Hypersensitivity - an inappropriate immune response that causes damage to the individual

Type I hypersensitivity - mediated by IgE
Type II hypersensitivity - mediated by IgG
Type III hypersensitivity - mediated by immune complexes
Type IV hypersensitivity - cell-mediated

Immediate hypersensitivity - Types I, II and III
Delayed hypersensitivity - Type IV

What makes an antigen to be an allergen?

Type I hypersensitivity = allergic reactions
- Mast cells and basophils possess receptors for the Fc region of IgE (FcεRI). Eosinophils but ONLY after activation!!
- IgE produced in response to an antigen (allergen) binds to mast cells and basophils.
- If antigen cross-links this IgE on the cell surface, the FcεRI are cross-linked– resulting in degranulation of the cell and release of vasoactive mediators (histamine, leukotrienes, prostaglandins, cytokines etc).

### TABLE 16-1 COMMON ALLERGENS ASSOCIATED WITH TYPE I HYPERSENSITIVITY

<table>
<thead>
<tr>
<th>Proteins</th>
<th>Foods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreign serum</td>
<td>Nuts</td>
</tr>
<tr>
<td>Vaccines</td>
<td>Seafood</td>
</tr>
<tr>
<td>Plant pollens</td>
<td>Eggs</td>
</tr>
<tr>
<td>Bee grass</td>
<td>Peas, beans</td>
</tr>
<tr>
<td>Ragweed</td>
<td>Milk</td>
</tr>
<tr>
<td>Timothy grass</td>
<td>Tree products</td>
</tr>
<tr>
<td>Birch trees</td>
<td>Bee venom</td>
</tr>
<tr>
<td>Drugs</td>
<td>Wasp venom</td>
</tr>
<tr>
<td>Penicillin</td>
<td>Ant venom</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Cockroach saliva</td>
</tr>
<tr>
<td>Local anesthetics</td>
<td>Dustmites</td>
</tr>
<tr>
<td>Salicylates</td>
<td>Mold spores</td>
</tr>
<tr>
<td>Animal hair and dander</td>
<td></td>
</tr>
</tbody>
</table>
1. The allergen enters the body and is recognized by IgG on a B-lymphocyte.
2. The B-lymphocyte then proliferates and differentiates into plasma cells.
3. The plasma cells produce and secrete IgE which binds to receptors on mast cells and basophils.
4. Allergen cross-reacting with IgE on mast cell.
5. The next time the allergen enters the body, it cross-links the Fab portions of the IgE bound to the mast cell.
6. This triggers the mast cell to degranulate and releases its histamine and other inflammatory mediators.
7. The inflammatory mediators are now able to bind to receptors on target cells which leads to dilation of blood vessels, constriction of bronchioles, excessive mucus secretion, and other symptoms of allergy.

**RECAP:**

1. Immediate Allergic Reaction – caused by mast cell degranulation
2. Late-phase response – involves the recruitment of Th2 cells, eosinophils, and basophils

**TABLE 14.3 PRINCIPAL MEDIATORS INVOLVED IN TYPE I HYPERSENSITIVITY**

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine</td>
<td>Increased vascular permeability, smooth muscle contraction, and bronchoconstriction</td>
</tr>
<tr>
<td>Leukotrienes (LTA4 and LTD4)</td>
<td>Increased vascular permeability, smooth muscle contraction, and bronchoconstriction</td>
</tr>
<tr>
<td>Eosinophil cationic protein (ECP)</td>
<td>Increased vascular permeability, smooth muscle contraction, and bronchoconstriction</td>
</tr>
<tr>
<td>Eosinophil-derived neurotoxin (EDN)</td>
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**Effector Mechanisms**

- Immediate Allergic Reaction – caused by mast cell degranulation
- Late-phase response – involves the recruitment of Th2 cells, eosinophils, and basophils
Localized allergic reactions - symptoms depend on the location of mast cell/basophil degranulation
- Skin ---> eczema
- Nasal mucosa ---> allergic rhinitis (hay fever)
- Respiratory tract ---> asthma
- Gastrointestinal tract ---> vomiting, diarrhea (food allergies)

Systemic allergic reaction = systemic anaphylaxis
- Systemic vasodilation results in an acute loss of blood pressure.
- Bronchoconstriction causes asphyxiation.
- Death can occur within minutes.

Epinephrine counteracts the effects of allergic mediators on smooth muscle and vasculature.

Causes of allergic reactions (factors predisposing to IgE responses):

Characteristics of the antigen
- Certain antigens are more likely to induce IgE responses (e.g. ragweed pollen)

Mode of presentation of the antigen
- Dosage, adjuvant may influence the IgE vs IgG response

Genetics of the individual
- Certain mouse strains are more likely to make IgE responses
- Parents with allergies are more likely to have children with allergies

-Due to histamine, prostaglandins, and other preformed mediators that cause rapid increase in vasc. Permeability and contraction of smooth muscle

Late-Phase Reaction by inducing synthesis and release of mediators including leukotrienes, chemokines, and cytokines from activated mast cells

-Blame it on your parents!!!!

Figure 12-16 part 1 of 2
Therapeutic approaches - Allergen immunotherapy

- The practice of administering gradually increasing quantities of an allergen extract to an allergic subject to ameliorate the symptoms associated with subsequent exposure to the causative allergen.

- Introduced in 1911

“The mechanisms of immunotherapy are complex....newer studies suggest that immunotherapy acts by modifying T-cell responses either by immune deviation [shift from Th2 to Th1], T-cell anergy, or more likely both.” - WHO, 1998.

Risk: systemic anaphylaxis (potentially fatal)

- In 1975, Godfrey (Clin. Allergy 5:201) investigated the occurrence of allergy and asthma in Gambian school children.

  - Showed their association with urban dwelling, higher socioeconomic status and lower total circulating IgE levels.

  - Suggested that in the rural setting, parasite infection was protective against the development of allergy and asthma.


<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Change in parasite load</th>
<th>Change in reactivity to house dust mite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td>68% → 5%</td>
<td>17% → 68%</td>
</tr>
<tr>
<td>Control group</td>
<td>43% → 70%</td>
<td>26% → 16%</td>
</tr>
</tbody>
</table>
1) Exposure to infectious diseases in early childhood
2) Environmental pollution
3) Allergen levels
4) Dietary changes

Eosinophils

- Eosinophils express FcεRI only after activation
- On activation – release toxic granule proteins and free radicals which can kill microorganisms and parasites
- On activation – synthesis of chemical mediators such as prostaglandins, leukotrienes, and cytokines which amplify the inflammatory response
Type II (antibody-dependent) hypersensitivity = IgG-mediated destruction of cells

Occur in any circumstance in which cells are exposed to high levels of cell-reactive IgG antibody.

Destruction via:
- complement-mediated lysis
- opsonization
- ADCC

Examples include:
- transfusion reactions
- Rh syndrome

Blood group antigens:
- Represent difference in terminal sugar residues on red cell glycoproteins
  A = terminal N-acetylgalactosamine (NAcGal)
  B = terminal galactose (Gal)
  O = no terminal residue

- Cross-react with antigens present on intestinal microorganisms.
**Drug-induced hemolytic anemia:**
- Some drugs bind to erythrocyte proteins and create novel epitopes.
- An individual may make an IgG response to the novel epitopes.
- The resulting IgG antibody may mediate complement-mediated lysis of red cells - leading to hemolytic anemia.

**Treatment** - cease using the drug.

**Localized Type III reaction (Arthus reaction):**
- Injection of antigen into the skin of an individual with high levels of antibody to the antigen (eg: insect bites [types I and III possible]).
- Intense localized inflammatory reaction characterized by influx of neutrophils.
Generalized Type III reactions:

- (systemic lupus erythematosus, Rheumatoid arthritis)

- injection of antigen intravenously into an individual with high levels of antibody to the antigen.

- e.g. injection of horse antitoxins into an individual previously sensitized to horse immunoglobulin

- "serum sickness" - various symptoms including fever, rashes and sometimes glomerulonephritis as a result of immune complex deposition in the kidneys; vasculitis (deposition in arteries) or arthritis (deposition on synovial joints)

- Damage of tissue due to enzymes from “angry” cells

- Large quantities of soluble Ag-Ab complexes form in the blood and are not completely removed by macrophages.
- These Ag-Ab complexes lodge in the capillaries between the endothelial cells and the basement membrane.
- These Ag-Ab complexes activate the classical complement pathway leading to vasodilation and attraction of leukocytes to the area.
- The leukocytes discharge their killing agents and promote massive inflammation.
- This can lead to tissue death and hemorrhage.

• Type IV. Hypersensitivity Type IV (delayed-type hypersensitivity, DTH)

– Macrophages
– Th1 T cells (DTH)
– Cytokines

– Examples: contact dermatitis (formaldehyde, nickel, cosmetics, jewelry, poison oak, poison ivy)
Cytokines:
- IFN-gamma
- IL-1beta
- TNF-α
- GM-CSF

Contact Dermatitis

- T-helper 1 (Th1) cells
  - IFN-γ
  - MIF
  - MCF

(a) Sensitization phase
- Intracellular bacteria
- APC
- CD4+ TH
- T-helper 1 (Th1) cells (generally)
- Antigen-presenting cells
  - Macrophages
  - Langerhans cells
- DTH-mediating cells: T-helper 1 (Th1) cells generally

(b) Effector phase
- Secreted IFN-γ
- Membrane TNF-β
- Activated macrophage
- TNF receptor
- Class II MHC
- Effects of macrophage activation:
  - Class II MHC molecules
  - TNF receptors
  - Oxygen radicals
  - Nitric oxide
Contact-sensitizing agent penetrates the skin and binds to self proteins, which are taken up by Langerhans' cells

Langerhans' cells present self peptides haptenated with the contact-sensitizing agent to $T_{H1}$ cells which secrete IFN-γ and other cytokines

Activated keratinocytes secrete cytokines such as IL-1 and TNF-α and chemokines such as CXCL8 (IL-8), CXCL11 (IP-10), and CXCL9 (Mig)

The products of keratinocytes and $T_{H1}$ cells activate macrophages to secrete mediators of inflammation

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Table 16-4: Mechanism of action of some drugs used to treat type I hypersensitivity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihistamines</td>
<td>Block $H_1$ and $H_2$ receptors on target cells</td>
</tr>
<tr>
<td>Cromolyn sodium</td>
<td>Blocks Ca$^{2+}$ influx into mast cells</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Prolongs cAMP levels in mast cells by inhibiting phosphodiesterase, which closes cAMP to 3'-AMP*</td>
</tr>
<tr>
<td>Epinephrine (adrenaline)</td>
<td>Stimulates cAMP production by binding to β-adrenergic receptors on mast cells*</td>
</tr>
<tr>
<td>Cortisone</td>
<td>Reduces histamine levels by blocking conversion of histidine to histamine and stimulates mast-cell production of cAMP</td>
</tr>
</tbody>
</table>

*Although cAMP rises transiently during mast-cell activation, degranulation is prevented if cAMP levels remain high.
The End