

Hypersensitivity

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

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Hypersensitivity

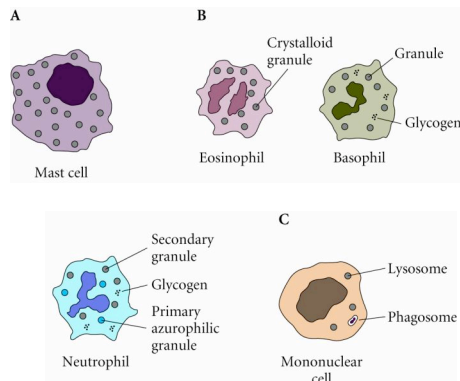
Table 25.1 Trends in allergy^a

Burden of asthma in the United States
6.8 million cases in 1980; 17.3 million in 2000
Prevalence increasing 5% per yr
500,000 new cases every yr
No. 1 reason for hospitalization of children
No. 1 reason for days lost from school
Estimated direct and indirect costs in 1998: \$12.7 billion
3,850 deaths among persons aged 0–24 yr from 1980 through 1993

^aThe prevalence of atopic diseases, primarily bronchial asthma, atopic dermatitis (eczema), and allergic rhinoconjunctivitis (hay fever) is increasing.

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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

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3 Types of Hypersensitivity

Immediate	Intermediate	Delayed	
Start within seconds, resolve within 2 hours. Ag cross-linking of IgE on surface of mast cells induces release of vasoactive mediators.	Start within hours, may resolve within 24 hours. Both involve IgG immune complex formation and cell damage through complement activation and either NK cells (type II) or neutrophils (type III).	Start ~48 hours after antigen exposure. T cells release cytokines that activate macrophages, resulting in cell damage.	
<p>Allergen-specific IgE, Fc receptor for IgE, Mast cell degranulation</p> <p>Type I: anaphylactic</p>	<p>ADCC, Cytotoxic cell, Fc receptor, Complement activation, Surface antigen, Immune complex, Target cell</p> <p>Type II: cytotoxic</p>	<p>Immune complex, C3b, Complement activation, Neutrophil</p> <p>Type III: immune complex</p>	
<p>Sensitized T_{H1}, APC, Cytokines, Activated macrophage</p> <p>Type IV: cell mediated</p>			
Manifestations: systemic anaphylaxis or local anaphylaxis, such as hay fever, asthma, hives, food allergies, and eczema	Manifestations: blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia	Manifestations: localized Arthus reactions and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus	Manifestations: contact dermatitis, reactions to <i>Mycobacterium tuberculosis</i> and graft rejection

Table 25.3 Type I hypersensitivity responses

Asthma
Wheezing
Cough
Chest tightness
Atopic rhinoconjunctivitis (hay fever)
Runny, itchy nose and eyes
Atopic urticaria (hives)
Atopic dermatitis (eczema)
Dry, itchy skin
Food allergies
Acute
Hives
Anaphylaxis
Flushing
Angioedema
Oral itching
Chronic (not all are type I responses)
Eczema
Asthma
Diarrhea
Vomiting

Type I Immediate Hypersensitivity

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Type I Immediate Hypersensitivity

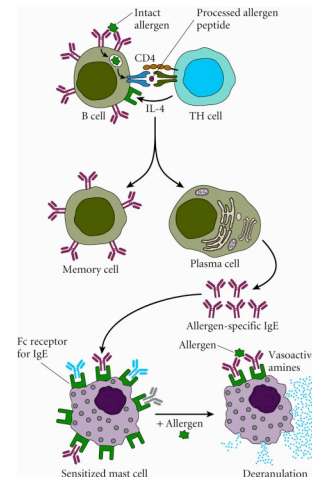
- Example Mosquito bites: the swelling and redness
- 1st bite generates immune response to mosquito salivary protein antigens =
 - IgE antibodies are produced.
- IgE abs are immobilized on surface of Mast cells by high affinity IgE FcR
- 2nd bite: salivary Ag bind IgE.
 - Signal transduction to Mast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

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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 “wheal” 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

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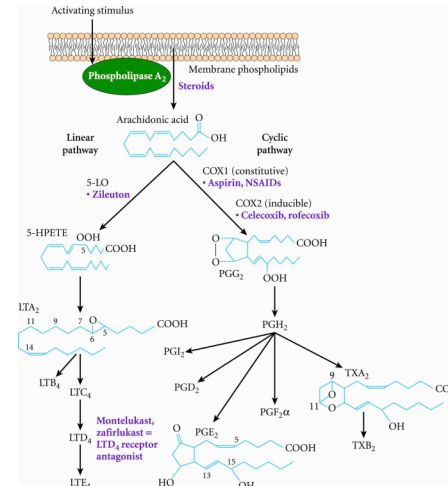
Type I Immediate Hypersensitivity

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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...

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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

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Table 25.2 Mediators of type I hypersensitivity reactions^a

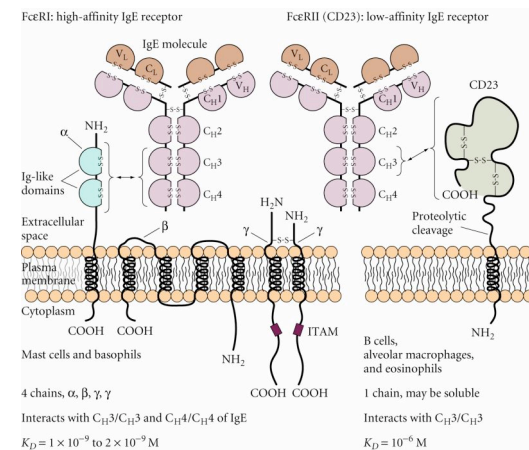
Mediator	Effects
Granule content release (immediate)	
Histamine	Increased vascular permeability, smooth-muscle contraction
Serotonin	Increased vascular permeability, smooth-muscle contraction
Eosinophil chemotactic factor	Eosinophil chemotaxis
Neutrophil chemotactic factor	Eosinophil chemotaxis
Proteases	Bronchial mucus secretion, degradation of blood vessel basement membrane, generation of complement split products
Membrane-derived lipid mediators (released over minutes)	
Prostaglandins	Vasodilation, contraction of pulmonary smooth muscle, platelet aggregation
Leukotrienes	Increased vascular permeability, contraction of pulmonary smooth muscle
Platelet-activating factor	Platelet aggregation and degranulation, contraction of pulmonary smooth muscle
Bradykinin	Increased vascular permeability, smooth-muscle contraction
Cytokine production (released over hours)	
IL-1, TNF- α	Systemic anaphylaxis, increased ICAM expression on endothelium
IL-3	Stimulates mast-cell growth and histamine secretion
IL-4	Stimulates mast-cell growth, induces activated B cells to class switch to IgG1 and IgE
IL-5	Promotes growth and differentiation of eosinophils
TGF- β	Chemotactically attracts monocytes and macrophages, induces IL-1 production by activated macrophages

^aIGF, transforming growth factor; ICAM, intercellular adhesion molecule.

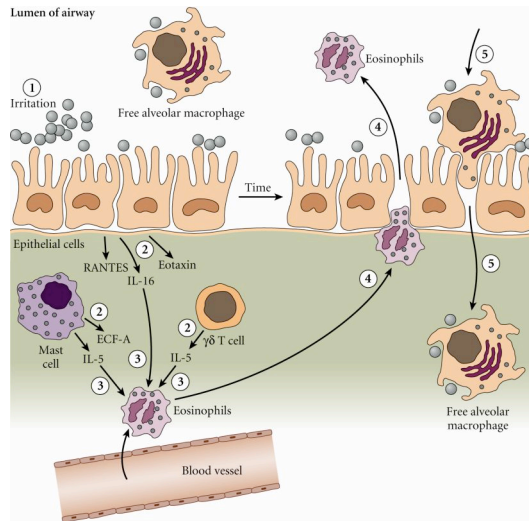
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Type I Immediate Hypersensitivity

IgE FcR



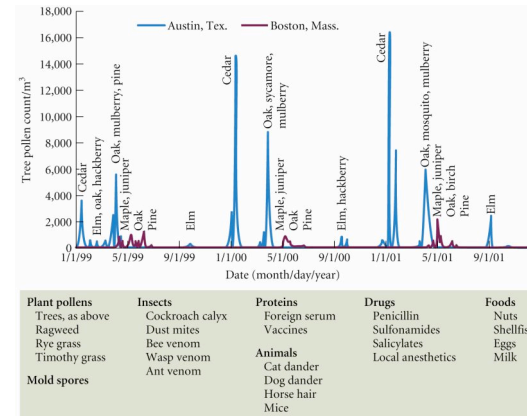
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- Origins of Allergic Responses
- Dendritic cells, macrophage, and eosinophils likely bring allergens to the lymph nodes for B cell activation and switching to IgE

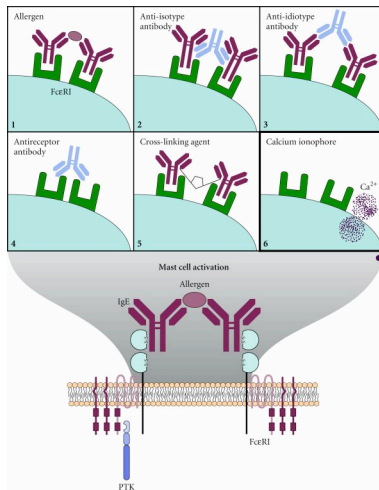
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Common Allergens



Exposure to allergens varies based on season and location

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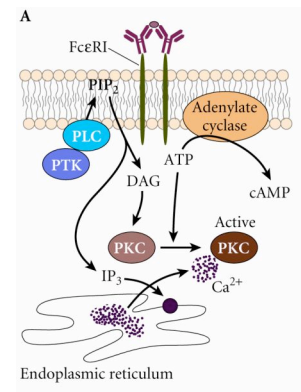


IgE FcR Activation

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

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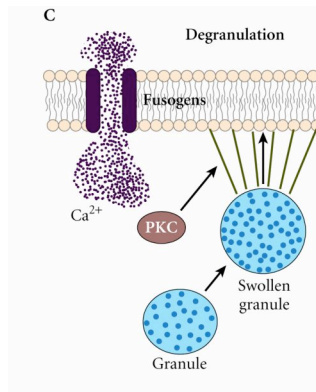
Mast Cell Activation and Degranulation



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

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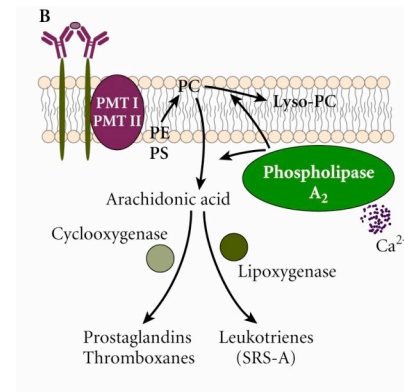
Mast Cell Activation and Degranulation



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

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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

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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

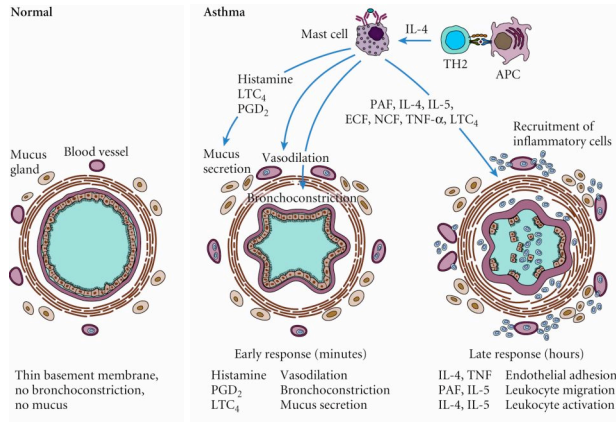
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Asthma Attack

- 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 contraction
- 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

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Asthma Attack



Industrialization and Allergies

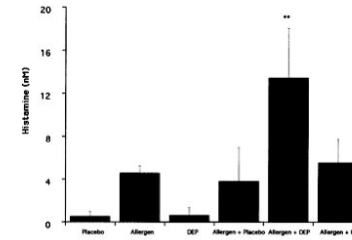


FIG 3. DEPs increase allergen-induced histamine release in nasal wash specimens. The concentration of histamine in nasal lavage fluid before and after nasal challenge with a one tenth dose of allergen (Derp 10) previously determined to induce a total symptom score of 6 (out of a possible 12) was measured. The mean \pm 1 SD for 10 subjects is shown. CE, Carbon black. ** $P < .01$ versus allergen control.

- David Diaz-Sanchez, PhD, Marisol Penichet-Garcia, MD, and Andrew Saxon, MD. (2000) Diesel exhaust particles directly induce activated mast cells to degranulate and increase histamine levels and symptom severity. *Journal of Allergy and Clinical Immunology*, 106:1140-6.

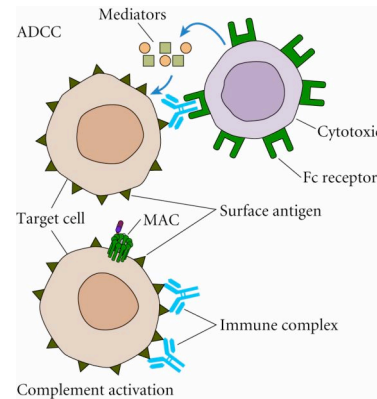
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Type II Intermediate Hypersensitivity

- 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

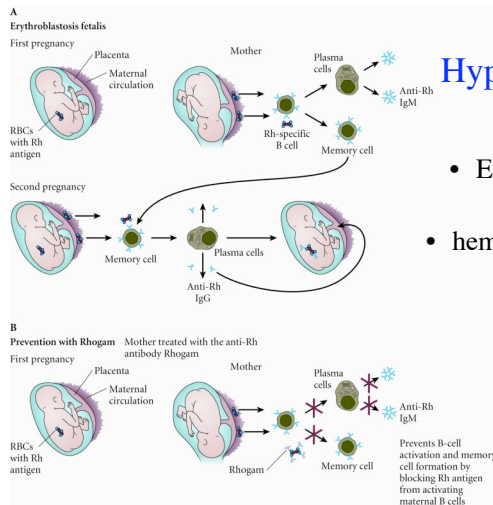
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Type II Intermediate Hypersensitivity



- 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

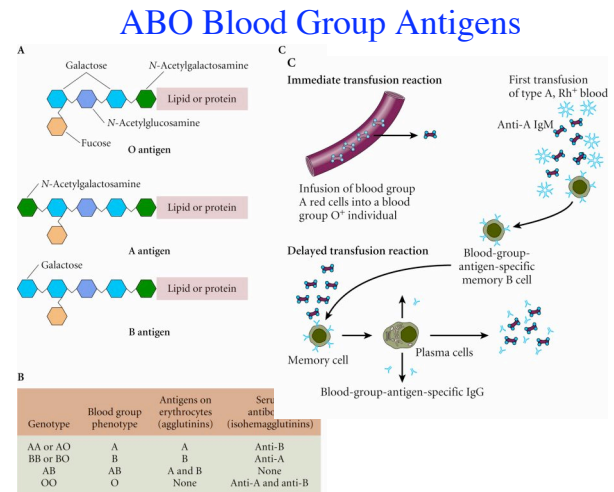
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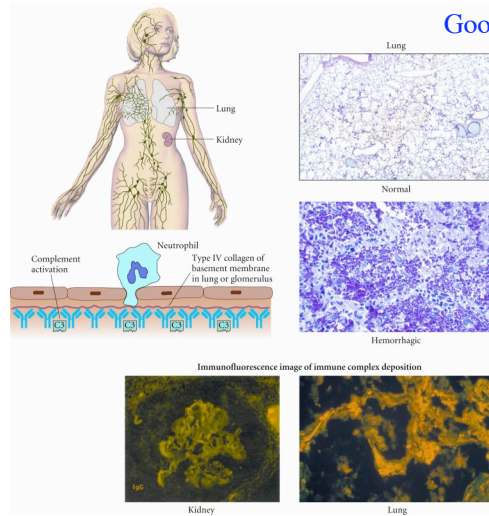
Type II Hypersensitivity

- Erythroblastosis fetalis or
- hemolytic disease of the newborn

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

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