Hypersensitive Reactions

1. Type I Hypersensitivity
2. Type II Hypersensitivity
3. Type III Hypersensitivity
4. Type IV Hypersensitivity

By: Huda Rafia Sabbar

1. Basic concepts

Hypersensitivity reactions are harmful antigen-specific immune responses , occur when an individual who has been primed by an innocuous antigen subsequently encounters the same antigen , produce tissue injury and dysfuntion. Hypersensitivity implies an increased response, inappropriate response to an antigen.

Allergen： the antigens that give rise to immediate hypersensitivity

Atopy： the genetic predisposition to synthesize inappropriate levels of IgE specific for external allergens

Types of hypersensitivity： I、II、III、IV

immediate hypersensitivity: the symptoms are manifest within minutes or hours after a sensitized recipient encounters antigen.

Delayed-type hypersensitivity (DTH) is so named in recognition of the delay of symptoms until days after exposure.

Mast cells are found throughout connective tissue, particularly near blood and lymphatic vessels. Some tissues, including the skin and mucous membrane surfaces of the respiratory and gastrointestinal tracts, contain high concentrations of mast cells; skin, for example, contains 10,000 mast cells per mm3.

Electron micrographs of mast cells reveal numerous membrane-bounded granules distributed throughout the cytoplasm, which, like those in basophils, contain pharmacologically active mediators

2. Type I hypersensitivity

1)、Characteristics

2)、Components and cells

3)、The process and mechanism

4)、Commen diseases of type I Hypersensitivity

5)、Therapy for type I Hypersensitivity

1) Characteristics

- Occur and resolve quickly
- Mediated by serum IgE
- Systemic and regional tissue dysfuntion
- Genetic predisposition

2) Components and cells in Type I hypersensitivity

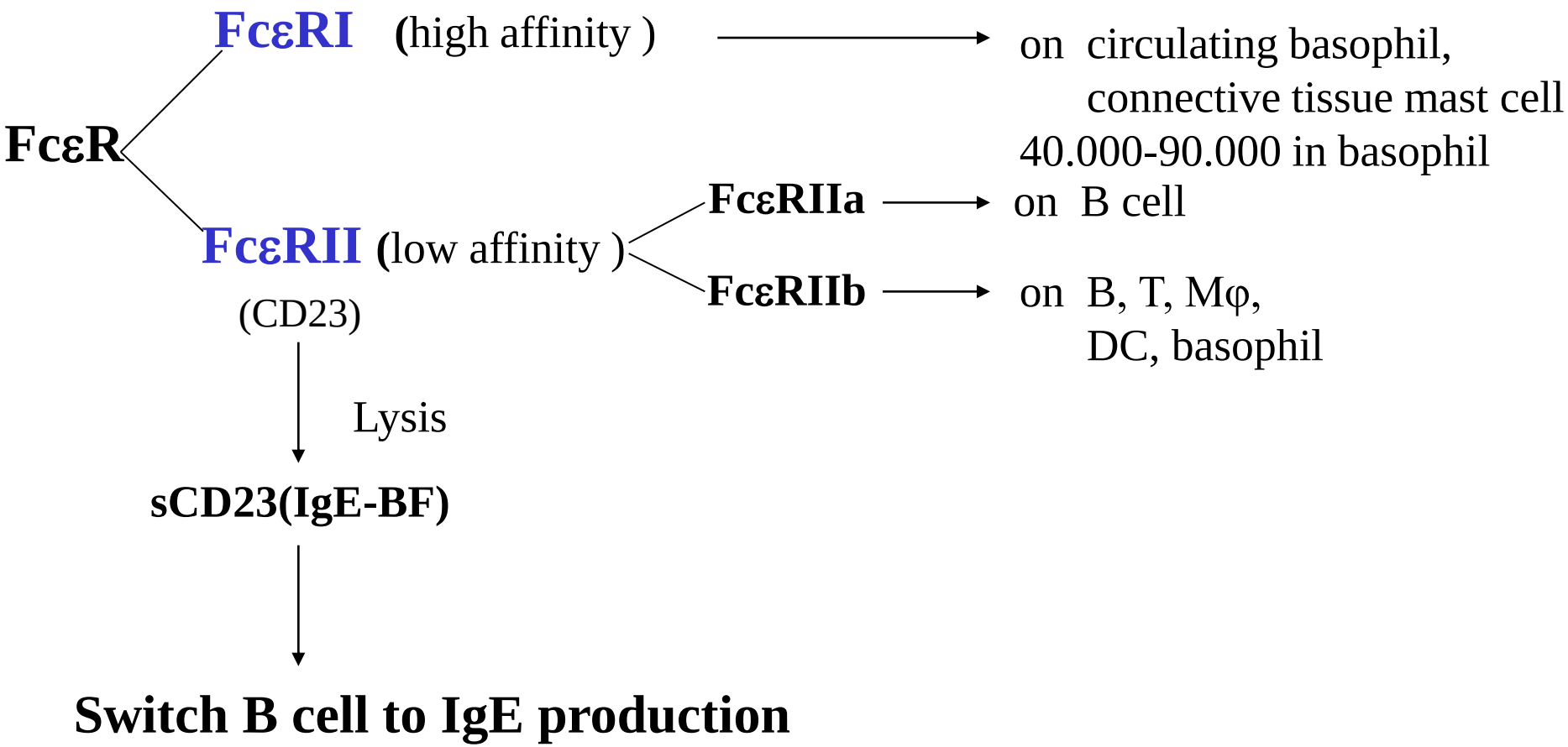
➢**Allergen ：** non parasitic Ag capable of stimulating type I hypersensitivite responses in allergic individuals on repeated exposure.ex; pollen、dust mite、insects etc

➢**Allergin（IgE）and its production :** The IgE regulatory defects suffered by atopic indivisuals allow nonparasitic Ag to stimulate inappropraite IgE production,leading to tissue damaging. IgE：mainly produced by mucosal B cells , IL-4 ,IL-5,IL-9,IL-13 and GM-CSF are essential to switch B cells to IgE production

➢Atopic individuals have abnormally high levels of circulating IgE and eosinophils

➢**High affinity receptor of the IgE on mast cell ,eosinophil and basophil**

High affinity receptor of the IgE on mast cell and basophil



FcεRI: High-affinity IgE receptor

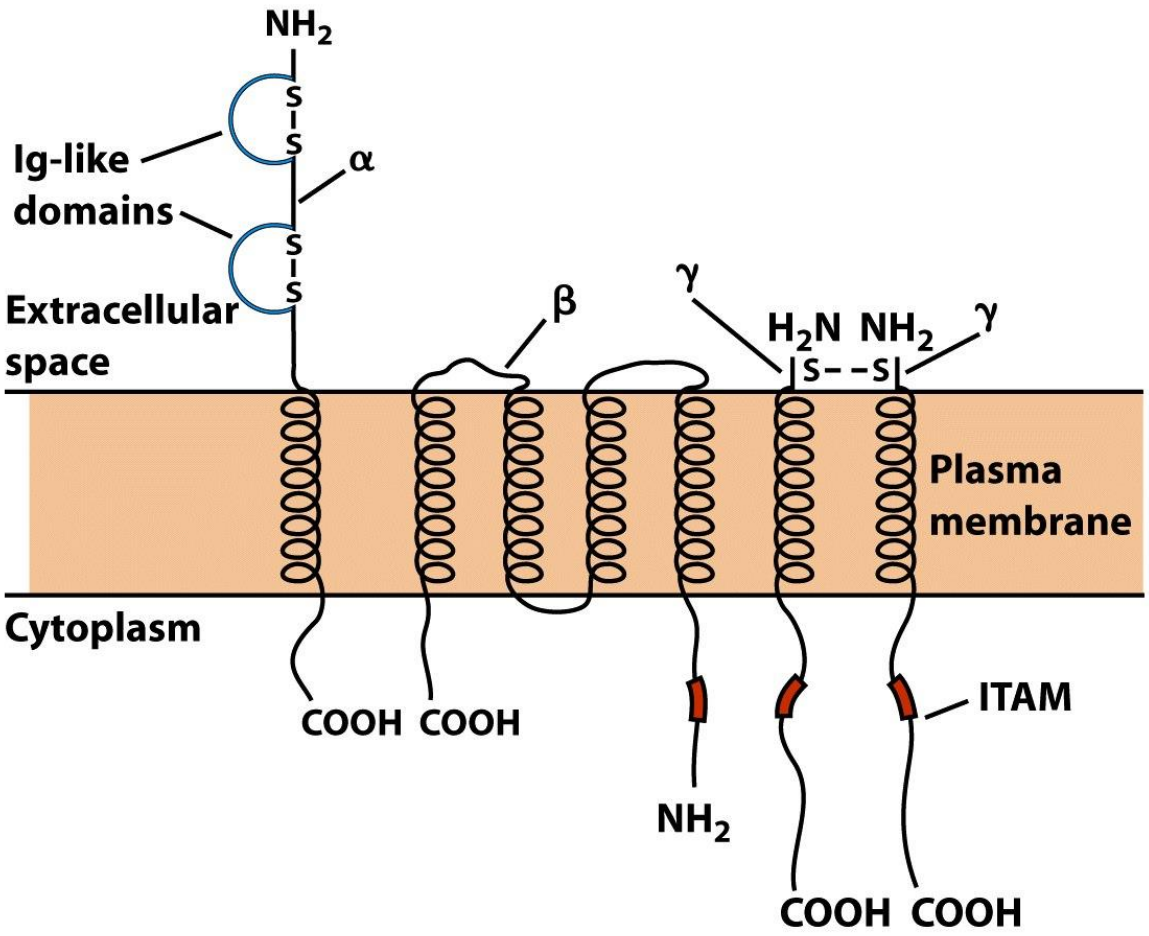


Figure 15-4a
Kuby IMMUNOLOGY, Sixth Edition

FcεRII (CD23): Low-affinity IgE

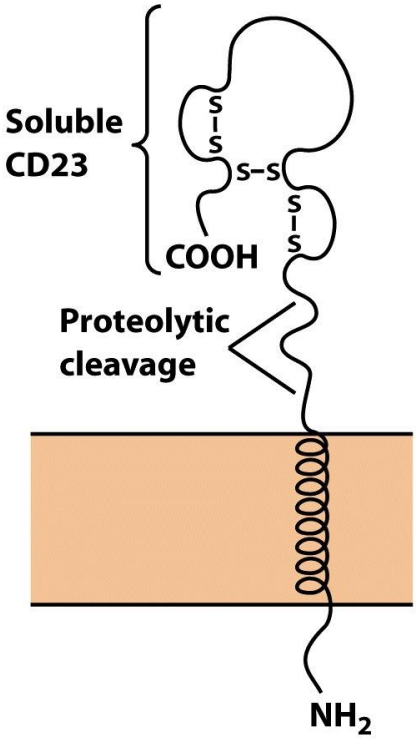
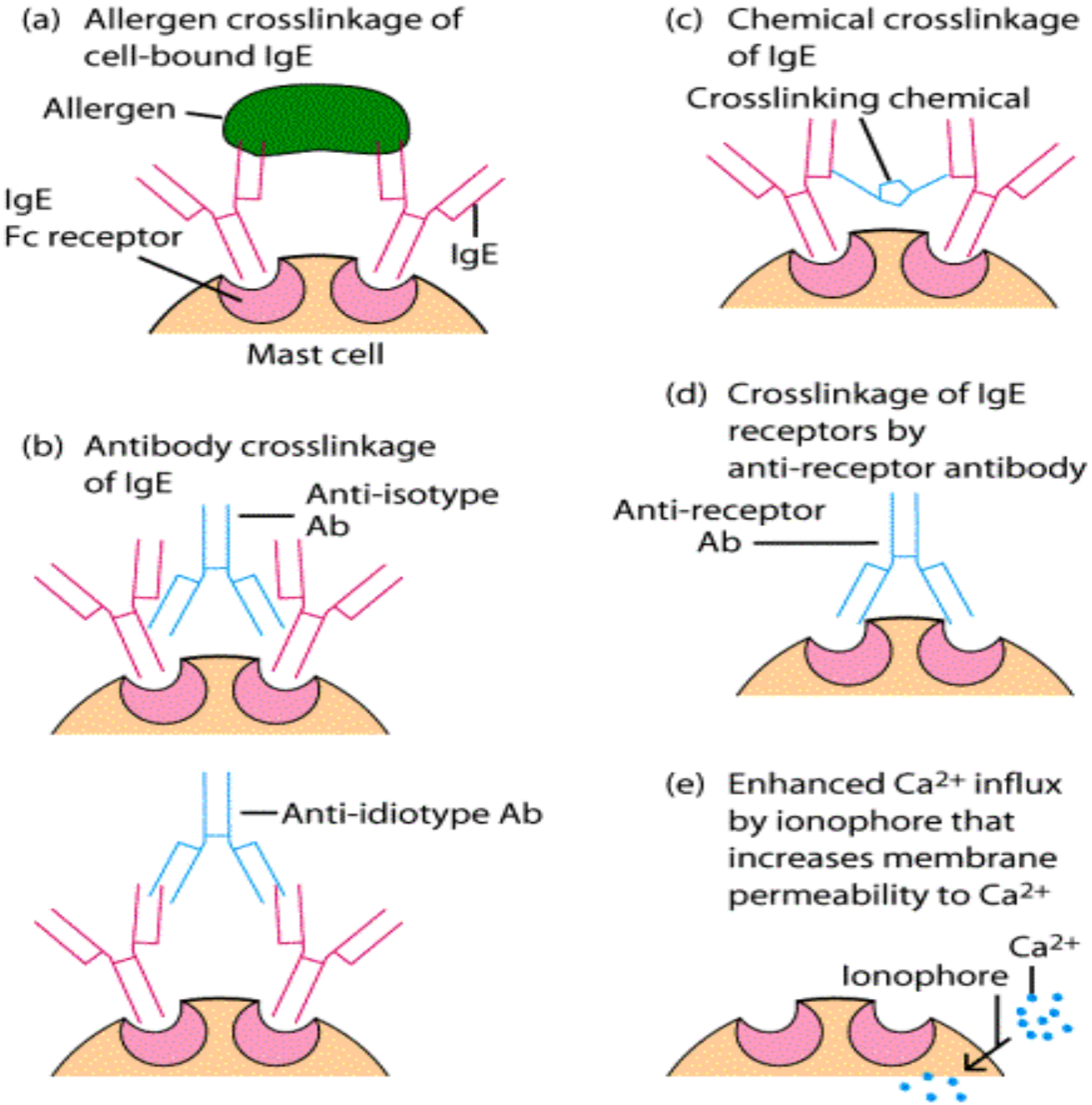
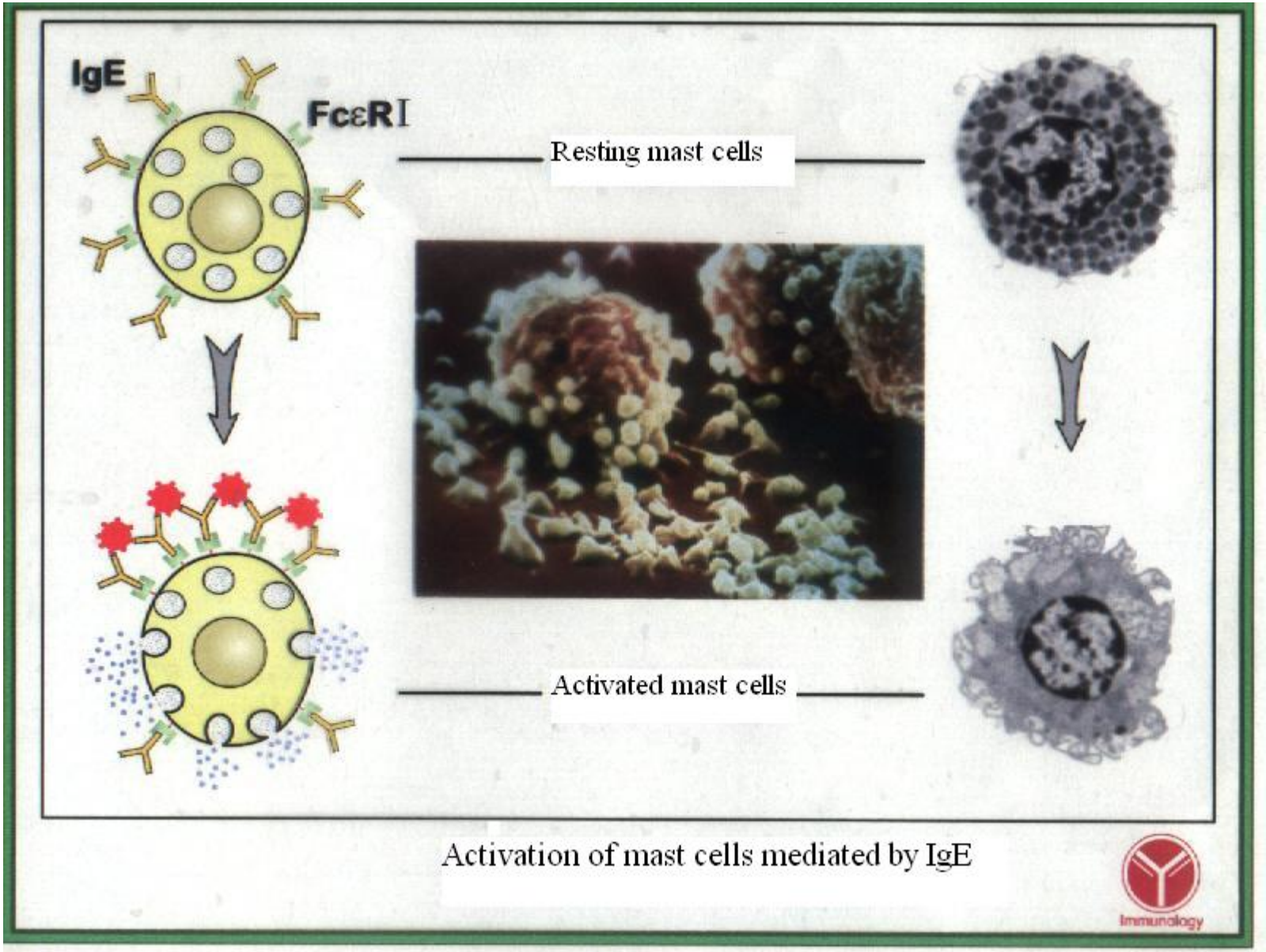
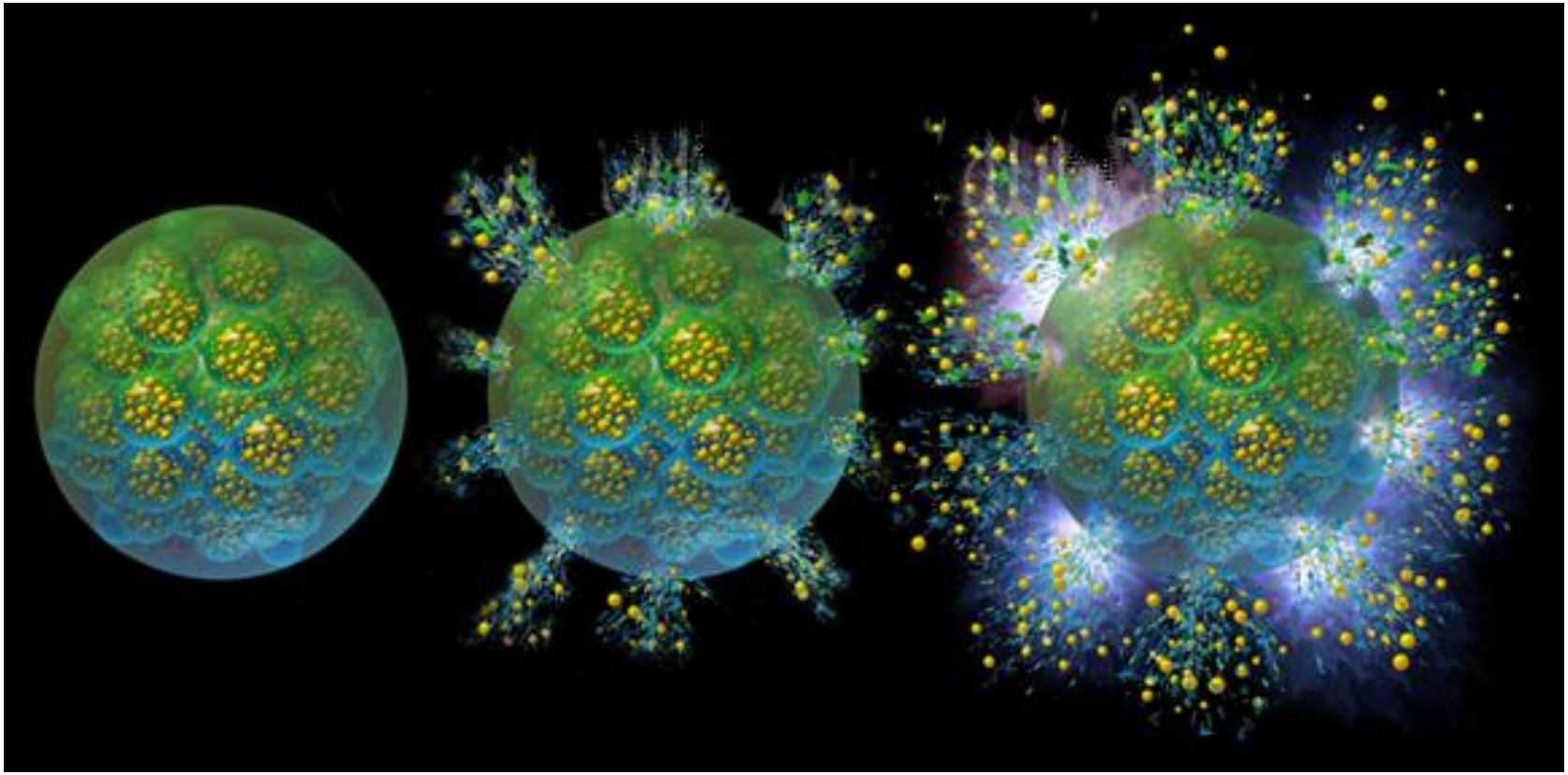


Figure 15-4b
Kuby IMMUNOLOGY, Sixth Edition


(a) Allergen crosslinkage of cell-bound IgE
Allergen
IgE
Fc receptor
IgE
Mast cell
(b) Antibody crosslinkage of IgE
Anti-isotype Ab
Anti-idiotype Ab
(c) Chemical crosslinkage of IgE
Crosslinking chemical
(d) Crosslinkage of IgE receptors by anti-receptor antibody
Anti-receptor Ab
(e) Enhanced Ca^{2+} influx by ionophore that increases membrane permeability to Ca^{2+}
Ca^{2+}
Ionophore



Activation of mast cells mediated by IgE



3 The process and mechanism of Type I hypersensitivity

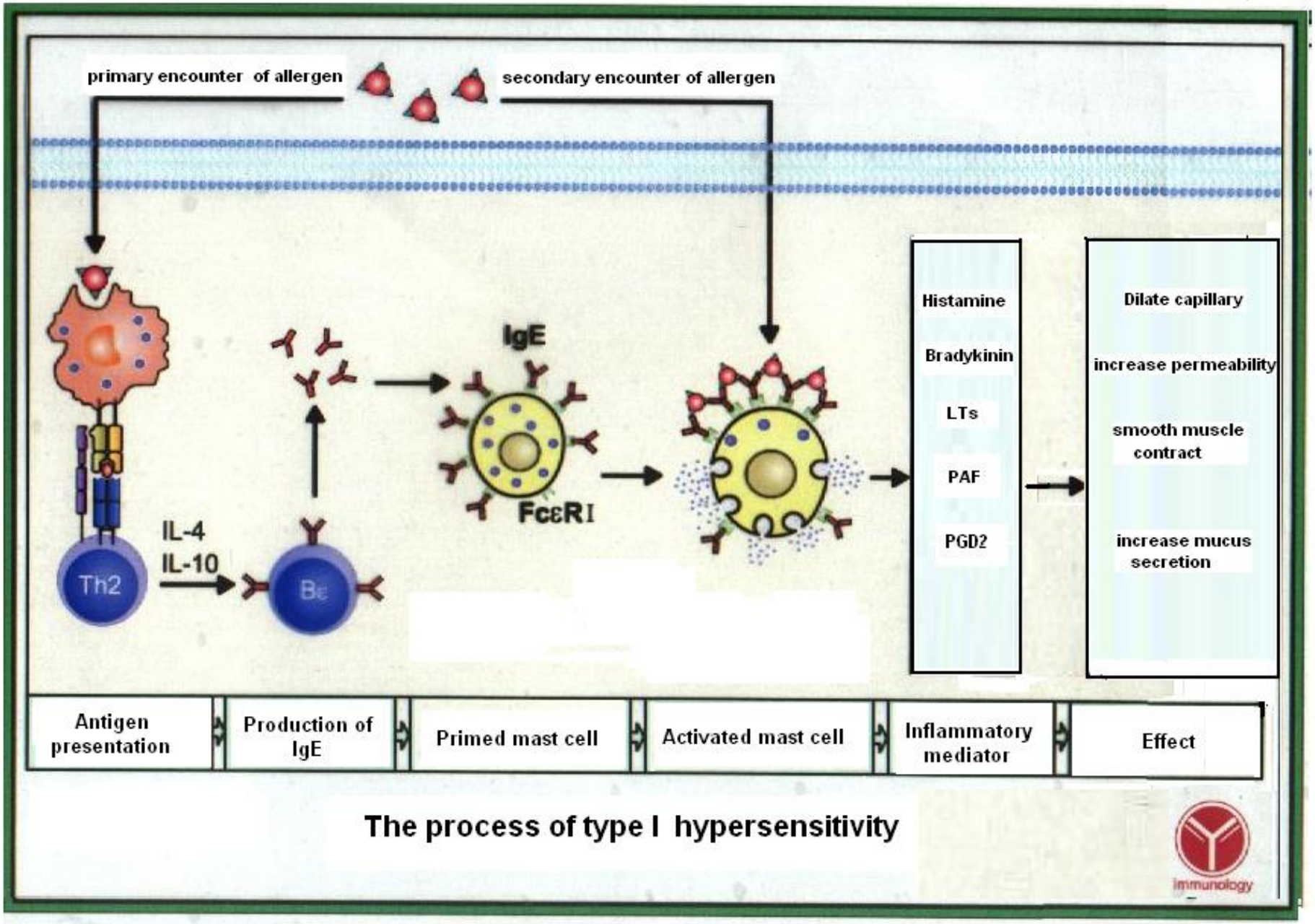
1) Priming stage: last more than half a year

2) Activating stage:

Crosslinkage → Enzyme reaction → Degranulation of mast cell , basophil

3) Effect stage:

Immediate/early phase response:	Mediated by histamine
	Start within seconds
	Last several hours
Late-phase response :	Mediated by new-synthesized lipid mediators
	Take up 8-12hours to develop
	Last several days


primary encounter of allergen
secondary encounter of allergen
IgE
FcεRI
IL-4
IL-10
Th2
Bε
Histamine
Bradykinin
LTs
PAF
PGD2
Dilate capillary
increase permeability
smooth muscle contract
increase mucus secretion
Antigen presentation
Production of IgE
Primed mast cell
Activated mast cell
Inflammatory mediator
Effect
The process of type I hypersensitivity
immunology

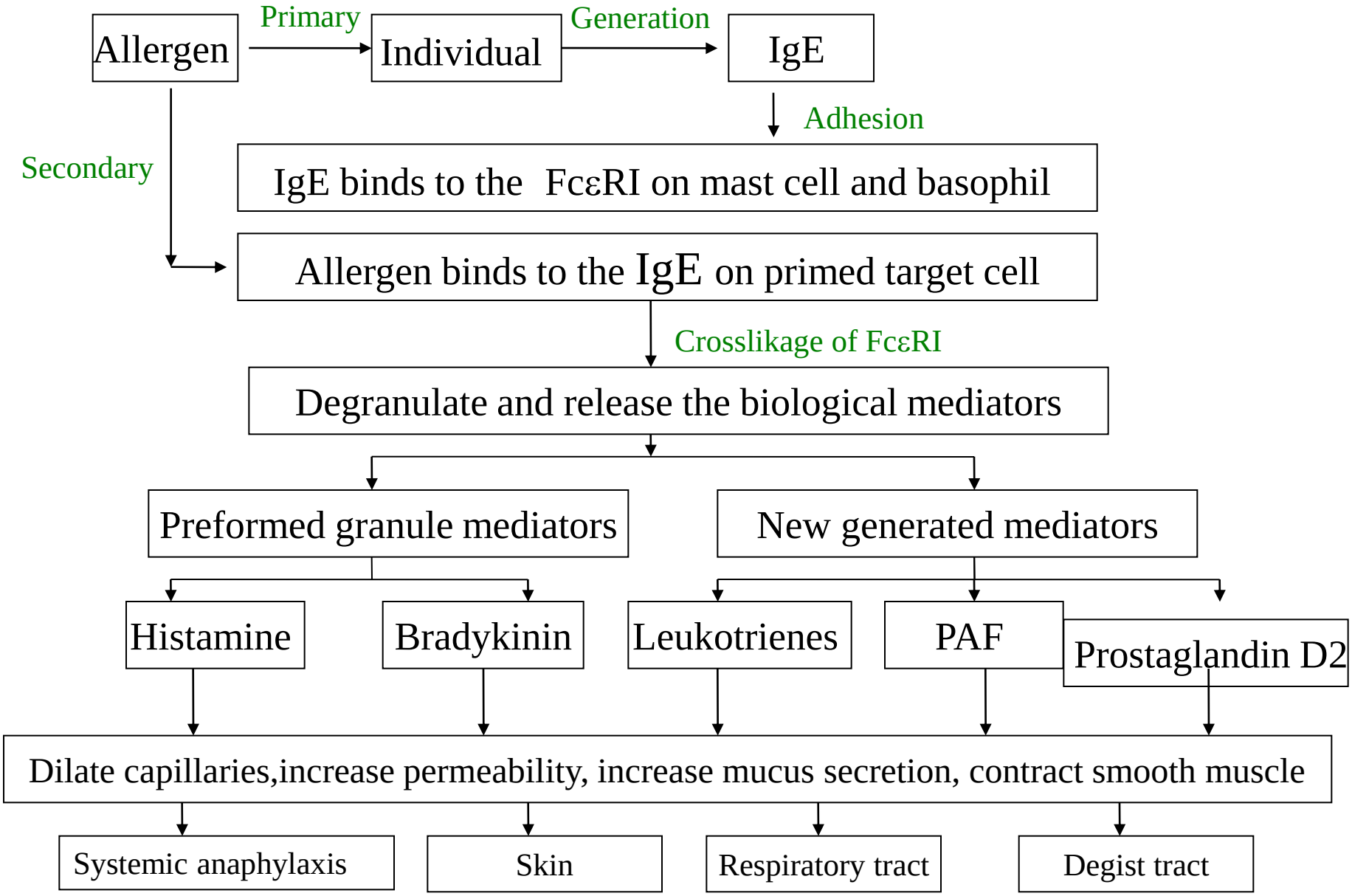
The mediators can be classified as either primary or secondary:

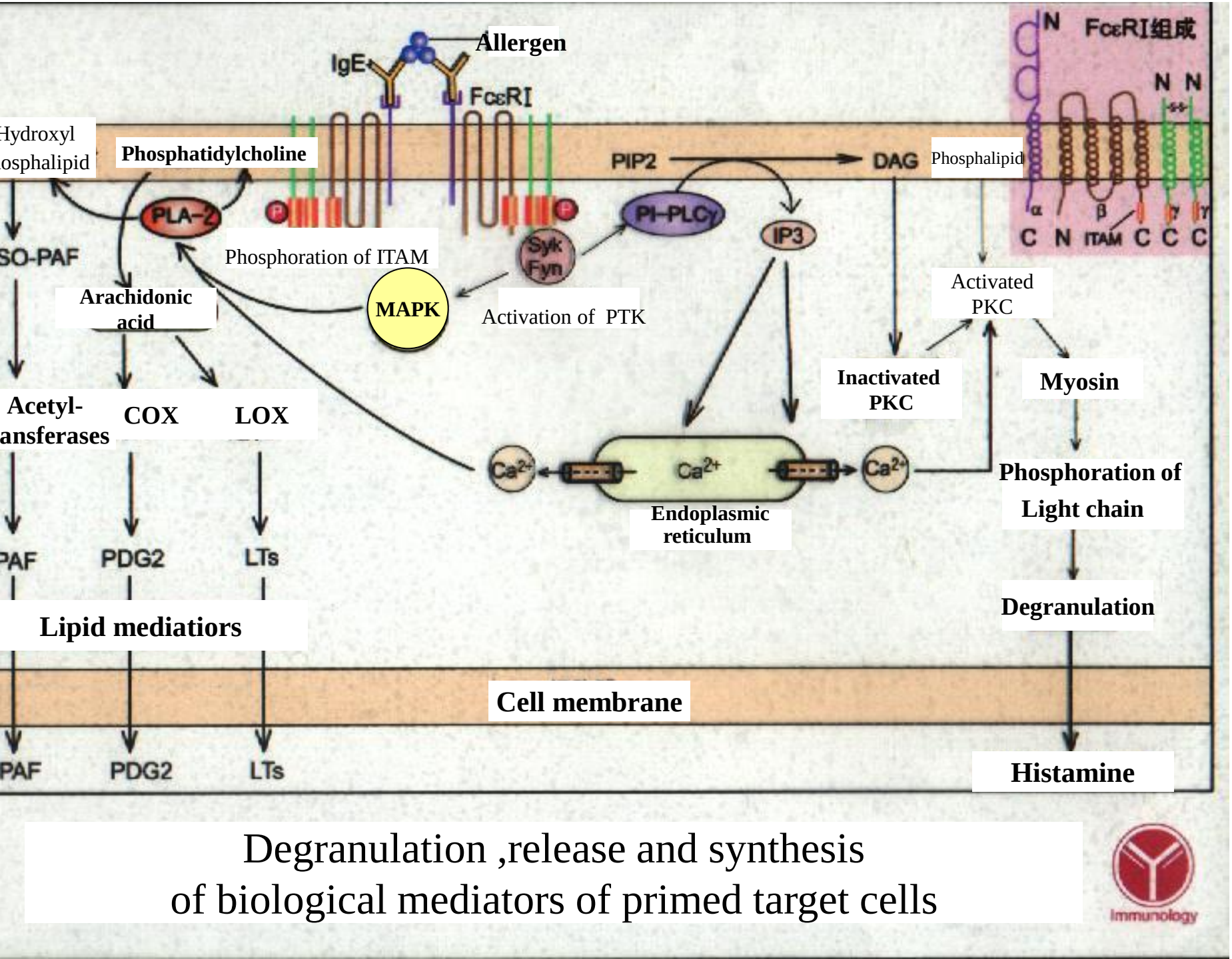
1- The primary mediators are produced before degranulation and are stored in the granules.
The most significant primary mediators are histamine, proteases,eosinophil chemotactic factor, neutrophil chemotactic factor,and heparin.

2-The secondary mediators either are synthesized after target-cell activation or are released by the breakdown of membrane phospholipids during the degranulation process.

The secondary mediators include platelet-activating factor, leukotrienes, prostaglandins, bradykinins, and various cytokines.

Mechanism of type I hypersensitivity





Degranulation ,release and synthesis
of biological mediators of primed target cells

Immunology

The biological mediator on effect stage

1. Histamine:

Dilate blood vessel, Increase vascular permeability

- Histamine, which is formed by decarboxylation of the amino acid histidine, is a major component of mast-cell granules,accounting for about 10% of granule weight.
- Most of the biologic effects of histamine in allergic reactions are mediated by the binding of histamine to H1 receptors
- This binding induces contraction of intestinal and bronchial smooth muscles, increased permeability of venules, and increased mucus secretion by goblet cells.

Interaction of histamine with H2 receptors increases vasopermeability and dilation and stimulates exocrine glands. Binding of histamine to H2 receptors on mast cells and basophils suppresses degranulation; thus, histamine exerts negative feedback on the release of mediators.

. Prostaglandin . Leukotrienes

secondary mediators, the leukotrienes and prostaglandins are not formed until the mast cell undergoes degranulation and the enzymatic breakdown of phospholipids in the plasma membrane.

Their effects are more pronounced and longer lasting,than those of histamine.

The leukotrienes mediate bronchoconstriction, increased vascular permeability, and mucus production.

Prostaglandin D2 causes bronchoconstriction

The contraction of human bronchial and tracheal smooth muscles appears at first to be mediated by histamine, but, within 30–60 s, further contraction is mediated by the leukotrienes and prostaglandins.

CYTOKINES

Adding to the complexity of the type I reaction is the variety of cytokines released from mast cells and eosinophils. Some of these may contribute to the clinical manifestations of type I hypersensitivity.

Human mast cells secrete IL-4, IL-5, IL-6,and TNF.

These cytokines alter the local microenvironment, eventually leading to the recruitment of inflammatory cells such as neutrophils and eosinophils.

IL-4 increases IgE production by B cells.

IL-5 is especially important in the recruitment and activation of eosinophils

4. Common disease of type I hypersensitivity

1. Systemic anaphylaxis: a very dangerous syndrome ,fatal state,occur by direct introduction of Ag into blood stream or absorbed from gut or skin

1) Anaphylactic drug allergy :

penicillin,insulin,anitoxin,also seafood and nut

2. Local reaction: Respiratory allergic diseases :

1) Allergic rhinitis

2)Asthma

3) Gastrointestinal allergic diseases :

Allergen crosslinking of IgE on mast cells along the upper or lower gastrointestinal tract can induce localized smooth-muscle contraction and vasodilation and thus such symptoms as vomiting or diarrhea. Mast-cell degranulation along the gut can increase the permeability of mucous membranes, so that the allergen enters the bloodstream.

Asthma :In some cases, airborne or blood-borne allergens, such as pollens, dust, fumes, insect products, or viral antigens, trigger an asthmatic attack (**allergic asthma**);
in other cases, an asthmatic attack can be induced by exercise or cold, apparently independently of allergen stimulation (**intrinsic asthma**)

asthma is triggered by degranulation of mast cells with release of mediators, but instead of occurring in the nasal mucosa, the reaction develops in the lower respiratory tract. The resulting contraction of the bronchial smooth muscles leads to bronchoconstriction. Airway edema, mucus secretion, and inflammation contribute to the bronchial constriction and to airway obstruction.

Asthmatic patients may have abnormal levels of receptors for neuropeptides. For example, asthmatic patients have been reported to have increased expression of receptors for substance P, a peptide that contracts smooth muscles,

The asthmatic response can be divided into **early** and **late** responses.

The early response occurs within minutes of allergen exposure and primarily involves histamine, leukotrienes (LTC4), and prostaglandin (PGD2).

The effects of these mediators lead to bronchoconstriction, vasodilation, and some buildup of mucus.

The late response occurs hours later and involves additional mediators, including IL-4, IL-5, IL-16,TNF-, eosinophil chemotactic factor (ECF), and platelet-activating factor (PAF).

The overall effects of these mediators is to increase endothelial cell adhesion as well as to recruit inflammatory cells, including eosinophils and neutrophils, into the bronchial tissue.

The neutrophils and eosinophils are capable of causing significant tissue injury by releasing toxic enzymes, oxygen radicals, and cytokines.

These events lead to occlusion of the bronchial lumen with mucus, proteins, and cellular debris; sloughing of the epithelium; thickening of the basement membrane; fluid buildup (edema); and hypertrophy of the bronchial smooth muscles.

A mucus plug often forms and adheres to the bronchial wall. The mucus plug contains clusters of detached epithelial-cell fragments, eosinophils, some neutrophils, and spirals of bronchial tissue known as Curschmann's spirals.

Other local hypersinsitive

LOCALIZED ANAPHYLAXIS (ATOPY)

including allergic rhinitis (hay fever), asthma, atopic dermatitis (eczema), and food allergies

5. Therapy of type I hypersensitivity

1. **Allergen avoidance**
2. **Desensitivity therapy / Hyposensitization :**

1) Allogenic serum desensitivity therapy:

Repeated injection small amounts of allergen, Temporality

2) Specific allergen desensitivity therapy

IgG+allergen Neutralizing antibody, Blocking antibody

3. **Drug therapy：**

1) Stabilization of triggering cells

sodium cromoglycate——stabilize the membrane, inhibit mast cell degranulation

2) Mediator antagonism

Chlor-Trimeton ——Antihistamine

Acetylsalicylic acid —— Bradykinin antagonism

3) Improve the responsibility of target organs

4. **New immunotherapy：** humanized monoclonal Ab anti-IgE .these Ab bind to IgE, but only if IgE is not already bound to FcERI.

Antihistamines have been the most useful drugs for symptoms of allergic rhinitis. These drugs act by binding to the histamine receptors on target cells and blocking the binding of histamine.

Several drugs block release of allergic mediators by interfering with various biochemical steps in mast-cell activation and degranulation.

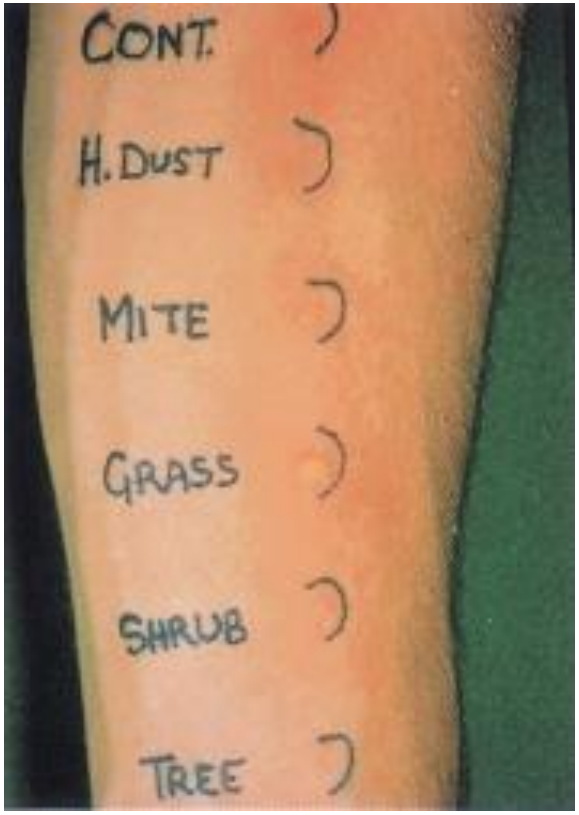
Disodium cromoglycate (cromolyn sodium) prevents Ca2+ influx into mast cells.

Theophylline, which is commonly administered to asthmatics orally or through inhalers, blocks phosphodiesterase, which catalyzes the breakdown of cAMP to 5-AMP.

The resulting prolonged increase in cAMP levels blocks degranulation

Several Methods Are Used to Detect Type I Hypersensitivity Reactions

Type I hypersensitivity is commonly identified and assessed by skin testing. Small amounts of potential allergens are introduced at specific skin sites either by intradermal injection or by superficial scratching.



Another method of assessing type I hypersensitivity is to determine the serum level of total IgE antibody by the radioimmunosorbent test **(RIST)**.

This highly sensitive technique, based on the radioimmunoassay, can detect nanomolar levels of total IgE. The patient's serum is reacted with agarose beads or paper disks coated with rabbit anti-IgE.After the beads or disks are washed, 125I-labeled rabbit anti-IgE is added The radioactivity of the beads or disks, measured with a gamma counter, is proportional to the level of IgE in the patient's serum

The similar radioallergosorbent test **(RAST)** detects the serum level of IgE specific for a given allergen. The allergen is coupled to beads or disks, the patient's serum is added, and unbound antibody is washed away. The amount of specific IgE bound to the solid-phase allergen is then measured by adding 125I-labeled rabbit anti-IgE, washing the beads, and counting the bound radioactivity

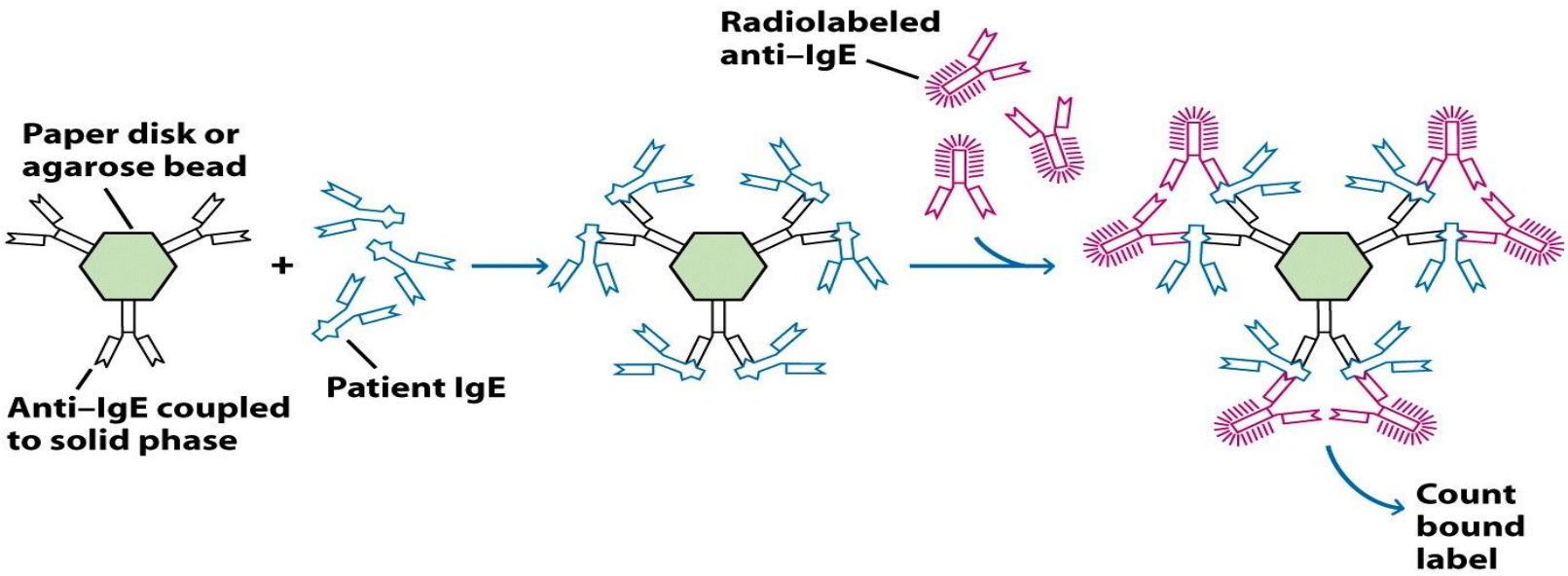


Figure 15-11a
Kuby IMMUNOLOGY, Sixth Edition

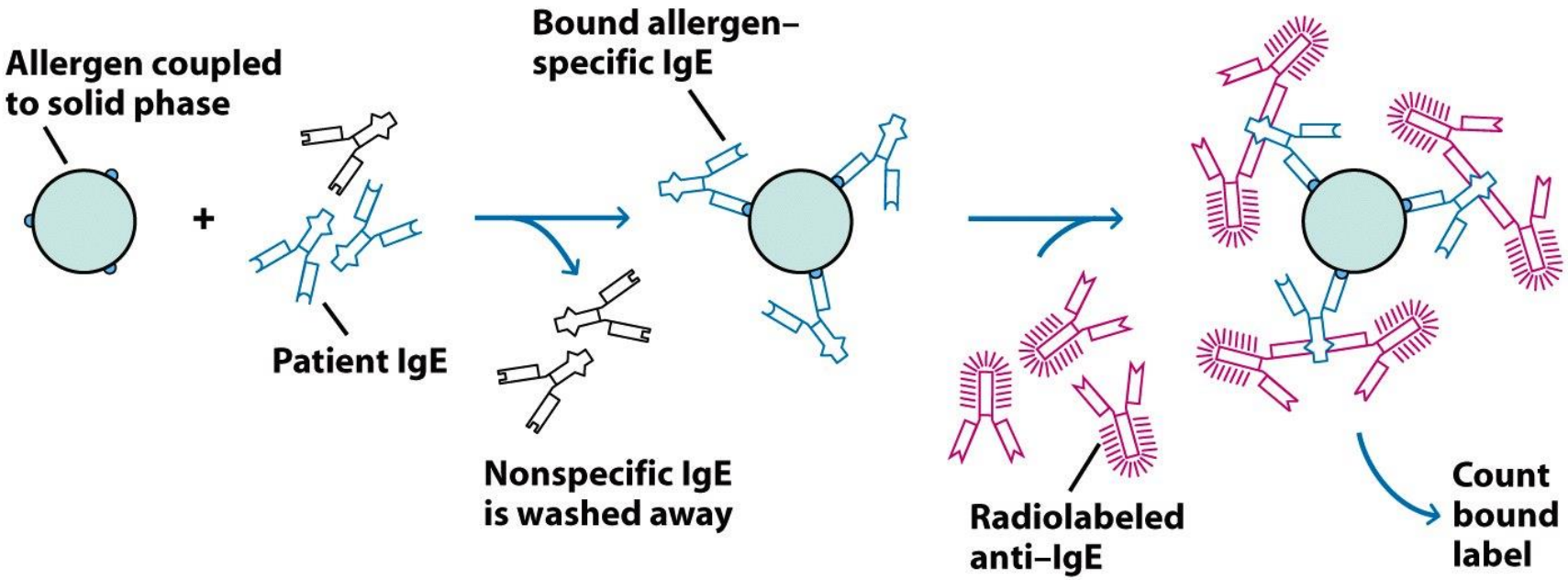


Figure 15-11b
Kuby IMMUNOLOGY, Sixth Edition

3. Type II Hypersensitivity

1. Characteristic features

2. Mechanism of Type II Hypersensitivity

3. Common diseases of Type II Hypersensitivity

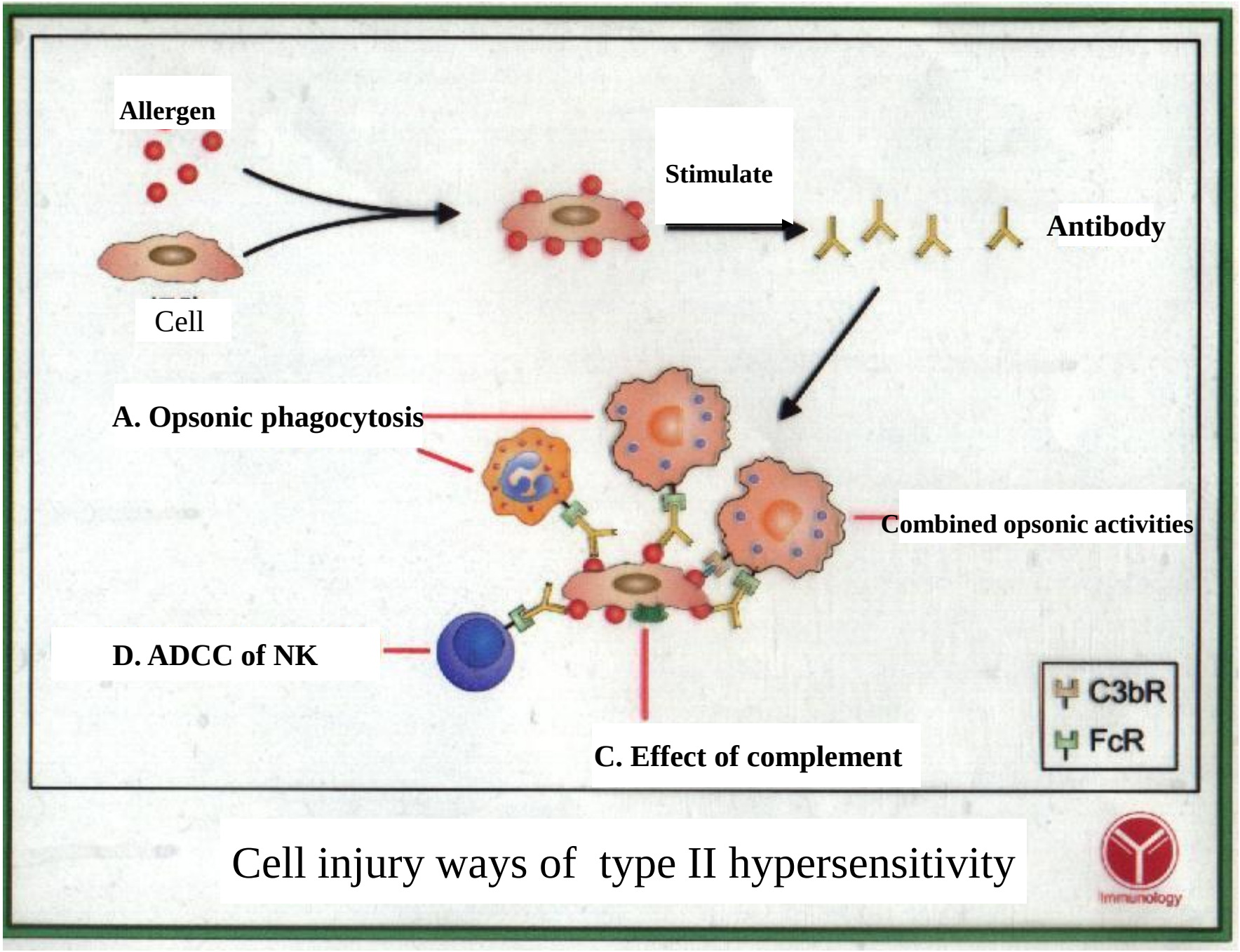
1. Characteristic features

Primed IgG or IgM + Antigen or hapten on membrane

Injury and dysfunction of target cells

Type II hypersensitive reactions involve antibody-mediated destruction of cells. Antibody can activate the complement system, creating pores in the membrane of a foreign cell , or it can mediate cell destruction by antibodydependent cell-mediated cytotoxicity (ADCC).

In this process, cytotoxic cells with Fc receptors bind to the Fc region of antibodies on target cells and promote killing of the cells Antibody bound to a foreign cell also can serve as an opsonin, enabling phagocytic cells with Fc or C3b receptors to bind and phagocytose the antibody-coated cell



Cell injury ways of type II hypersensitivity

2. Mechanism of Type II hypersentivity

1. Surface antigen on target cells

Target cells: Normal tissue cell, changed or modified self tissue cells

Antigen : Blood group antigen, Common antigen, Drug antigen,

Self-antigen modified by physical factors or infection

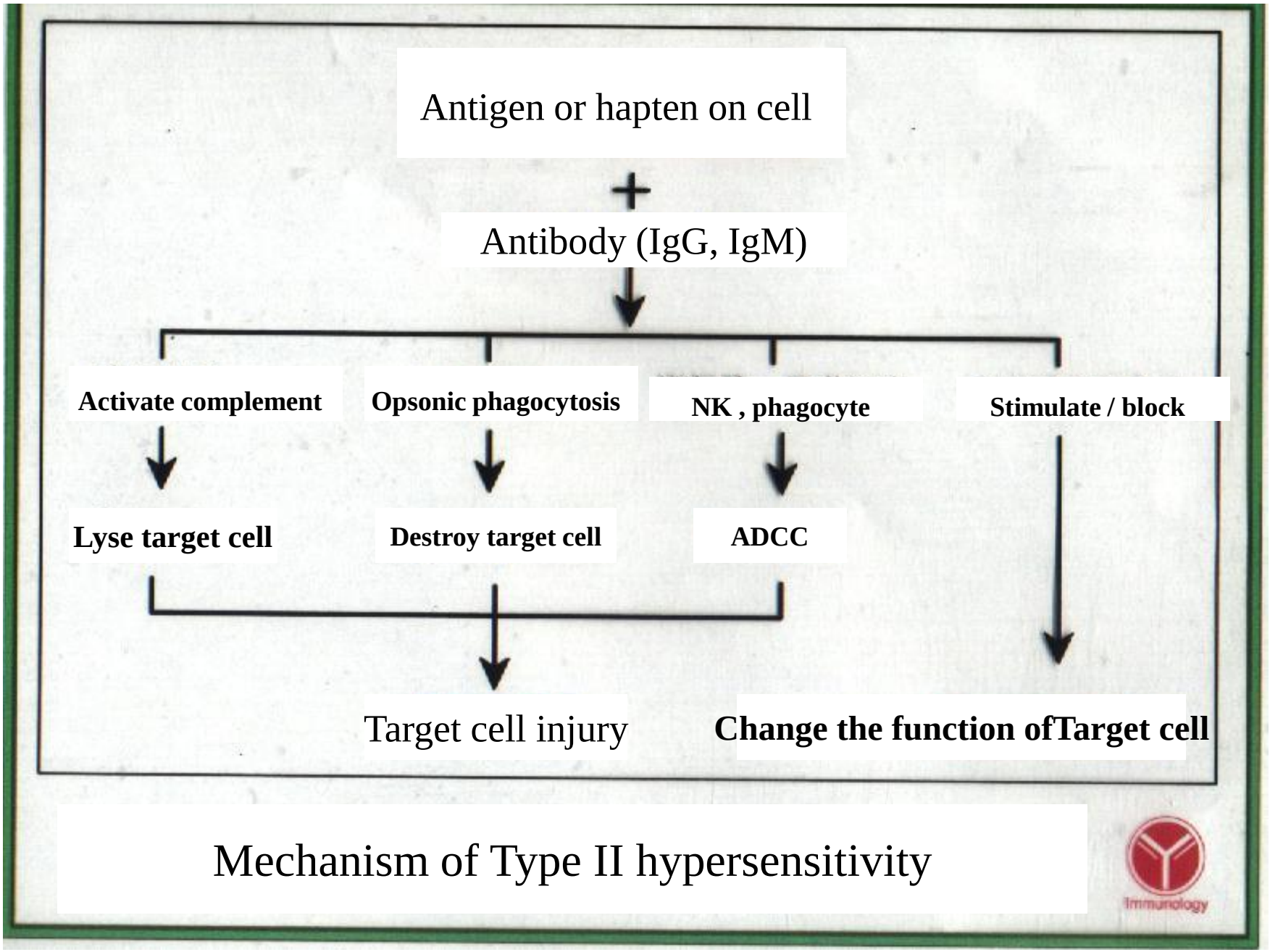
Antigen-antibody complex

2. Antibody, complement and modified self-cell

Activate complement——— Lyse target cells

Opsonic phogacytosis——— Destroy target cells

Mϕ、NK、 T ——— ADCC



Mechanism of Type II hypersensitivity

3. Common disease of type II hypersensitivity

1)Transfusion reaction

hemolysis : mismatch of ABO blood group, severely destroy RBC

2) Hemolytic disease of newborn

Mother Rh^- : first baby Rh^+(Ab), second baby Rh^+,

fetal RBC destroyed

3) Autoimmune hemolytic anemia and type II drug reaction

i. Foreign antigen or hapten

Penicillin	**RBC**	**hemolytic anemia**
Quinin	**Platlet**	**thrombocytopenic purpura**
Pyramidone	Granulocyte	agranulocytosis

ii. Self-antigen

Drug conversion from a hapten to a full antigen

induce self antibody autoimmune hemolytic anemia

4.Anti -glomerular basement membrane nephritis

β-Hemolytic streptococcus and human glomerular basement membrane ---- cross reaction

Common antigen ---nephrotoxic nephritis

5. Super acute rejection in allogenic organ transplantation

6. Goodpasture syndrome

7.Hyperthyroidism or hypothyroidism—receptor diseases

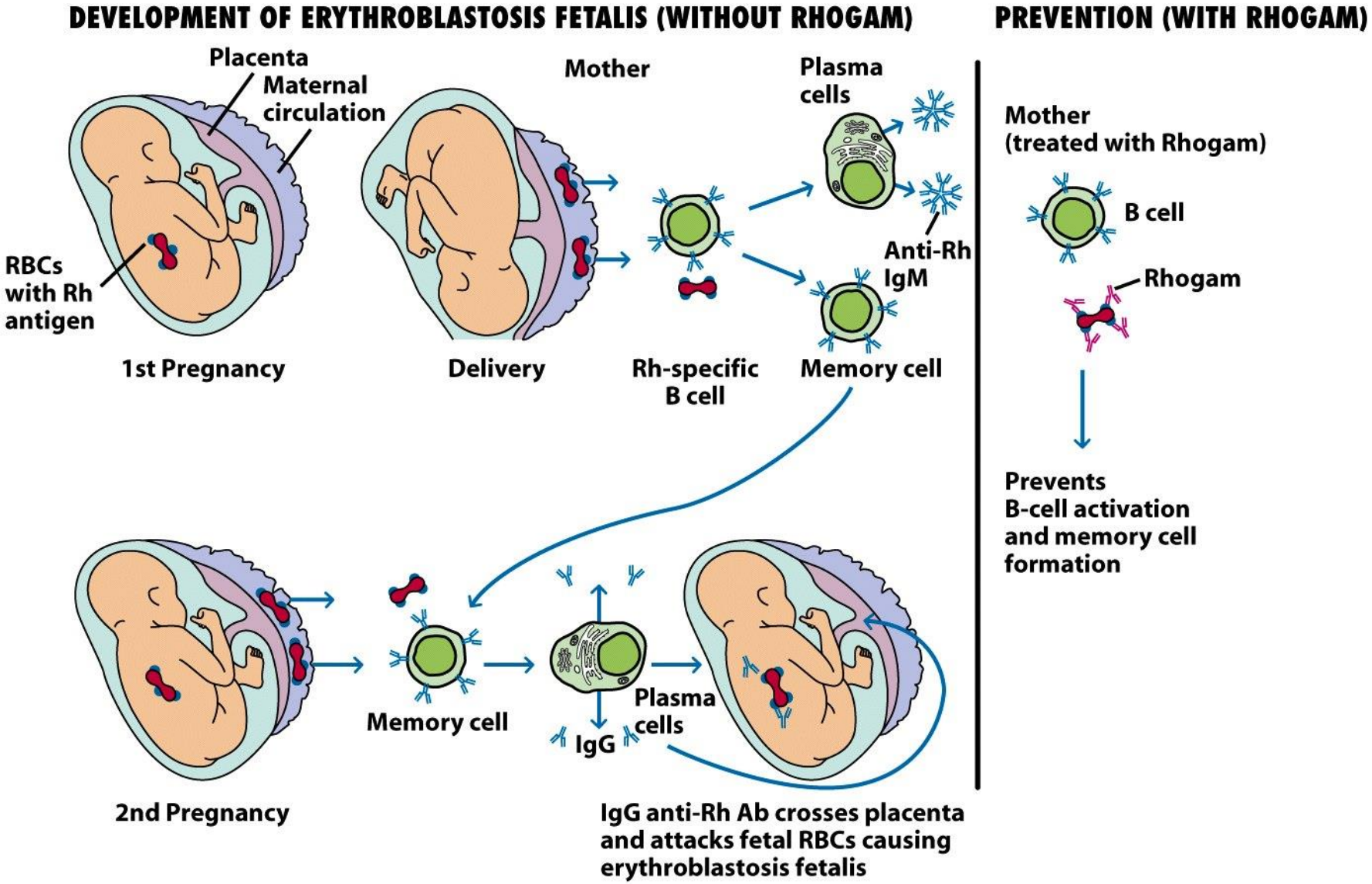


Figure 15-14
Kuby IMMUNOLOGY, Sixth Edition

4. type III hypersensitivity

1. Characteristics
2. Mechanism of type III hepersensitivity
3. Common disease of type III hepersensitivity

1、characteristics

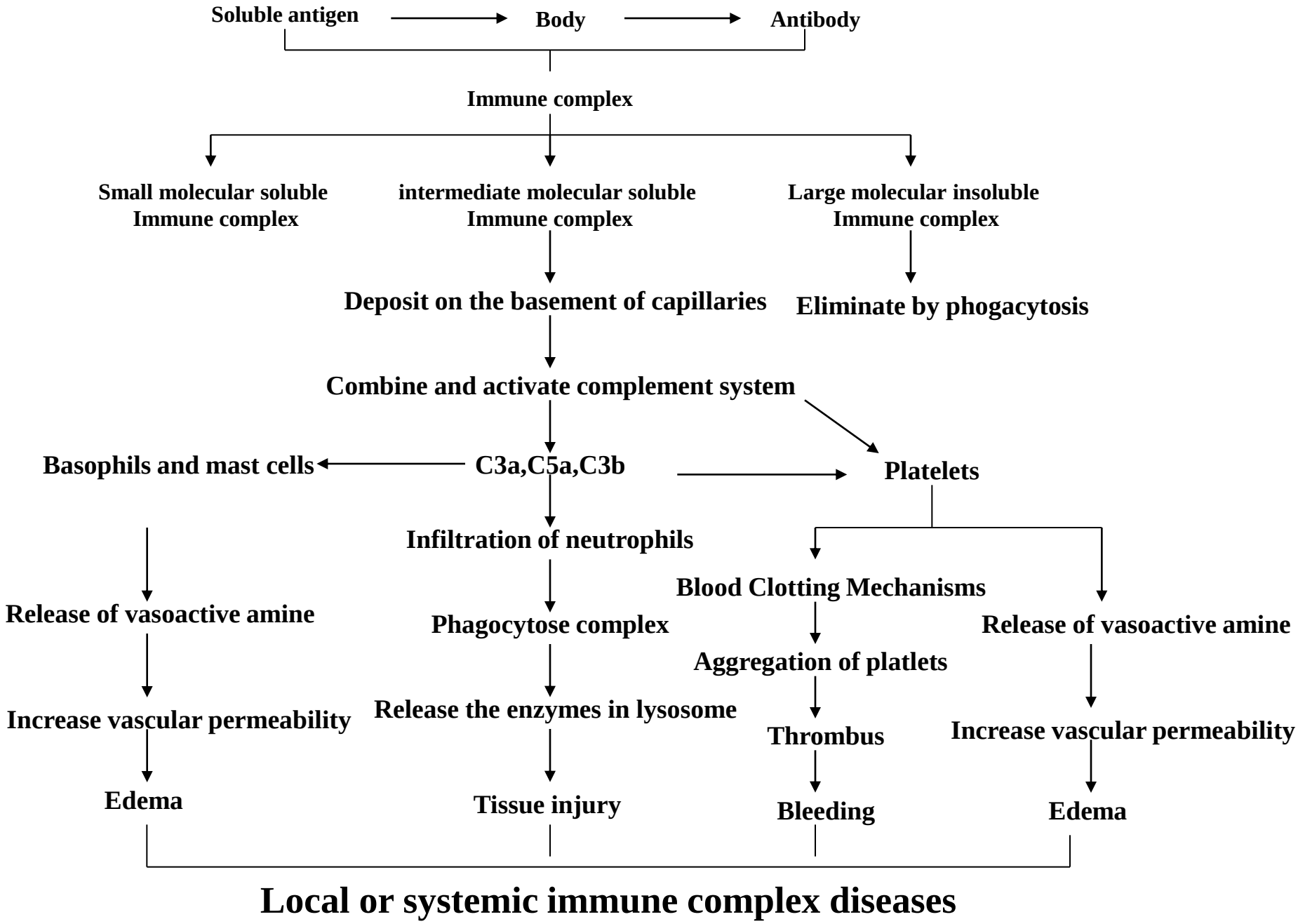
Free Ag + Primed Ab ——— Larger immune complex

Deposit in tissue or blood vessel wall

Inflammation

2、Mechanism of type III hypersensitivity

- Formation of the intermediate immune complex
- Deposition of the intermediate immune complex
- Tissue injury by the immune complex


Soluble antigen
Body
Antibody
Immune complex
Small molecular soluble Immune complex
intermediate molecular soluble Immune complex
Large molecular insoluble Immune complex
Deposit on the basement of capillaries
Eliminate by phogacytosis
Combine and activate complement system
Basophils and mast cells
C3a,C5a,C3b
Platelets
Infiltration of neutrophils
Blood Clotting Mechanisms
Release of vasoactive amine
Phagocytose complex
Release of vasoactive amine
Aggregation of platlets
Increase vascular permeability
Release the enzymes in lysosome
Thrombus
Increase vascular permeability
Edema
Tissue injury
Bleeding
Edema
Local or systemic immune complex diseases

3. common disease of type III hypersensitivity

1. Local immune complex disease

Arthus reaction： Experimental local reaction,

Necrotic vasculitis vasculitis, Ulcer

Human local reaction: insulin-dependent diabetes mellitus (IDDM)

2. Acute systemic immune complex disease

serum sickness

Anti-serum ⟶ Ab+Ag ⟶ systemic tissue injury ,fever, arthritis, skin rash

Pinicillin、Sulfanilamide

Acute immune complex glomerulonephritis : Streptococcus infection

3. Chronic immune complex disease

SLE

Rheumatoid arthritis： RF+IgG ⟶ Deposit on synovial membrane

1)The C3b complement component acts as an opsonin, coating immune complexes.
2)A neutrophil binds to a C3b-coated immune complex by means of the type I complement receptor, which is specific for C3b. Because the complex is deposited on the basement membrane surface,
3)phagocytosis is impeded, so that lytic enzymes are released during the unsuccessful attempts of the neutrophil to ingest the adhering immune complex.
Further activation of the membrane-attack mechanism of the complement system can also contribute to the destruction of tissue.
4) the activation of complement can induce aggregation of platelets, and the resulting release of clotting factors can lead to formation of microthrombi.

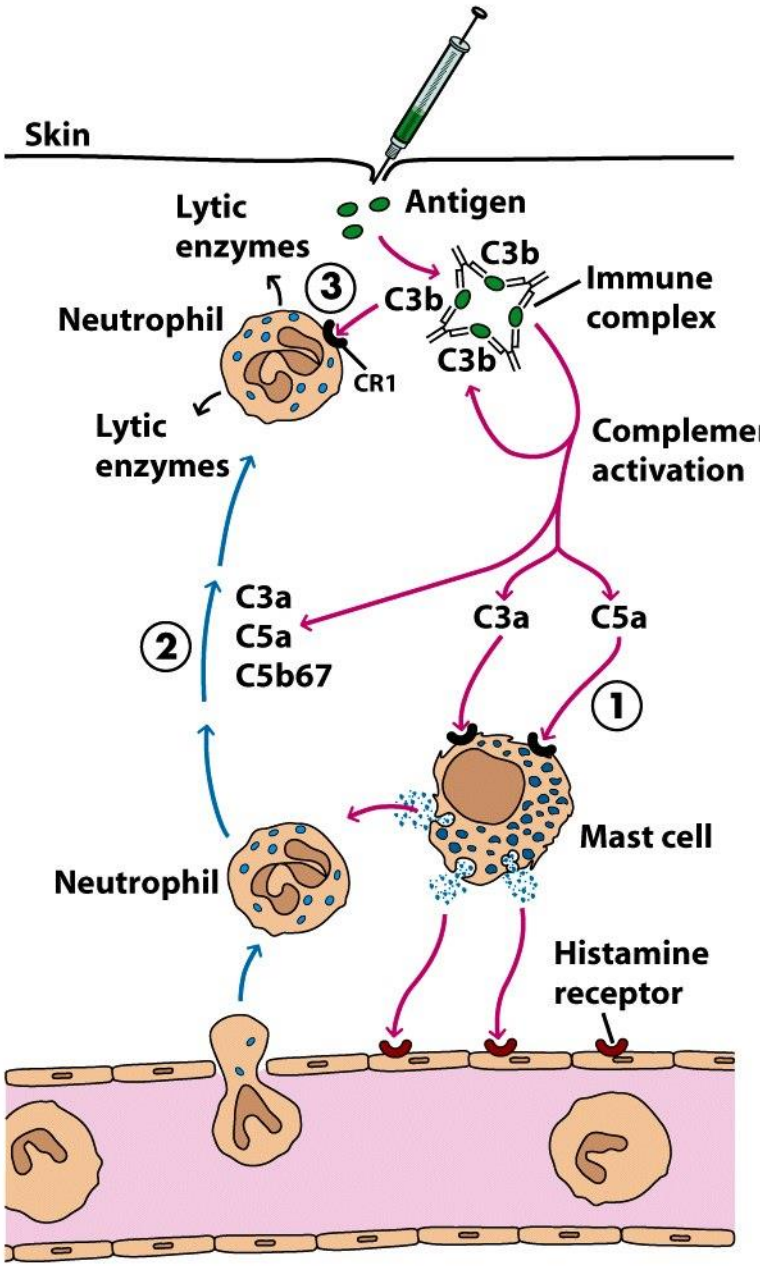


Figure 15-15
Kuby IMMUNOLOGY, Sixth Edition

1. Complement initiates mast cell degranulation
2. Neutrophils are chemotactically attracted to the site
3. Neutrophils release lytic enzyme after failed attempts to endocytose the immune complex

5. Type IV hypersensitivity

1、characteristics of type IV hepersensitivity

2、 mechanism of type IV hepersensitivity

3、common diseases of type IV hepersensitivity

1. Characteristics

Interaction of primed T cells and associated antigen

Infiltration of Mononuclear Cells, Inflammatory response

2. Mechanism of type IV hypersensitivity

Formation of effector and memory T cells

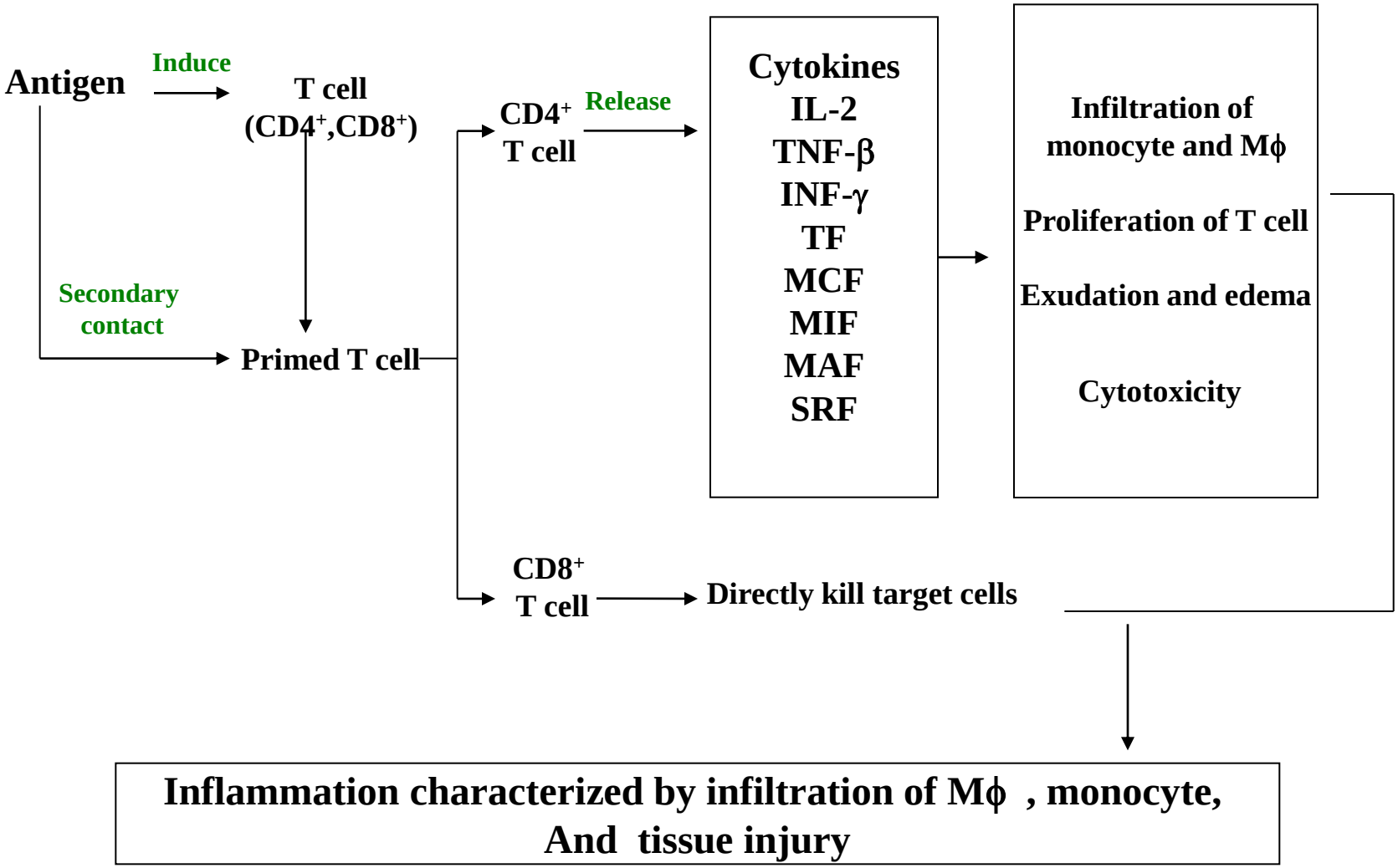
Inflammation and cytotoxicity caused by effector T cells

1) **Inflammation and tissue injury mediated by CD4+Th1**

Release chemokines and cytokines

Immune injury mainly caused by infiltration of mononuclear cells and lymphocytes

2) **Cytotoxicity** of **CD8+CTL**



Mechanism of type IV hypersensitivity

TABLE 15-6 Intracellular pathogens and contact antigens that induce delayed-type (type IV) hypersensitivity

Intracellular bacteria
- *Mycobacterium tuberculosis*
- *Mycobacterium leprae*
- *Listeria monocytogenes*
- *Brucella abortus*

Intracellular fungi
- *Pneumocystis carinii*
- *Candida albicans*
- *Histoplasma capsulatum*
- *Cryptococcus neoformans*

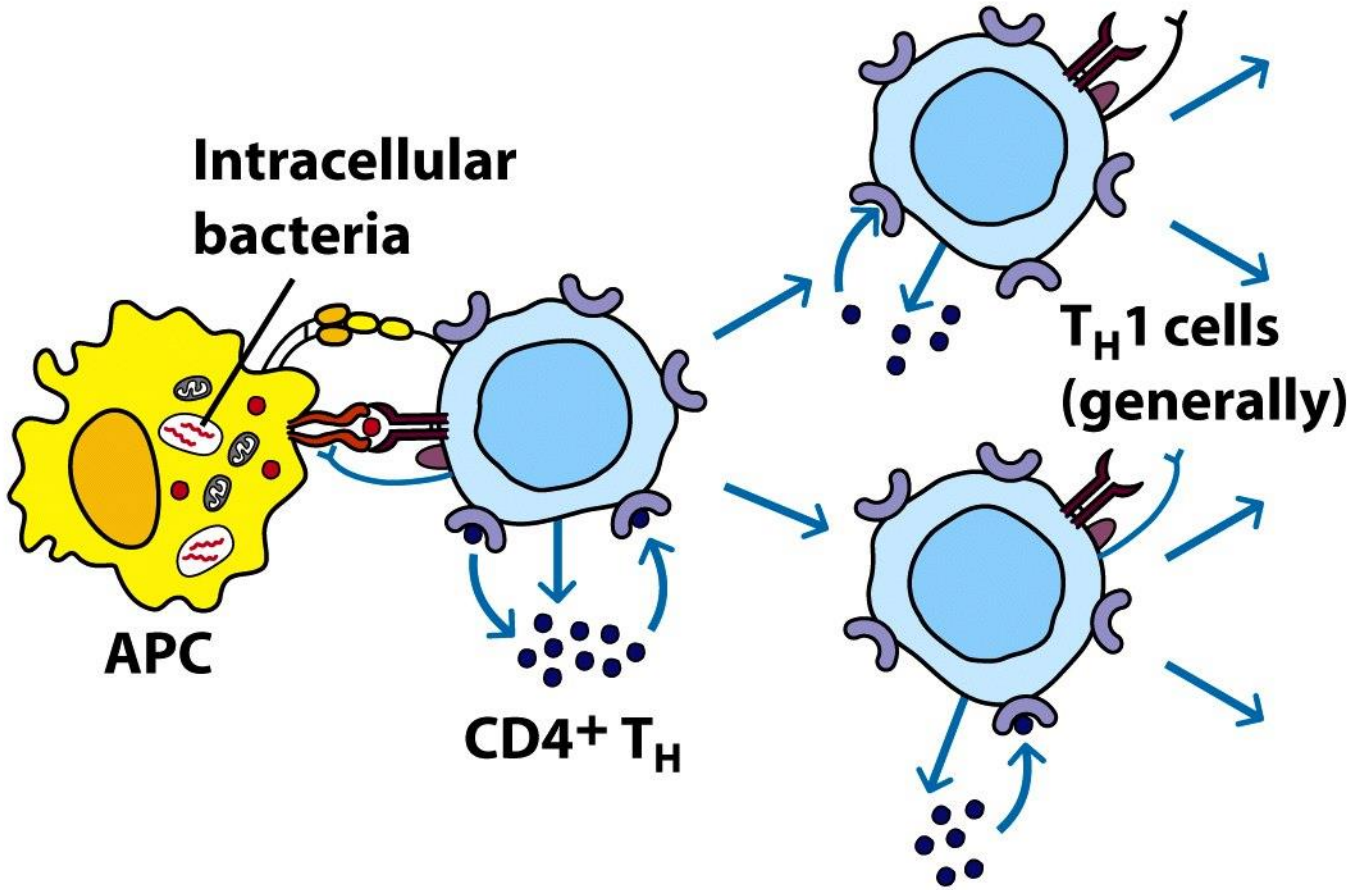
Intracellular parasites
- *Leishmania* sp.

Intracellular viruses
- Herpes simplex virus
- Variola (smallpox)
- Measles virus

Contact antigens
- Picrylchloride
- Hair dyes
- Nickel salts
- Poison ivy
- Poison oak

Table 15-6
Kuby IMMUNOLOGY, Sixth Edition

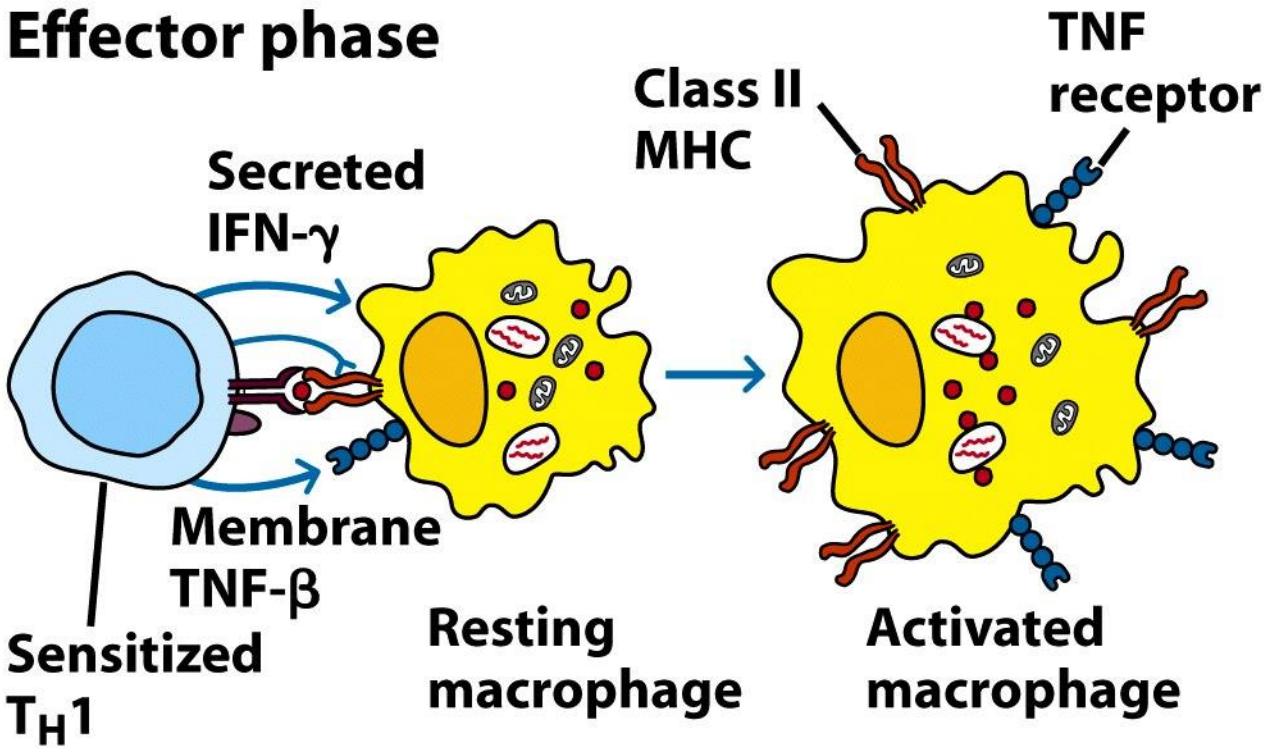
Sensitization phase



Antigen-presenting cells: Macrophages Langerhans cells

DTH-mediating cells: T_H1 cells generally CD8 cells occasionally

Figure 15-17a
Kuby IMMUNOLOGY, Sixth Edition



T_H1 secretions:

Cytokines: IFN-γ, TNF-β, IL-2, IL-3, GM-CSF, MIF

Chemokines: IL-8/CXCL8, MCP-1/CCL2

Effects of macrophage activation:

- ↑ Class II MHC molecules
- ↑ TNF receptors
- ↑ Oxygen radicals
- ↑ Nitric oxide

Figure 15-17b
Kuby IMMUNOLOGY, Sixth Edition

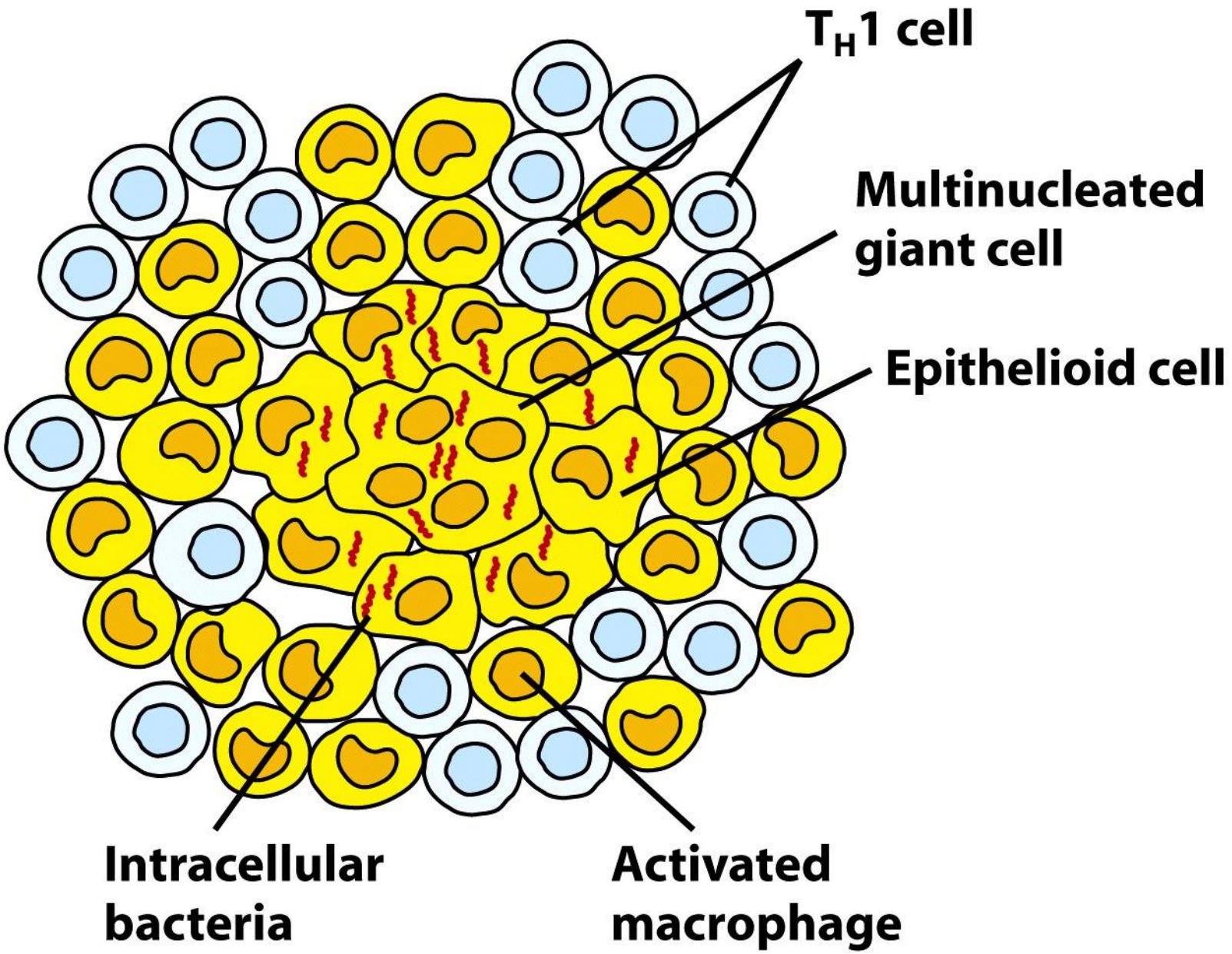


Figure 15-18
Kuby IMMUNOLOGY, Sixth Edition

3. Common disease of type IV hypersensitivity

1) Infectious delayed type hypersensitivity

OT(Old Tuberculin) test

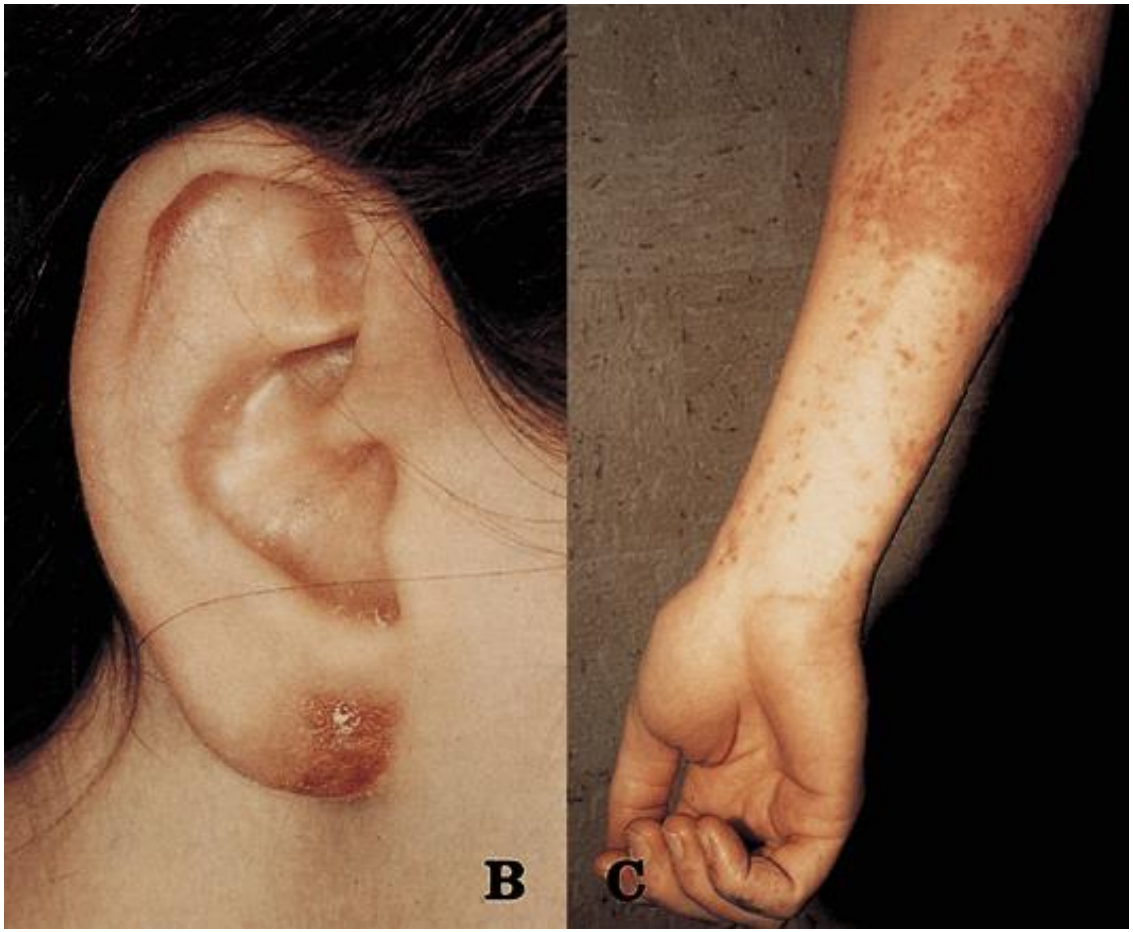
2) Contact dermatitis :

Paint, drug red rash, papula, water blister, dermatitis

3) Acute rejection of allogenic transplantation and immune response in local tumor mass

Same disease (SLE), multiple immune injury ,hypersensitivity involved

Same drug (penicillin), several types of hypersensitivity



Contact Dermatitis

Maybe due to either T_H1 or CTL mediated hypersensitivity

Many contact-dermatitis reactions, including the responses to formaldehyde, trinitrophenol, nickel, turpentine, and active agents in various cosmetics and hair dyes, poison oak, and poison ivy, are mediated by TH1 cells.

This complex is internalized by antigen-presenting cells in the skin (e.g., Langerhans cells), then processed and presented together with class II MHC molecules, causing activation of sensitized TH1 cells.

In the reaction to poison oak, for example, a pentadecacatechol compound from the leaves of the plant forms a complex with skin proteins.

When TH cells react with this compound appropriately displayed by local antigen-presenting cells, they differentiate into sensitized TH1 cells.

A subsequent exposure to pentadecacatechol will elicit activation of TH1 cells and induce cytokine productionApproximately 48–72 h after the second exposure, the secreted cytokines cause macrophages to accumulate at the site.

Activation of these macrophages and release of lytic enzymes result in the redness and pustules that characterize a reaction to poison oak.

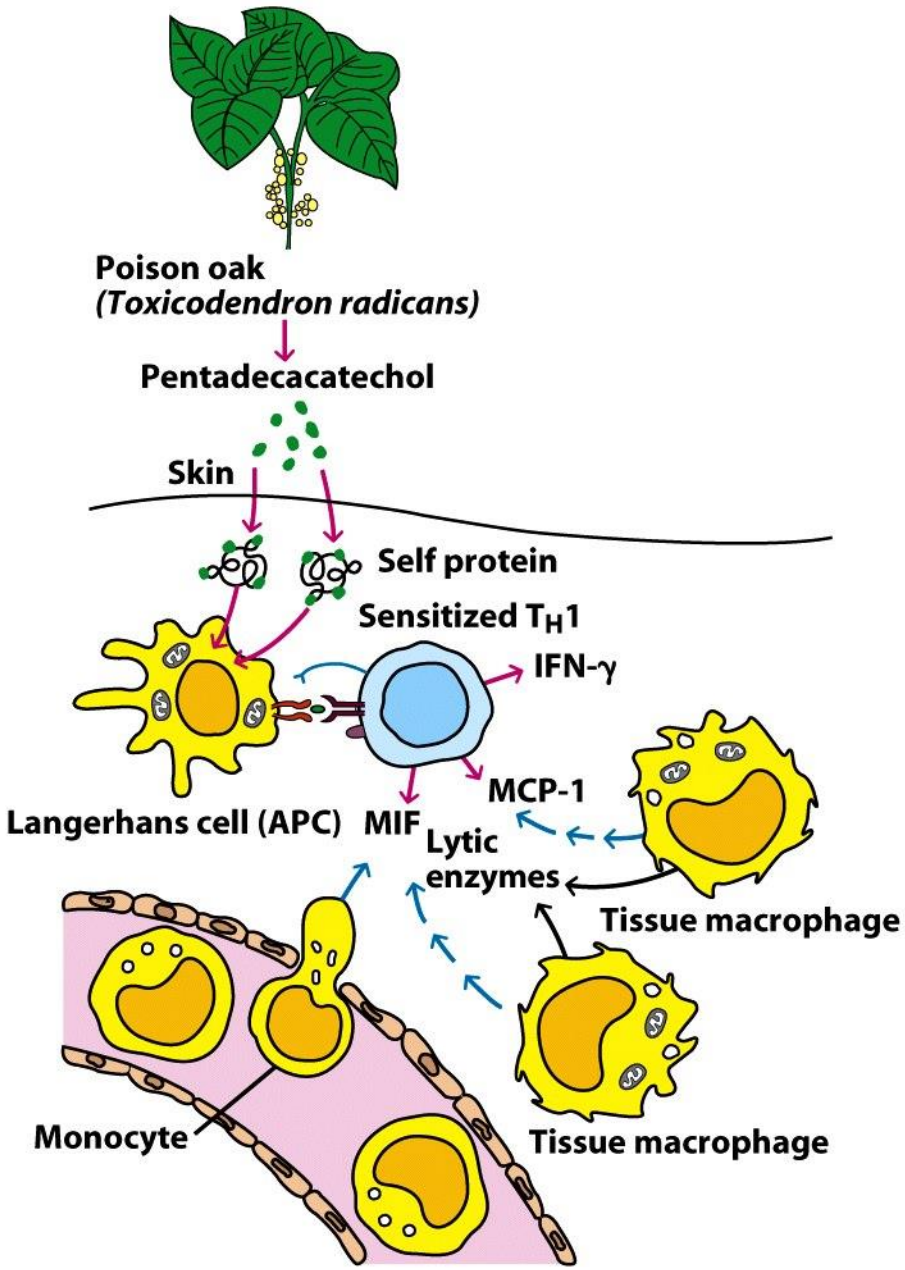


Figure 15-20
Kuby IMMUNOLOGY, Sixth Edition