

Hypersensitivity Reactions

Hypersensitive reactions are inflammatory reactions within the humoral or cell-mediated branches of the immune system that lead to extensive tissue damage or even death.

An **allergy** is a hypersensitivity disorder of the immune system. Allergic reactions occur when a person's immune system reacts to normally harmless substances in the environment

Four Types of Hypersensitivity Reactions:

- **Type I (Anaphylactic) Reactions**
- **Type II (Cytotoxic) Reactions**
- **Type III (Immune Complex) Reactions**
- **Type IV (Cell-Mediated) Reactions**

Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death. It typically causes a number of symptoms including an itchy rash, throat swelling, and low blood pressure. Common causes include insect bites/stings, foods, and medications.

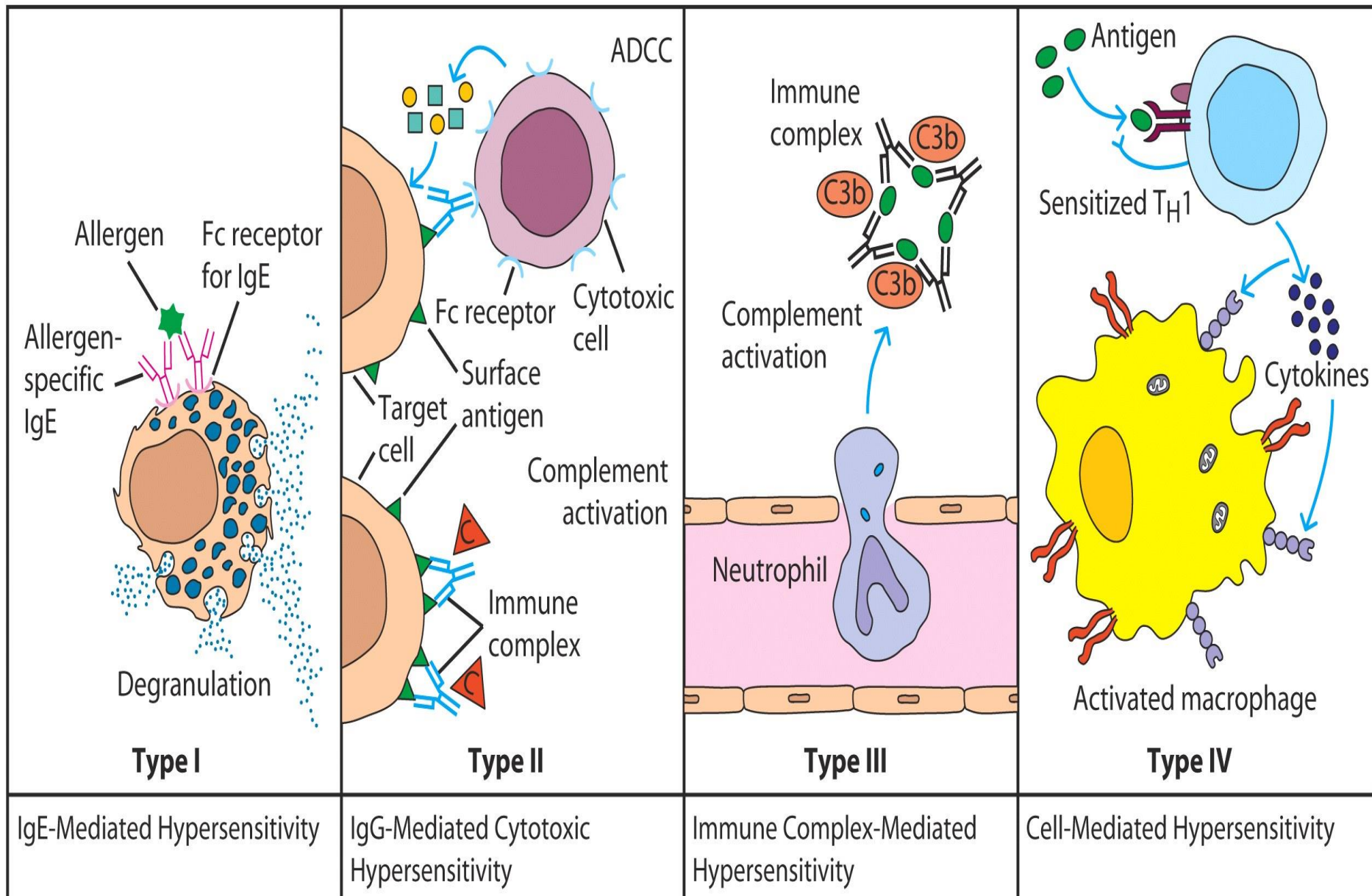
Hypersensitivity

- 4 types of HS (Gell & Coombs)
 - Type I: IgE-mediated degranulation of mast cells → acute anaphylactic response
 - Type II: IgG / IgM on cells → c' lysis or ADCC
 - Type III: Immune complexes → c' activation, inflammation
 - Type IV: T_{DTH} activate Macrophages → chronic inflammation
- Types I – III involve Abs, Type IV is Cell mediated immune response

DTH: delayed Type Hypersensitivity, is so named in recognition of the delay of symptoms until days after exposure.

Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) is a mechanism of cell-mediated immune defense whereby an effector cell of the [immune system](#) actively [lyses](#) a target cell that has been bound by specific [antibodies](#).

Hypersensitivity Reactions



Type I (Anaphylactic) Reactions

- Occur within minutes of exposure to antigen
- Antigens combine with IgE antibodies
- IgE binds to mast cells and basophils, causing them to undergo *degranulation* and release several mediators:
 - **Histamine:** Dilates and increases permeability of blood vessels (swelling and redness), increases mucus secretion (runny nose), smooth muscle contraction (bronchi).
 - **Prostaglandins:** Contraction of smooth muscle of respiratory system and increased mucus secretion.
 - **Leukotrienes:** Bronchial spasms.
- **Anaphylactic shock:** Massive drop in blood pressure. Can be fatal in minutes.

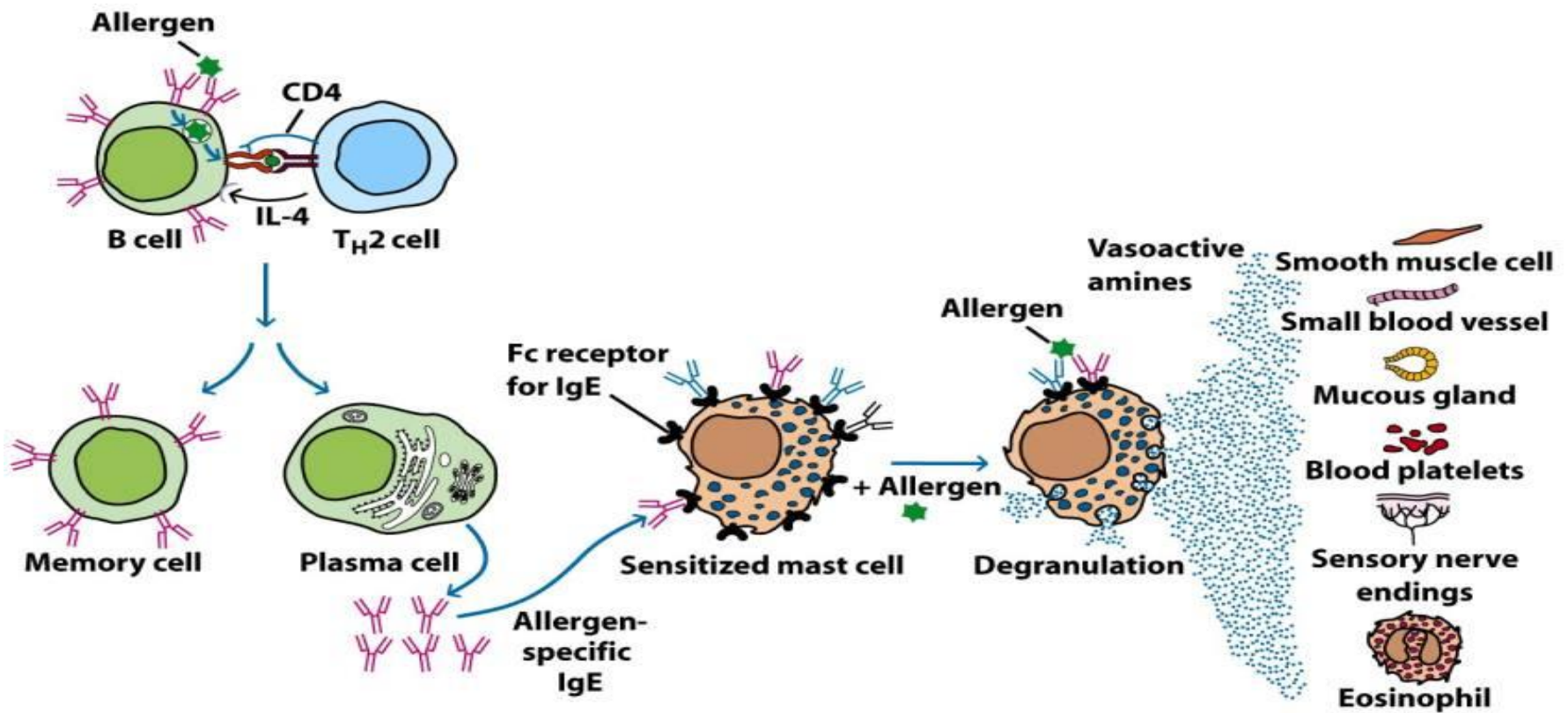


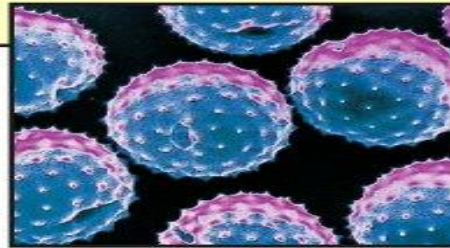
Figure 15-2
Kuby IMMUNOLOGY, Sixth Edition
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FIGURE: General mechanism underlying a type I hypersensitive reaction. Exposure to an allergen activates B cells to form IgE secreting plasma cells. The secreted IgE molecules bind to IgE specific Fc receptors on mast cells and blood basophils. (Many molecules of IgE with various specificities can bind to the IgE-Fc receptor.) Second exposure to the allergen leads to cross linking of the bound IgE, triggering the release of pharmacologically active mediators, vasoactive amines, from mast cells and basophils. The mediators cause smooth muscle contraction, increased vascular permeability, and vasodilation.

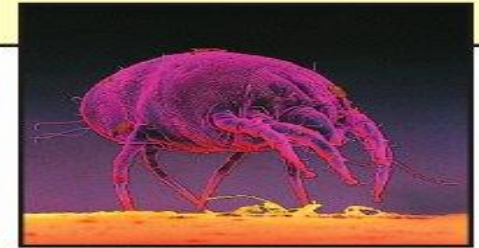
Common sources of allergens

Inhaled materials

Plant pollens
Dander of domesticated animals
Mold spores
Feces of very small animals
e.g., house dust mites



pollen



house dust mite

Injected materials

Insect venoms
Vaccines
Drugs
Therapeutic proteins



wasp



drugs

Ingested materials

Food
Orally administered drugs



peanuts



shellfish

Contact materials

Plant leaves
Industrial products made from plants
Synthetic chemicals in industrial products
Metals



poison ivy



nickel coin

Type I Hypersensitivity (HS-I)

- classic allergic reactions
 - **allergens** – Ags that trigger HS-I reactions
 - **atopic** people tend to mount IgE responses
 - get hay fever, asthma, etc.
- **mast cells / basophils** are major effectors
 - have high-affinity Fc receptors for IgE
 - granules contain mediators of HS-I reaction

Type I Hypersensitivity

- **primary mediators** in mast / baso granules
 - histamine
 - serotonin ~ effects to histamine
 - heparin – anticoagulant
 - chemotactic factors recruit eos, neutrophils
- **secondary mediators** made later
 - arachadonic acid metabolites (PG, LT)
 - platelet activate factors (PAF): that causes platelet aggregation and release of histamine, heparin and vasoactive amines.
 - bradykinins

platelet is a small colourless disc-shaped cell fragment without a nucleus, found in large numbers in blood and involved in clotting.

Arachadonic acide = fatty acide

bradykinin is noun Biochemistry a compound released in the blood which causes contraction of smooth muscle and dilation of blood vessels.

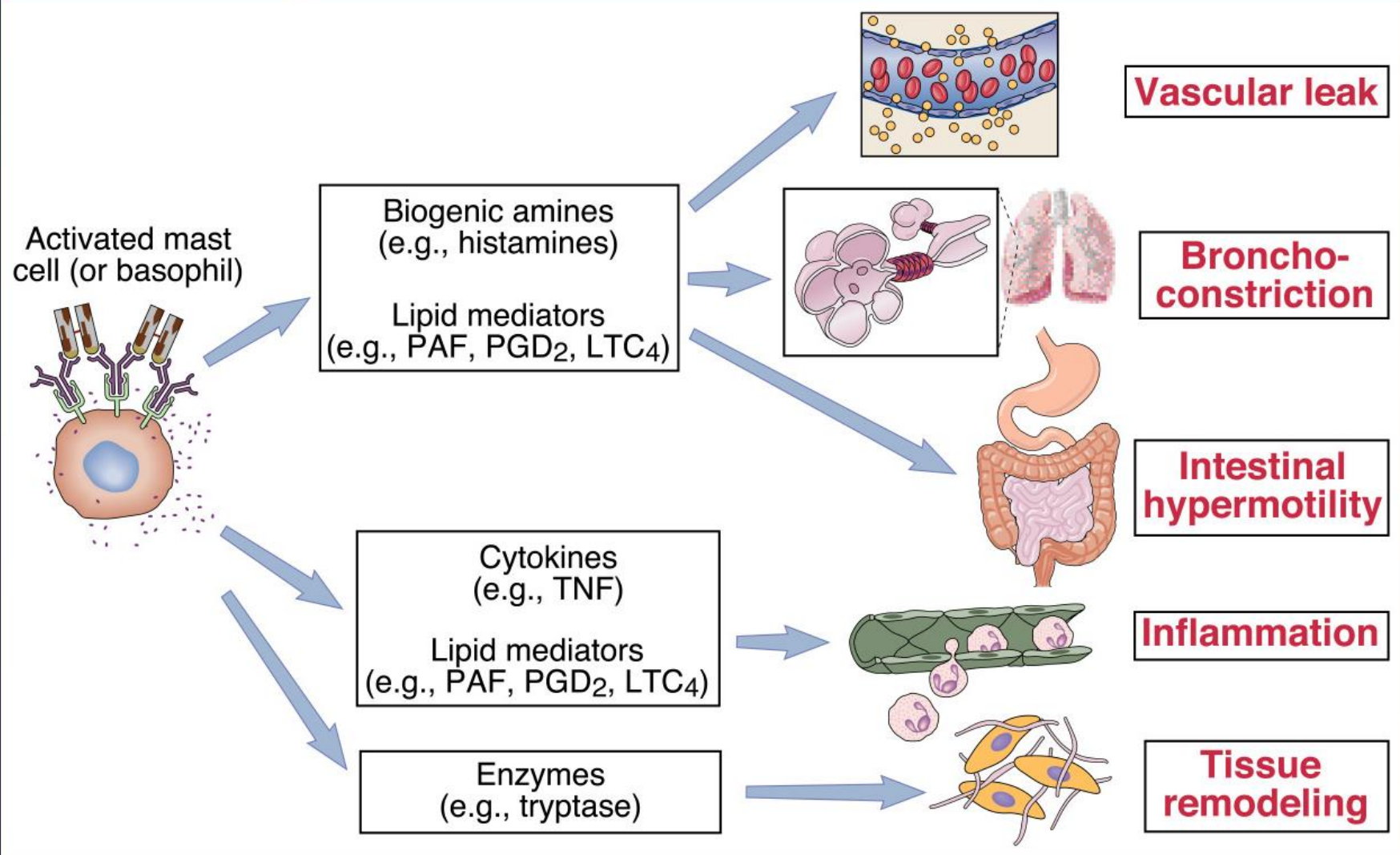
Type I Hypersensitivity

- **Cytokines** contribute to HS-I response
 - mast cells secrete IL-4, IL-5, IL-6, TNF- α
 - IL-4 helps activate B cells; increases IgE production
 - IL-5 recruits eosinophils
 - IL-6, TNF contribute to inflamm. (fever, etc.)
- **Eosinophils** increased in atopic individuals
 - have low-affinity FcR for IgE
 - degranulation \rightarrow PAF, PG, LT
 - important in late-phase asthma

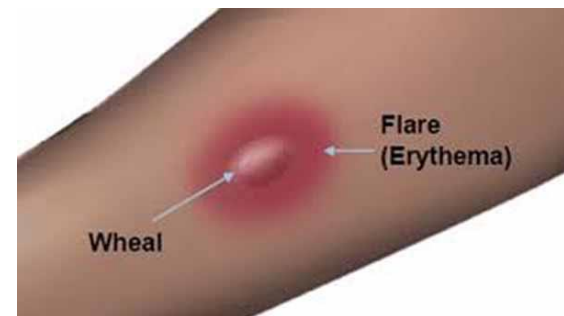
Type I Hypersensitivity

- **Sensitization** phase: IgE produced in response to allergen
 - IgE binds to FcR on mast cells / basophils
 - mast cells sensitized
- **Activation** phase: on next encounter with allergen
 - allergen cross-links IgE receptors on mast cell → immediate degranulation
 - (mast cell degran. can also occur w. anti-IgE Abs, some chemicals, or c' anaphylatoxins C3a, C5a)
- **Effector** phase: tissue Rx to degranulation
 - vasc. perm. , mucous secretions, influx of eos, neuts, etc.

Biological effects of mast cell mediators



Diagnostic tests for immediate hypersensitivity include skin (prick and intradermal) tests resulting in wheal and flare reaction, measurement of total IgE and specific IgE antibodies against the suspected allergens. Total IgE and specific IgE antibodies are measured by a modification of enzyme immunoassay (ELISA). Increased IgE levels are indicative of atopic condition, although IgE may be elevated in some non atopic diseases (e.g., myelomas,).



Type I HS Reactions

- Localized anaphylaxis (atopy)
 - cutaneous anaphylaxis – wheal & flare
 - allergic rhinitis (hay fever)
 - food allergies
 - atopic dermatitis (allergic eczema)
 - asthma (lower respiratory tract)



IgE-mediated allergic reactions			
Syndrome	Common allergens	Route of entry	Response
Systemic anaphylaxis	Drugs Serum Venoms Peanuts	Intravenous (either directly or following rapid absorption)	Edema Increased vascular permeability Tracheal occlusion Circulatory collapse Death
Wheal and flare	Insect bites Allergy testing	Subcutaneous	Local increase in blood flow and vascular permeability
Allergic rhinitis (hay fever)	Pollens (ragweed, timothy, birch) Dust-mite feces	Inhaled	Edema of nasal mucosa Irritation of nasal mucosa
Bronchial asthma	Pollens Dust-mite feces	Inhaled	Bronchial constriction Increased mucus production Airway inflammation
Food allergy	Shellfish Milk Eggs Fish Wheat	Oral	Vomiting Diarrhea Pruritis (itching) Urticaria (hives) Anaphylaxis

Figure 10-12 The Immune System, 2/e (© Garland Science 2005)

IgE mediated reactions to extrinsic Ags. All IgE mediated response involve mast cell degranulation, but the symptoms experienced by the patient can be very different depending on whether the allergen is injected, inhaled, or eaten, and depending also on the dose of the allergen

Identifying HS-I: Allergy Testing

- skin test: small doses of allergen
 - look for wheal & flare
- measure IgE levels



Treatment for HS-I Disorders

- avoid allergen (Reaction can get worse each time)
- drugs
 - anti-histamines (not Abs) compete with histamine for receptors
 - quick acting, but short duration
 - cortisone blocks histamine synthesis

Treatment for HS-I Disorders

- immunological treatment
 - hyposensitization – repeat injections of allergen
 - may work by shifting from IgE to IgG production
 - MAb anti-IgE that binds mIgE on B cells
 - (if binds IgE on mast cells → degranulation)

Type II (Cytotoxic) Reactions

- Involve activation of **complement** by IgG or IgM binding to an antigenic cell.
- Antigenic cell is lysed.
- Transfusion reactions:
 - **ABO Blood group system:** Type O is universal donor. Incompatible donor cells are lysed as they enter bloodstream.
 - **Rh Blood Group System:** 85% of population is Rh positive. Those who are Rh negative can be sensitized to destroy Rh positive blood cells.
 - **Hemolytic disease of newborn:** Fetal cells are destroyed by maternal anti-Rh antibodies that cross the placenta.

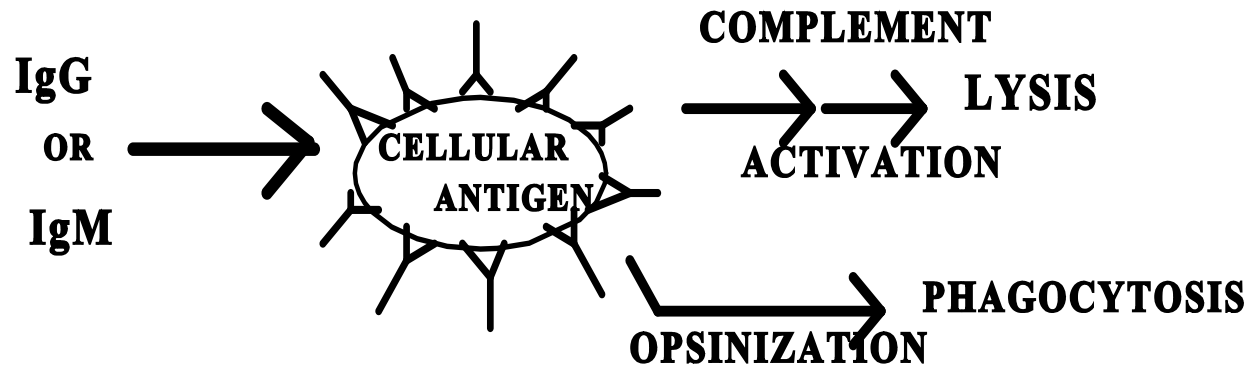
Type II Hypersensitivity

- Ab-mediated cytotoxicity
- Abs vs. cell surface Ags → C' lysis or ADCC
- most common HS-II Rx involve rbc
 - transfusion Rx
 - hemolytic disease of the newborn (HDN)
 - autoimmune hemolytic anemic (AIHA)

TYPE II HYPERSENSITIVITY

B. Type II Cytotoxic Reactions - IgG or IgM mediated, complement involved, reactions most often effect cellular elements in intimate contact with circulating plasma

examples: hemolytic anemia, transfusion reactions



Type II Hypersensitivity

- Other HS-II = autoimmune hemolytic anemia (AIHA)