In the presence of ASA arachidonic acid metabolism is shunted through the lipoxygenase pathway and this causes an excess of leukotrienes to be produced

• Because of this, in about 20% of asthmatics ASA can induce a marked worsening of their asthma

Inflammatory Mediators

Mast Cells and Basophils

Histamine

Leukotrienes C₄, D₄, E₄

Platelet Activating Factor (PAF)

TNF-α, IL-4, IL-13

Mast Cells Only

PGD₂

Tryptase (Used to detect anaphylaxis)

IL-5, -6
**Positive Feedback Loop**

- B cells
- IL-4
- IgE
- Mast Cells

**Innate Immunity and Mast Cells**

- Mast cells can be activated without involving IgE
- Anaphylatoxins (C3a, C4a, C5a) generated by complement activation can trigger mediator release
- Mast cells have receptors that recognize bacterial and viral products and thus can be directly activated by foreign pathogens (Toll-like receptors, Mannose binding receptors & others)

**IgE-mediated Inflammation**

**Late Phase**
- Time -- Hours after antigen challenge
- Example -- Chronic asthma
- Cause -- Mediators released by cells attracted to area of inflammation during and after the early phase
- Cells Involved -- Eosinophils, Basophils, Neutrophils, Lymphocytes

**Eosinophils**

1. Late response
2. Development - IL-3, GM-CSF
3. Eosinophilia induced by IL-5
4. Receptors for IgG (Fcγ receptors) and IgE (Fcε receptors)

**Vascular Endothelium**

- ICAM-1, ICAM-2
- VCAM-1
- CD11a/CD18 (LFA-1)
- CD11b/CD18 (CR3)
- VLA-4

**Promoters of Eosinophil Chemotaxis**

**Lipid Derived Mediators**
- Leukotriene B4
- Platelet Activating Factor (PAF)

**Chemokines**
- Eotaxins-1 and -2
- RANTES
- MCP-3
- MCP-4
**Inflammatory Mediators Released from Eosinophils**

- Major Basic Protein (MBP) – toxic to membranes
- PAF, LTC₄
- IL-1, -3, -4, -5, -6, -10, -16
- GM-CSF, TNF-α
- Chemokines (RANTES, MIP-1α)
- Toxic oxygen metabolites

**Late Phase IgE-induced Inflammation**

Role of Lymphocytes
- Depletion of eosinophils diminishes, but does not abolish the late-phase response
- Lymphocyte-derived mediators also play an important role

**Treatment of Allergy**

1. Avoidance
2. Medication
3. Immunotherapy

**Medications Used to Treat Allergy & Asthma**

1. **Antihistamines**
   - (Example: diphenhydramine)
2. **Leukotriene Inhibitors**
   - (Example: montelukast)
3. **Anti-inflammatory Agents**
   - Corticosteroids
   - Calcineurin inhibitors (tacrolimus)
   - Cromalyn

**Adrenergic Agents**

- **Examples**
  - Adrenalin – Bronchodilators (epinephrine) Vasoconstricts
  - Inhibits mediator release from mast cells and basophils
  - Mainstay in treatment of anaphylaxis
  - Albuterol - More a pure bronchodilator
    - Used for acute relief of bronchospasm asthma
**Arachadonic Acid Metabolism**

- 5-LO Inhibitor
- 5-Lipoxygenase: LTB₄, Cysteiny-LTs, Thromboxanes
- Cyclooxygenase: Prostaglandins (e.g., LTC₄), Thromboxanes (e.g., PDG₂)

**Anti IgE Antibody**

- Antibody to portion of IgE heavy chain that binds to the high affinity IgE receptor
- Decreases binding of IgE
- Decreases number of receptors on mast cells and basophils
- Decreases severity of asthma in some patients
- Decreases severity of reactions in severe food allergy

**Some Results of Immunotherapy**

- Specific IgE Decrease
- Specific IgG Increases
- Conversion from a Th2 to a Th1 Response
  - ↓ IL-4
  - ↑ IL-2, IFN-γ
- Decreased eosinophil accumulation
- Decreased mediator response
- Non-specific decrease in basophil sensitivity