

IMMUNE BASIS OF ALLERGIC DISEASES

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IMMUNOLOGY (V19)

INTEGRATED ACADEMIC STUDIES OF PHARMACY



Hypersensitivity reactions

- **pathological immune reactions** - excessive or inappropriate immune response
- the basic characteristic of hypersensitivity reactions is that they do not correspond to the causative agent that caused them by the type of cells and molecules involved in pathogenesis, or by **intensity** (**hypersensitivity reactions**)
- can occur in two cases:
 - the immune response to foreign antigens can be impaired (**qualitatively inadequate**) or uncontrolled (**quantitatively altered**), resulting in tissue damage
 - the immune response can be directed towards one's own antigens - **autoimmunity**

Hypersensitivity reactions

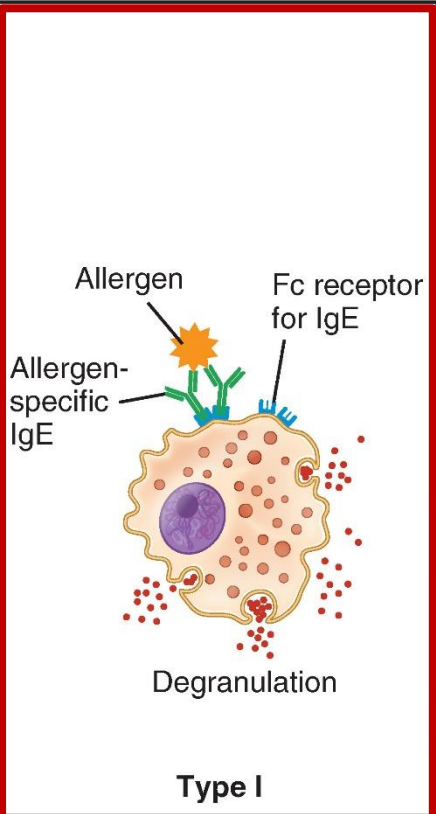
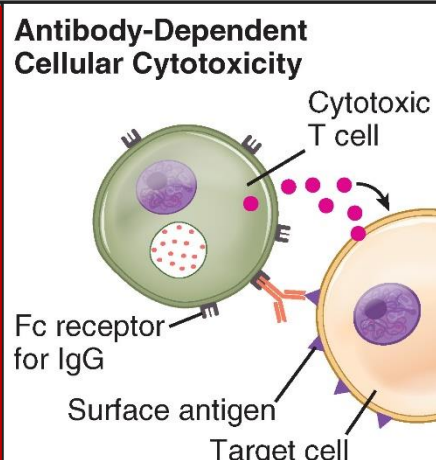
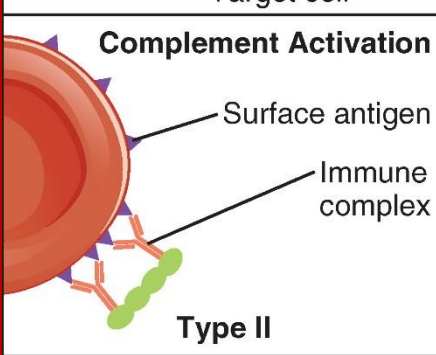
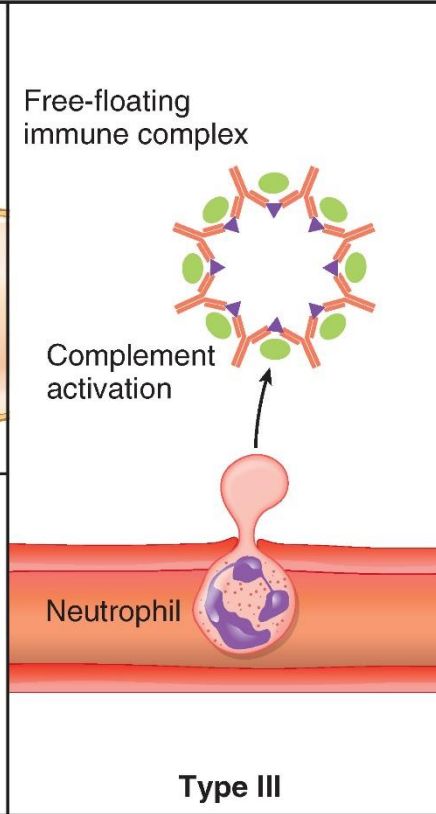
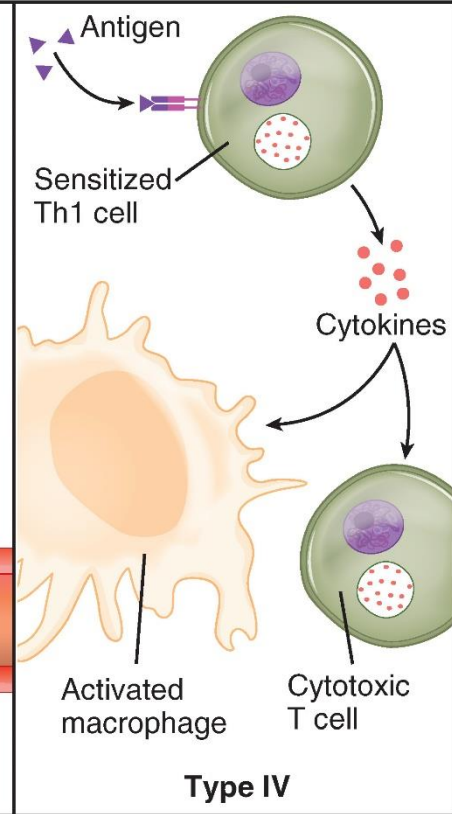
According to the time required for the reaction to occur from contact with the antigen: **early** and **late**

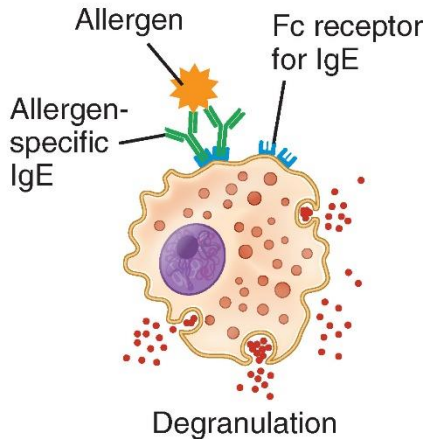
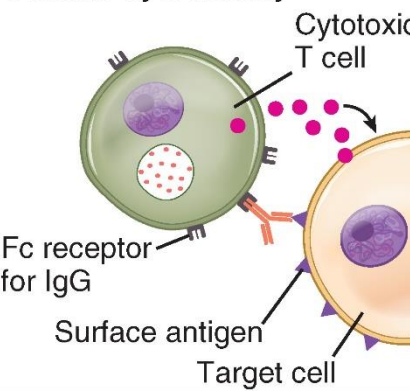
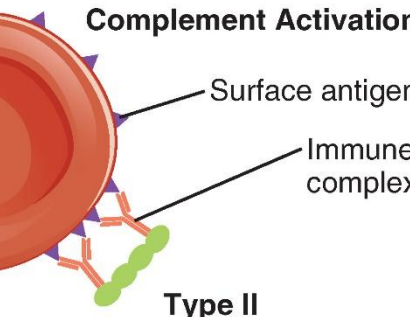
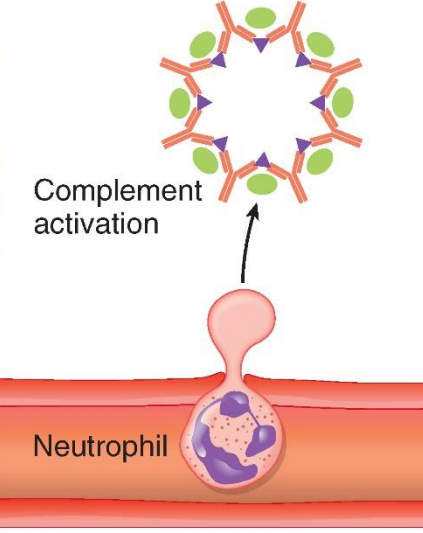
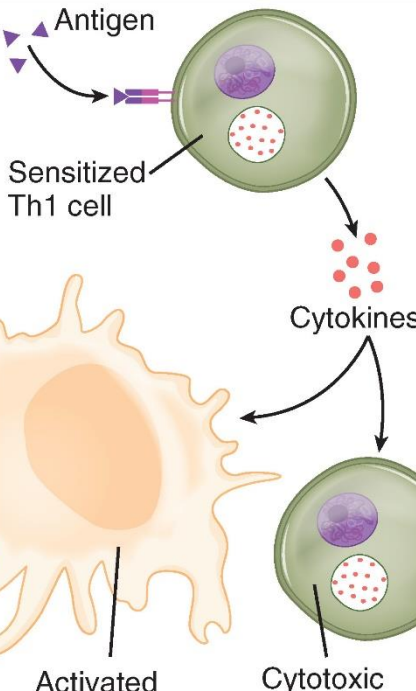
According to the pathogenesis of immune damage:

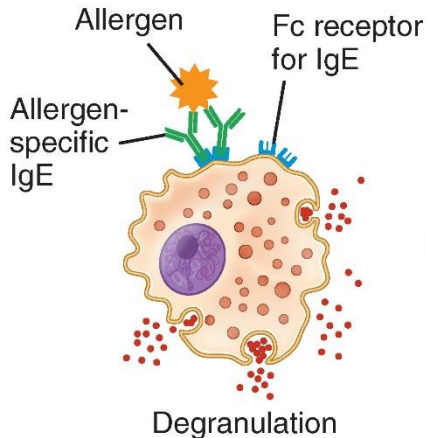
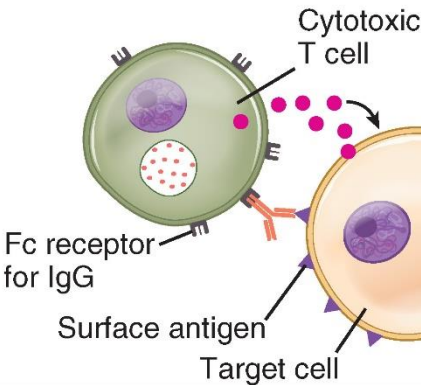
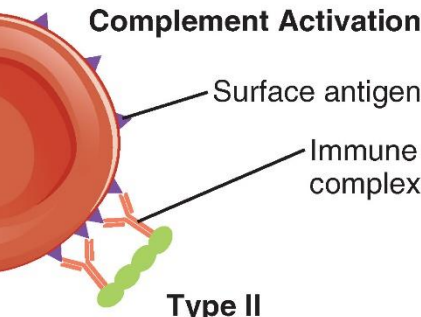
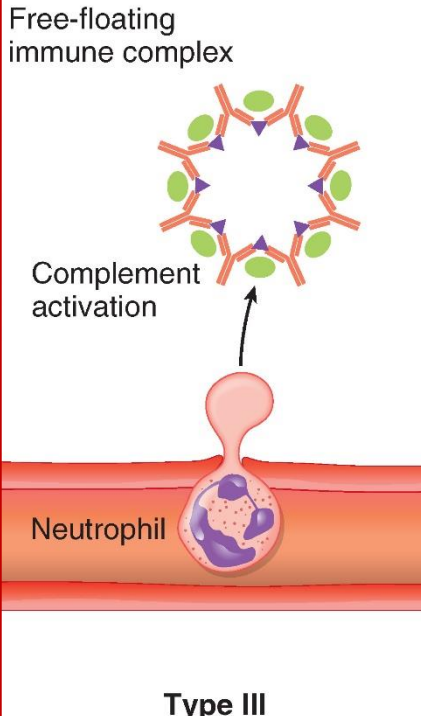
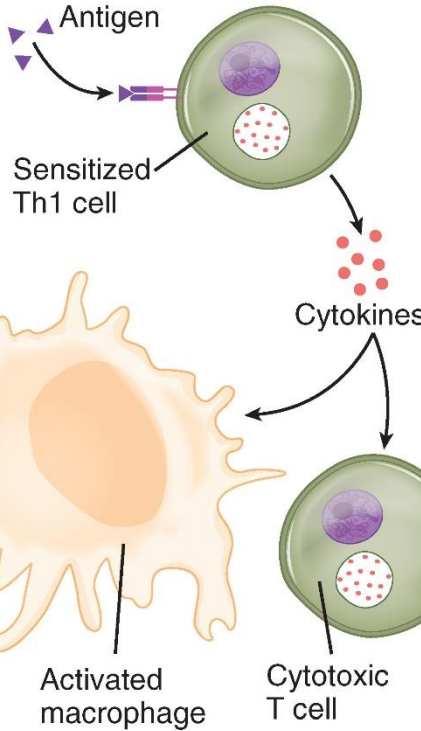
- **Type I hypersensitivity** (early hypersensitivity, anaphylactic type)
- **Type II hypersensitivity** (cytotoxic type)
- **Type III hypersensitivity** (immunocomplex type)
- **Type IV hypersensitivity** (late type, T cell-mediated hypersensitivity)

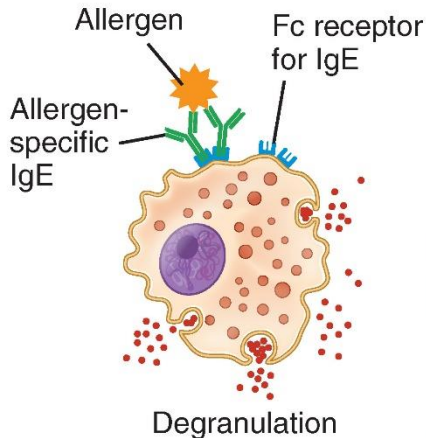
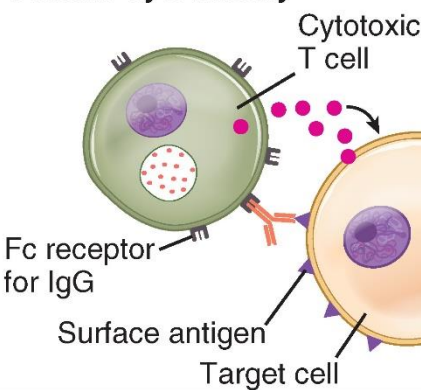
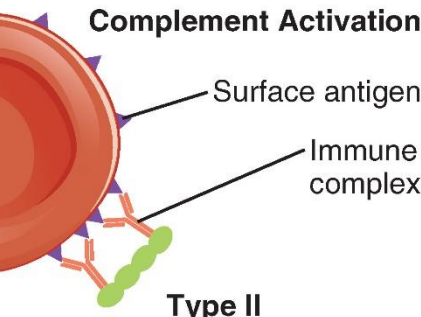
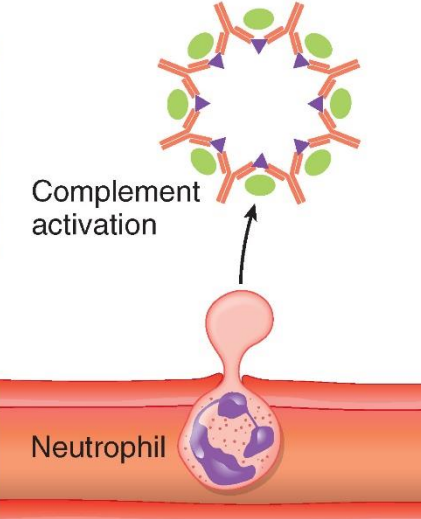
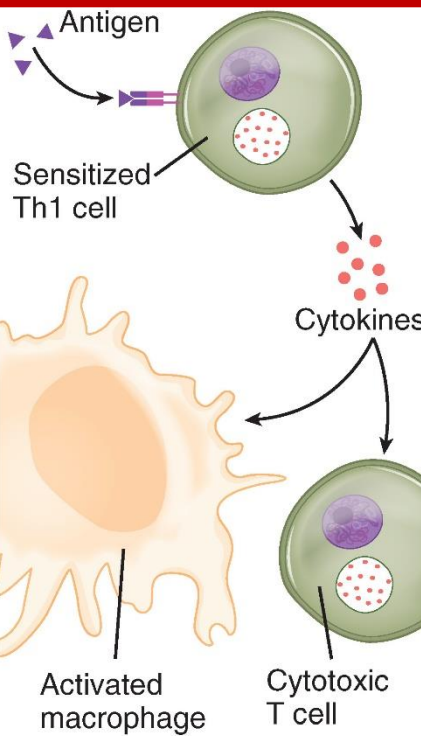
Hypersensitivity reactions

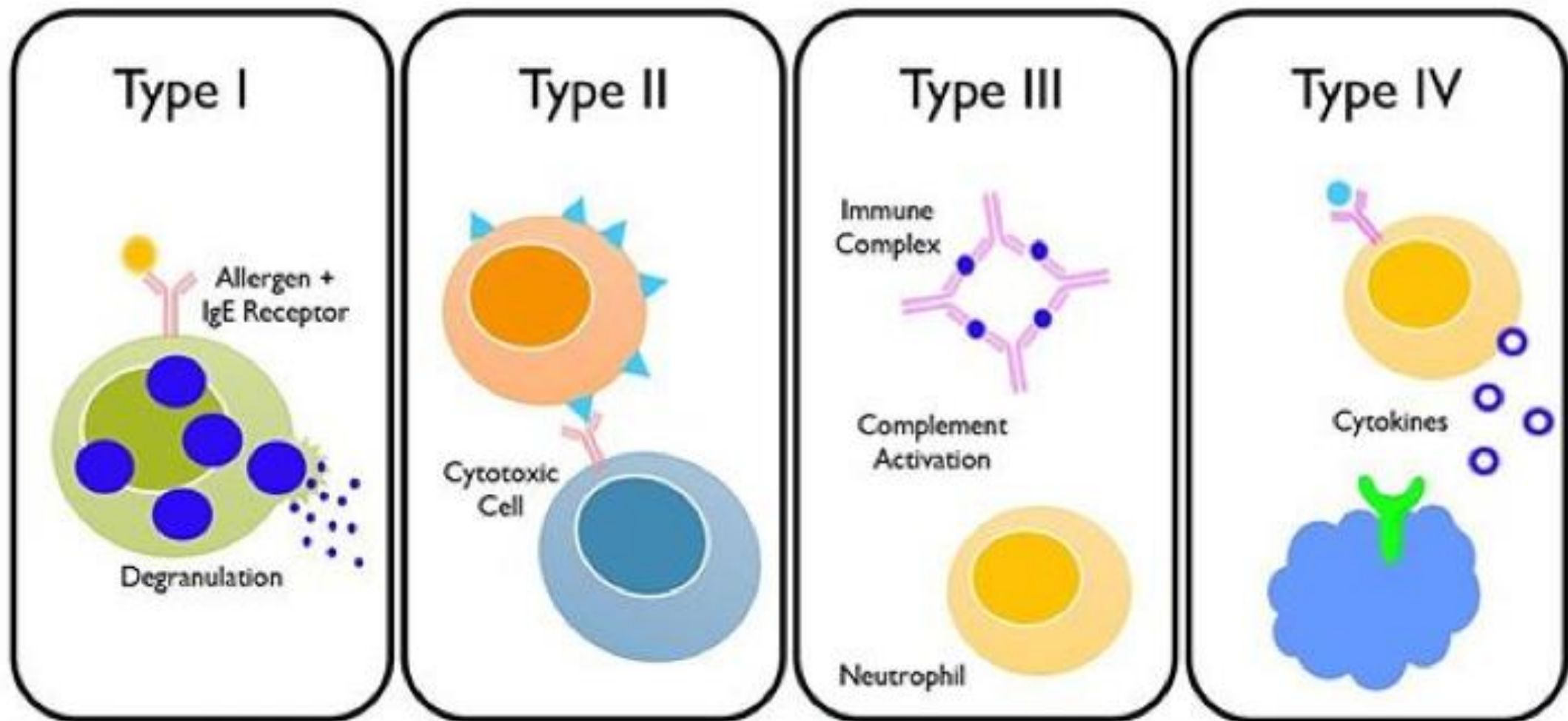
- The first type of hypersensitivity is characterized by the creation of allergen-specific antibodies of the IgE class and the binding of these antibodies to the membrane of mast cells and basophilic leukocytes.
- The second type of hypersensitivity is characterized by the binding of IgG and IgM class antibodies to antigens on the membrane of one's own cells
- The third type of hypersensitivity develops when the formed immune complexes are deposited and cause the activation of the complement system and the accumulation of neutrophil leukocytes.
- The fourth type of hypersensitivity is the only form of hypersensitivity that is not mediated by antibodies, but by antigen-specific T cells

 <p>Type I</p>	<p>Antibody-Dependent Cellular Cytotoxicity</p>  <p>Complement Activation</p>  <p>Type II</p>	<p>Free-floating immune complex</p>  <p>Type III</p>	 <p>Type IV</p>
<p>IgE-Mediated Hypersensitivity</p>	<p>IgG-Mediated Cytotoxic Hypersensitivity</p>	<p>Immune Complex-Mediated Hypersensitivity</p>	<p>Cell-Mediated Hypersensitivity</p>
<p>IgE is bound to mast cells via its Fc portion. When an allergen binds to these antibodies, crosslinking of IgE induces degranulation.</p>	<p>Cells are destroyed by bound antibody, either by activation of complement or by a cytotoxic T cell with an Fc receptor for the antibody (ADCC)</p>	<p>Antigen–antibody complexes are deposited in tissues, causing activation of complement, which attracts neutrophils to the site</p>	<p>Th1 cells secrete cytokines, which activate macrophages and cytotoxic T cells and can cause macrophage accumulation at the site</p>
<p>Causes localized and systemic anaphylaxis, seasonal allergies including hay fever, food allergies such as those to shellfish and peanuts, hives, and eczema</p>	<p>Red blood cells destroyed by complement and antibody during a transfusion of mismatched blood type or during erythroblastosis fetalis</p>	<p>Most common forms of immune complex disease are seen in glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus</p>	<p>Most common forms are contact dermatitis, tuberculin reaction, autoimmune diseases such as diabetes mellitus type I, multiple sclerosis, and rheumatoid arthritis</p>

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Type of hypersensitive reactions

Type I of hypersensitivity

- Allergic reactions of type I hypersensitivity are also called **anaphylactic reactions** (*anaphylaxis*), in contrast to protective reactions or prophylaxis (*prophylaxis*)
- genetic and environmental factors contribute to **early** hypersensitivity reactions

Genetic factors

- polygenetic heritage
- familial tendency to the occurrence of type I hypersensitivity reactions is called **atopy**, and people prone to the occurrence of type I hypersensitivity are called **atopies**
- atopic patients react atypically to common allergens by activating **Th2 lymphocytes**, which results in excessive production of **IgE antibodies**

Etiology – genetic factors

Chromosome	Gene	The potential role of gene products in disease
5q	Cytokine group genes (IL-3, IL-4, IL-5, IL-13, GM-CSF), CD14 gene, β 2-adrenergic receptor gene	IL-4 and IL-13 stimulate the synthesis of IgE, and IL-5 stimulates the proliferation and activation of eosinophils; CD14 is a component of the LPS receptor that, interacting with TLR4, can influence the balance between Th1 vs. Th2 response to antigen; The β 2-adrenergic receptor regulates the contraction of bronchial smooth muscles
6p	MHC class II gene	Неки алели могу да регулишу Т-ћелијски одговор на алергене
11q	β chain Fc ϵ RI	It participates in the activation of mast cells
16	IL-4 receptor α chain gene	Receptor subunit for both IL-4 and IL-13
20p	ADAM33	A metalloproteinase involved in airway remodeling
2q	DPP10	Peptidases that can regulate the action of chemokines and cytokines

Etiology – environment factors

ALLERGENS are antigens that cause allergic reactions in genetically predisposed individuals

Characteristics of allergens:

- proteins and glycoproteins
- enzymatic activity
- very soluble
- stable
- low molecular weight
- low concentrations in the environment

TABLE 15-1		Common allergens associated with type I hypersensitivity	
Proteins		Foods	
Foreign serum		Nuts	
Vaccines		Seafood	
		Eggs	
Plant pollens		Peas, beans	
Rye grass		Milk	
Ragweed			
Timothy grass		Insect products	
Birch trees		Bee venom	
		Wasp venom	
Drugs		Ant venom	
Penicillin		Cockroach calyx	
Sulfonamides		Dust mites	
Local anesthetics			
Salicylates		Mold spores	
		Animal hair and dander	
		Latex	

Allergens

The most common allergens are:

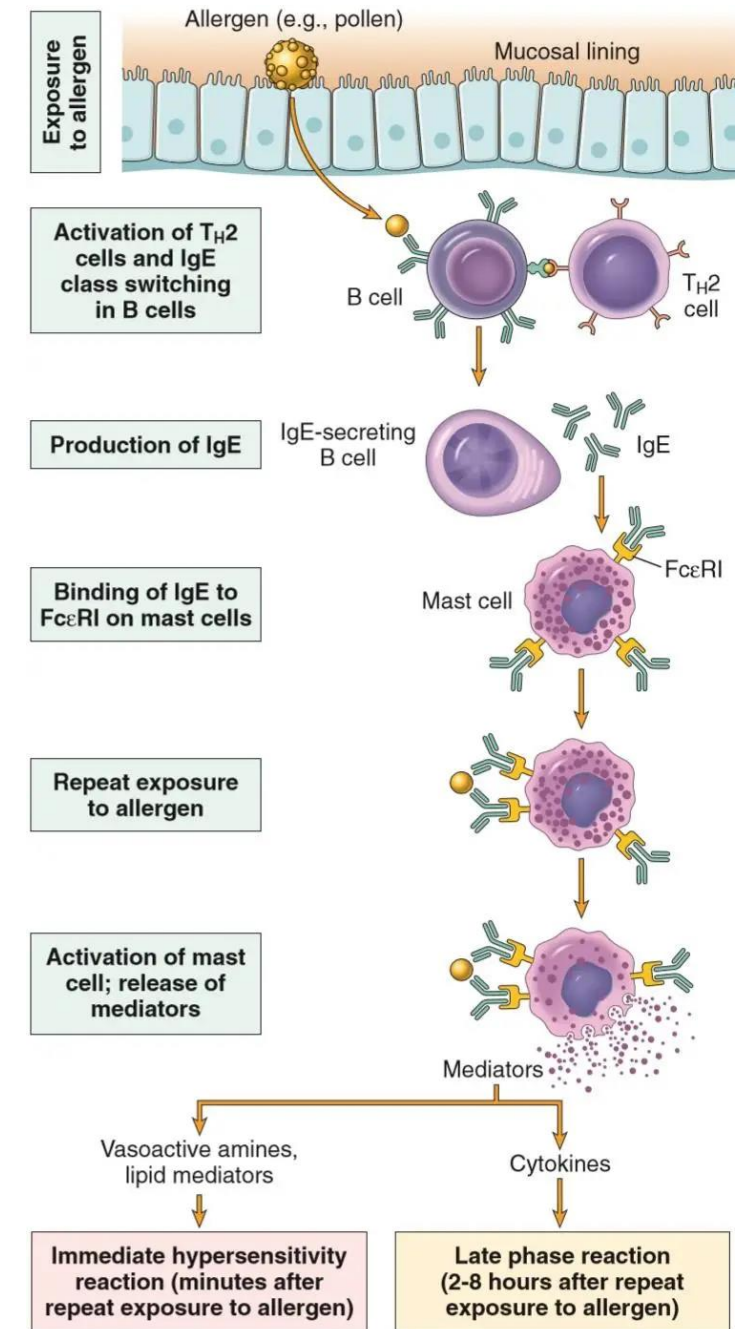
- pollen
- mites
- dust
- pet hair
- drugs
- insect products
- nutritional allergens (peanuts, nuts, milk, eggs, soy, fish, seafood, sesame...)



I type hypersensitive reactions

- pathogenesis -

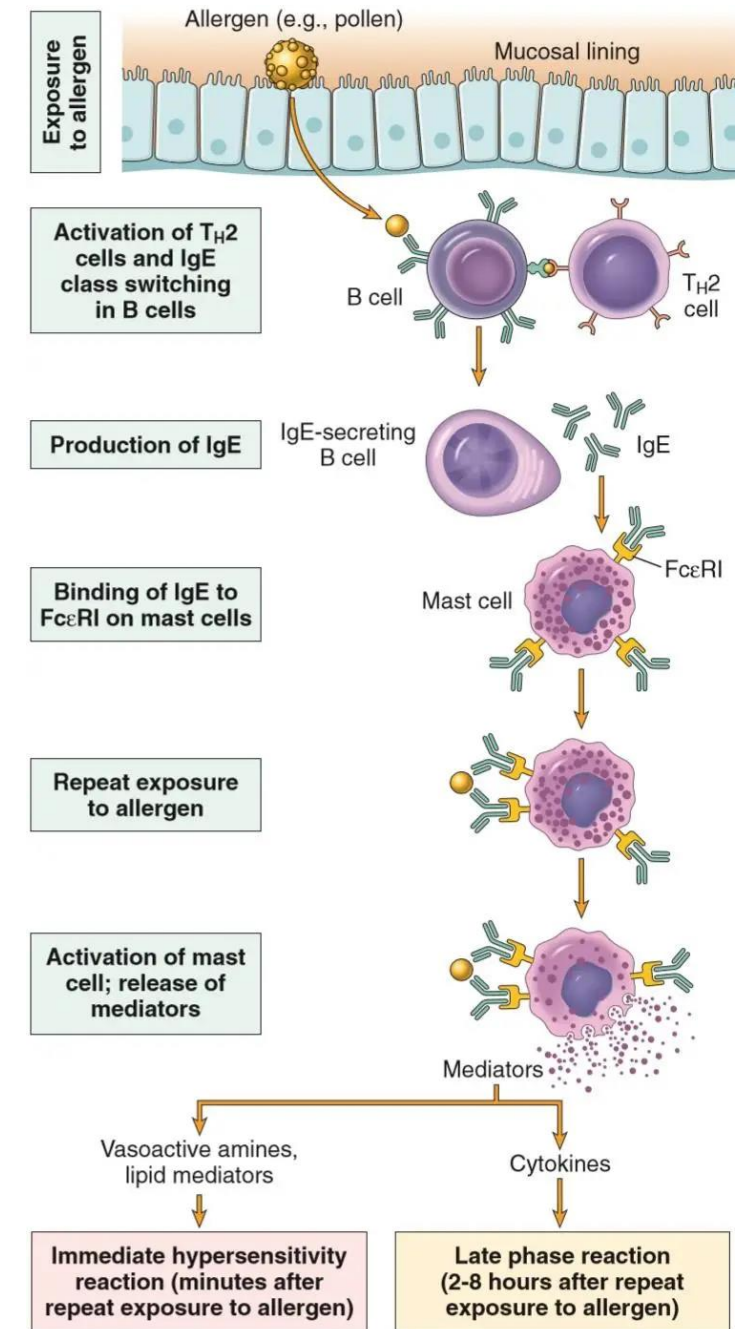
- during the first contact with an **allergen**, a specific clone of **B lymphocytes** is activated, which begins the synthesis of **IgE class** antibodies
- the production of IgE antibodies depends on the activation of T lymphocytes specific for allergen epitopes
- one part of the synthesized IgE antibodies immediately binds to **high-affinity receptors on the mast cell membrane (FcεRI)**, while the other part in circulation binds to identical receptors on **basophilic leukocytes**

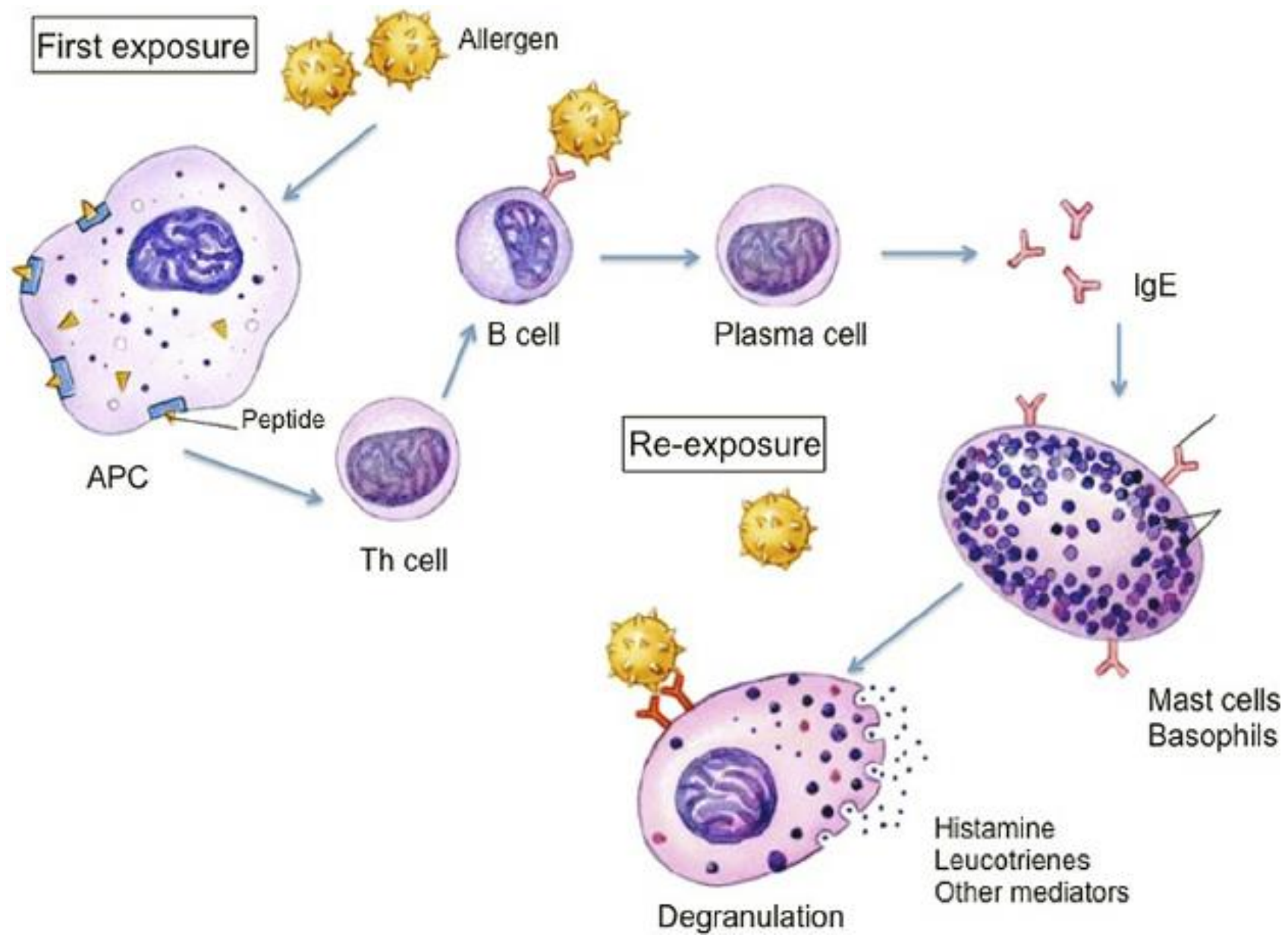


I type hypersensitive reactions

- pathogenesis -

- upon **re-exposure** (another contact), the allergen binds to antibodies on the membrane of mast cells and basophilic leukocytes and occurs:
 - **degranulation** of previously formed mediators from granules
 - **activation of enzymes** that synthesize lipid mediators (cyclooxygenase and lipoxygenase) and
 - transcription, translation and secretion of **cytokines**





The role of IgE antibodies in early hypersensitivity

- **FcεRI** receptor on the membrane of **mast cells** and **basophils**
- activation of mast cells with degranulation of previously formed and synthesis of new mediators begins after binding of allergens to IgE antibodies on the mast cell membrane

FcεRI: High-affinity IgE receptor

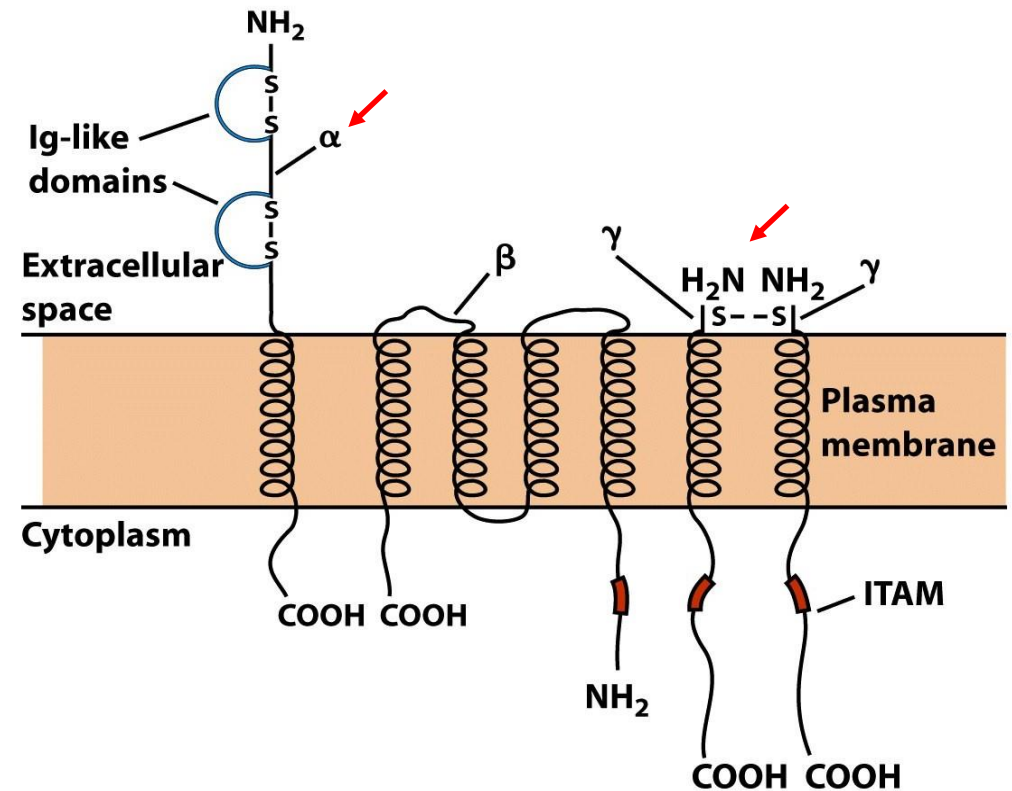


Figure 15-4a
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The role of IgE antibodies in early hypersensitivity

- during the first contact with the allergen, IgE binds (CH3 domain) to high-affinity receptors on the mast cell membrane (FcεRI)
- the amount of IgE in the serum is very small, it is found in traces (0.0003 mg/ml)

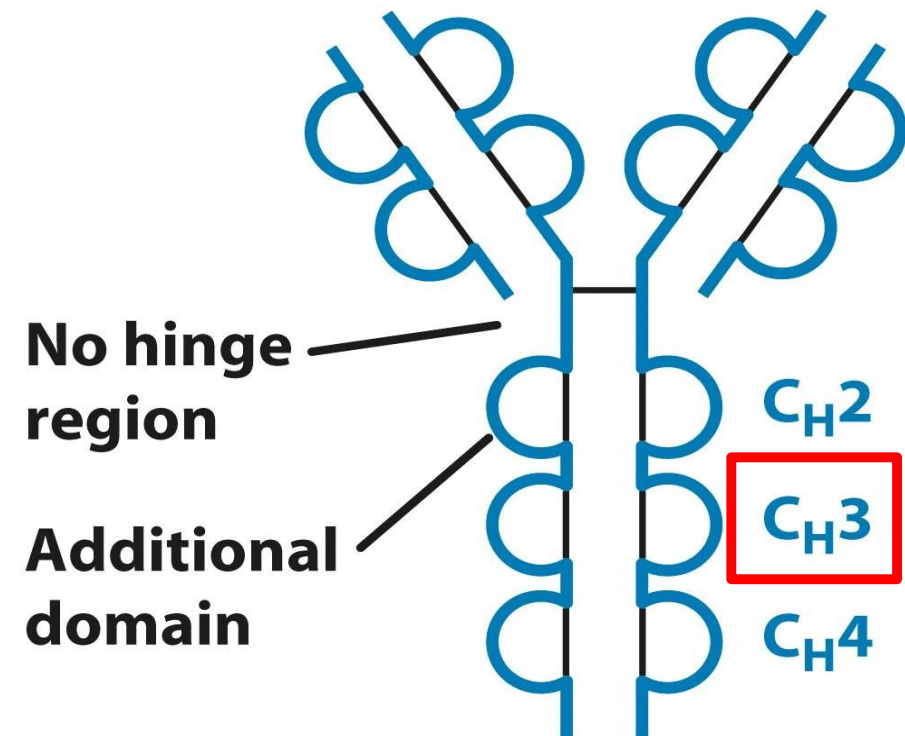


Figure 4-10b
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The role of IgE antibodies in early hypersensitivity

- upon re-contact, there is bridging of IgE antibodies attached to the mast cell membrane and the process of degranulation
- **anaphylactoid reaction**: basically has a direct stimulation of mast cell degranulation (iodine contrast agents, local anesthetics, dextran, lectins-phytohemagglutinin, concavalin A...)

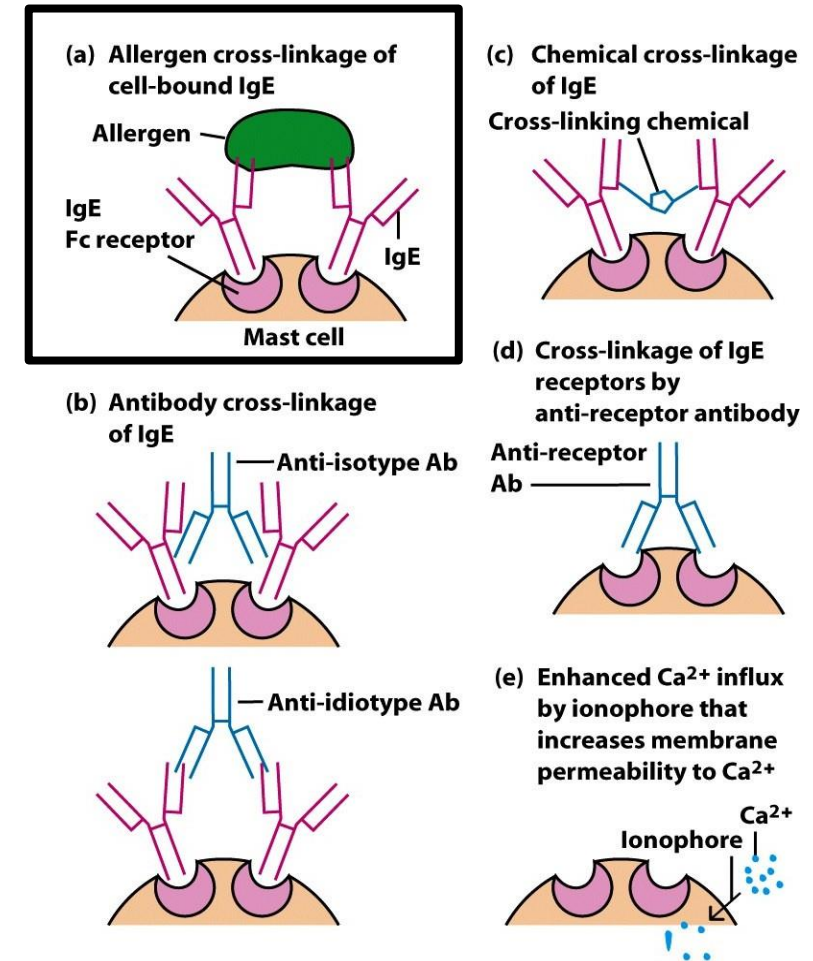


Figure 15-5
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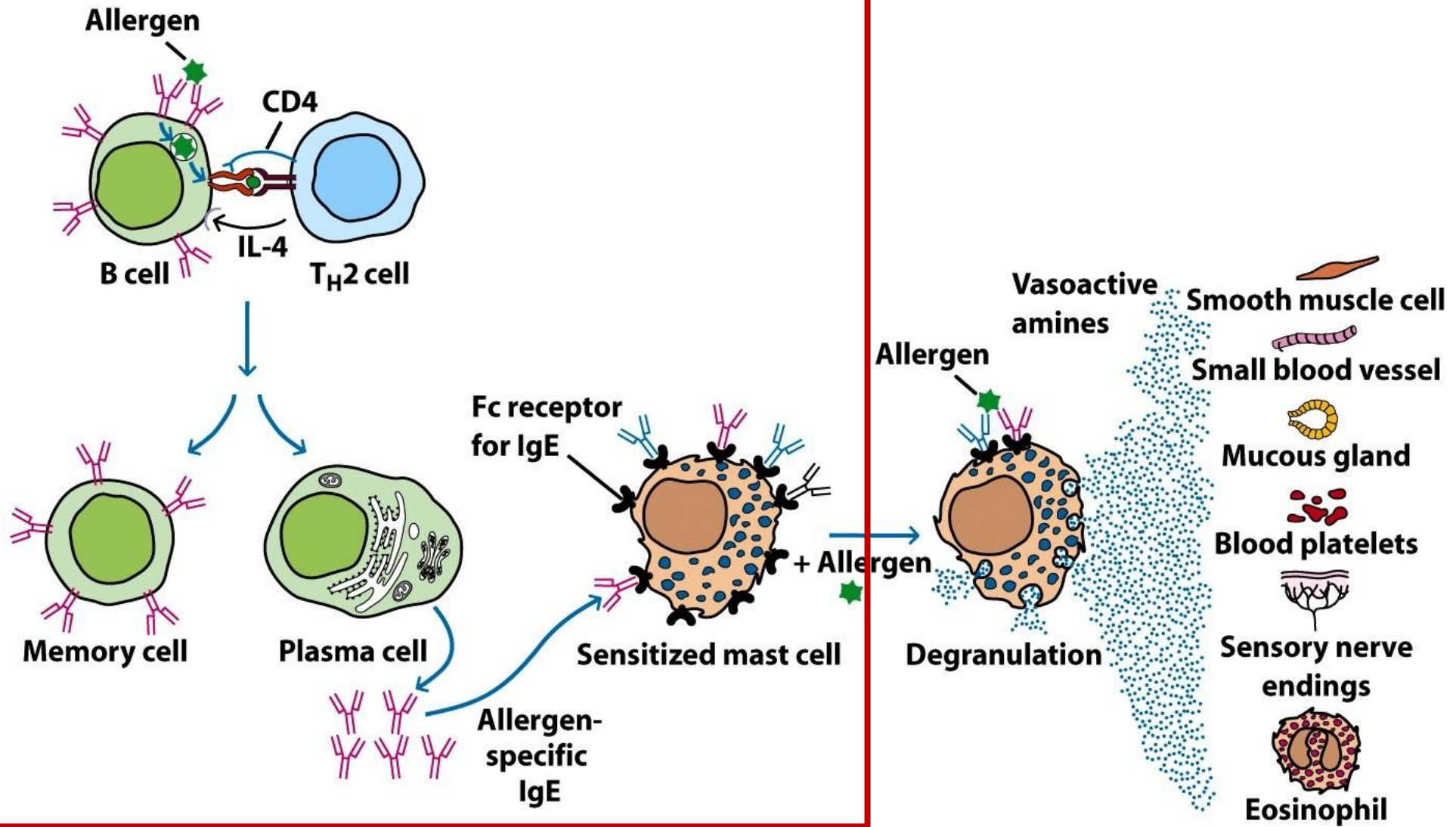


Figure 15-2
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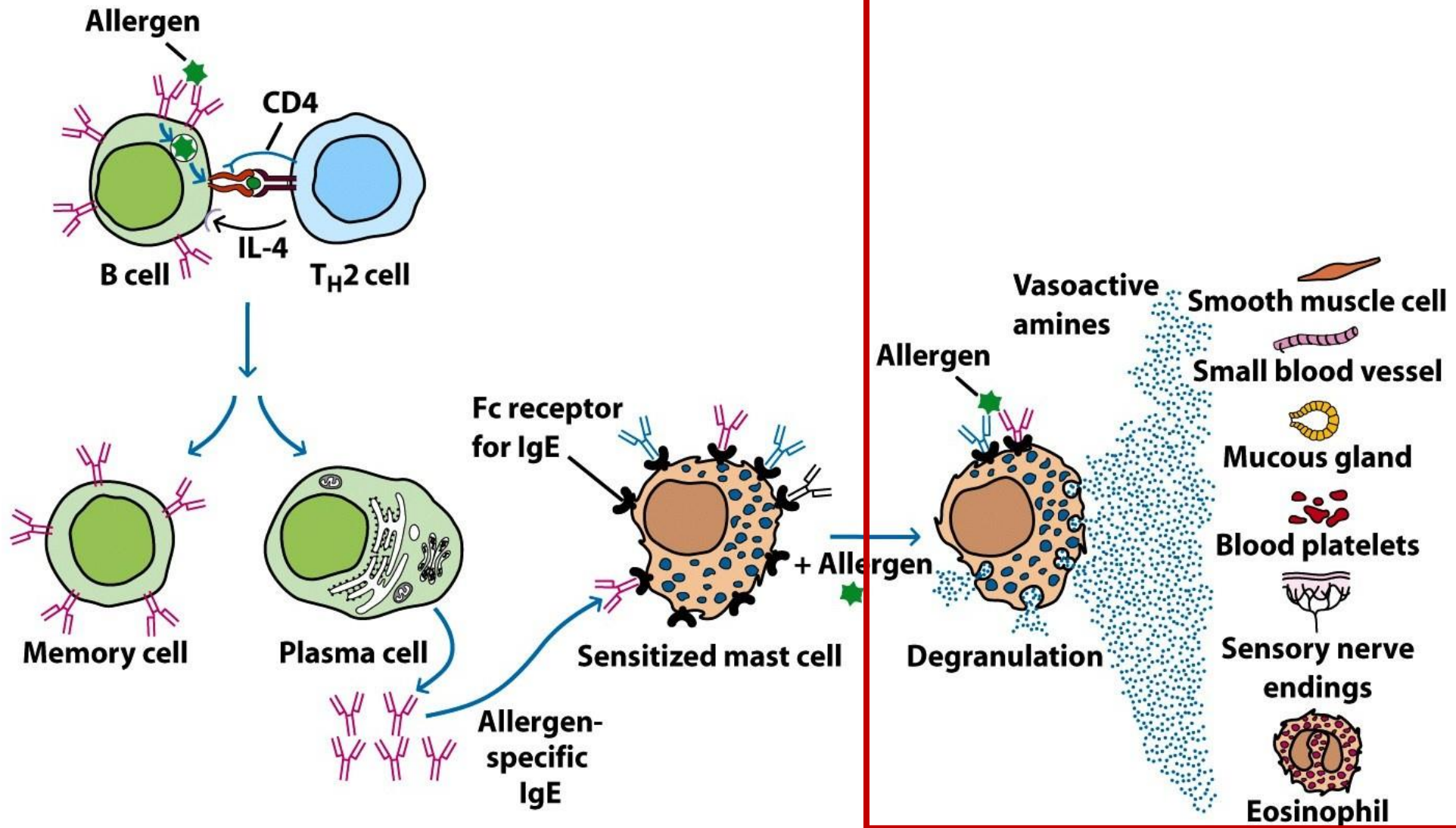
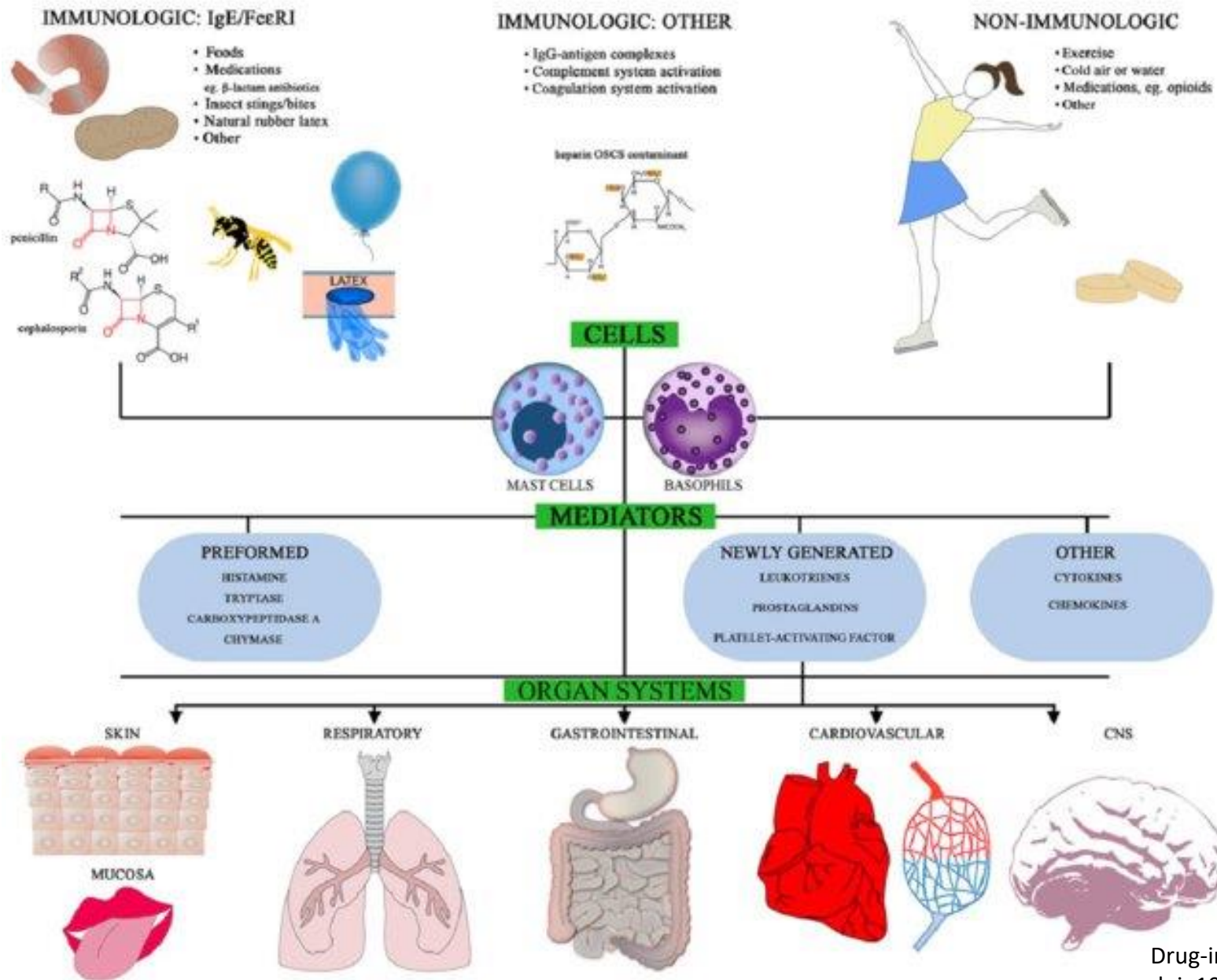


Figure 15-2
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MECHANISMS AND TRIGGERS



Type I hypersensitive reactions

- pathogenesis -

- **early phase:**

- it is a consequence of the activation of mast cells and the production of mediators
- vasodilatation, increased permeability of blood vessels and spasm of smooth muscles occur

- **late phase:**

- begins 2-24 hours after contact with the allergen
- it is characterized by the accumulation of inflammatory cells (especially eosinophilic leukocytes) and the occurrence of tissue damage

Mediators – type I hypersensitivity

The most important mediators are:

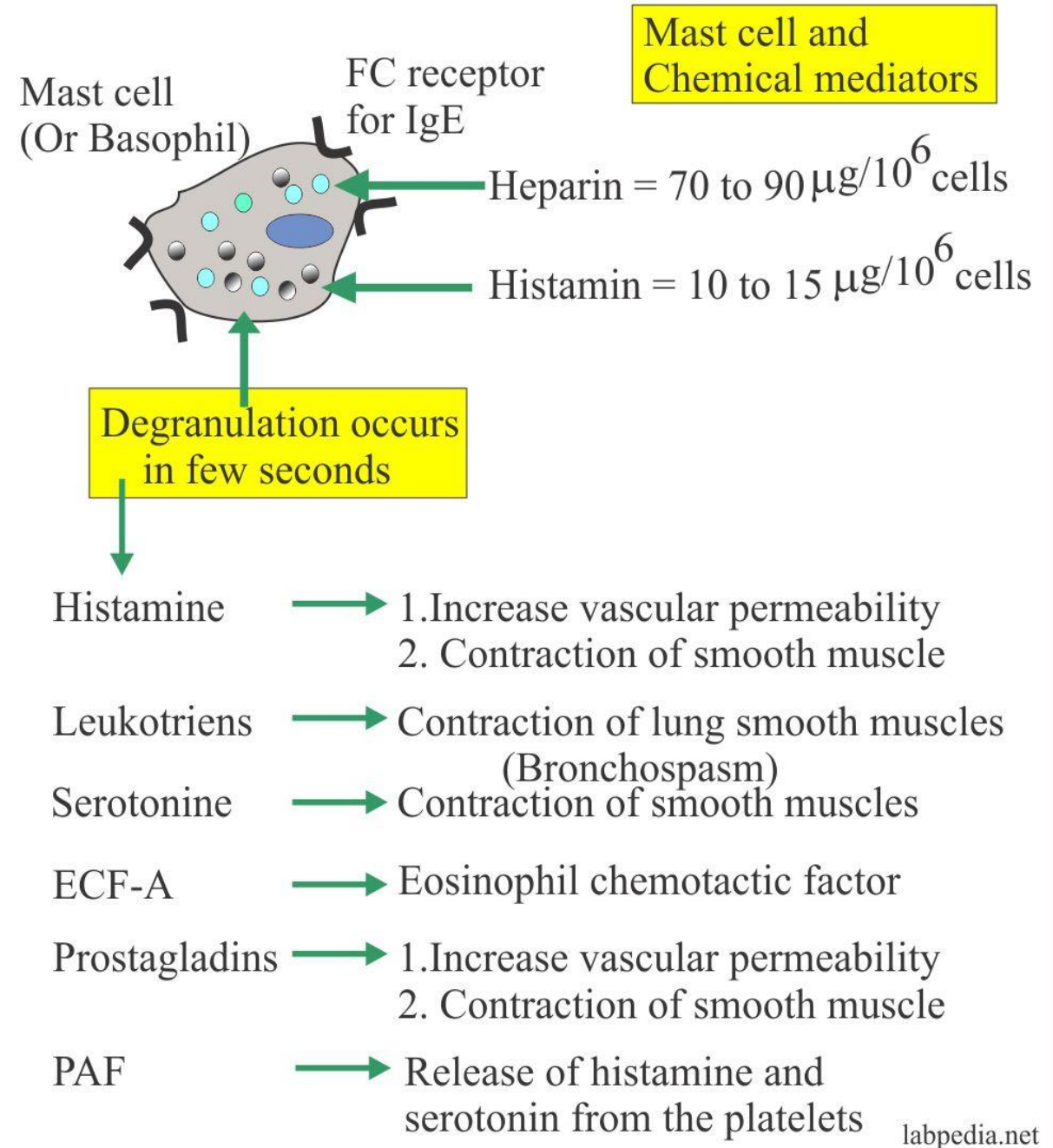
- Histamine
 - causes dilation of small blood vessels
 - increases vascular permeability
 - stimulates transient contraction of smooth muscles
- Proteases
 - they damage the surrounding tissue

Arachidonic acid metabolites

- Prostaglandins
 - that cause vasodilation
- Leukotrienes
 - that stimulate prolonged contraction of smooth muscles
- Cytokines
 - induce the occurrence of a local inflammatory reaction
 - stimulate the mobilization of leukocytes (eosinophils, neutrophils and Th2 cells)

Chemical Mediator	Function	Clinical Symptoms (dependent on amount of allergen exposure and location of reaction)
Toxic Mediator: Histamine	Inflammatory amine, increases localized blood flow and blood vessel permeability. Initiates smooth muscle contraction.	Loss of blood pressure, constriction of airways, difficulty breathing. Diarrhea, vomiting. In severe cases, suffocation and anaphylactic shock occur and are fatal.
Enzymes: mast-cell chymase, tryptase, and serine esterases	Activates matrix metalloproteinases	Destruction of tissues
Cytokine: Tumor Necrosis Factor (TNF)	Initiates influx of inflammatory leukocytes and lymphocytes into tissues.	Systemic inflammation
Lipid Mediators: Leukotrienes and platelet-activating factor (PAF)	Cause smooth muscle contraction, vascular permeability, mucus secretion, and activates leukocytes. Contribute to late-phase response.	Constriction of airways, difficulty breathing. Diarrhea, vomiting.
Cytokine: IL-4 and IL-3	Amplifies T _H 2 Response: Increased production and activation of eosinophils. Signals body to produce more IgE.	Inflammation, tissue damage, swelling, shortness of breath.

Mediators



Mediators of Activation

Receptor-binding agonists

IgE + antigen or IgE alone
Ig light chain
Complement
Neuropeptides
Microbial products
Cytokines
Chemokines



Physical activators

Temperature
Pressure



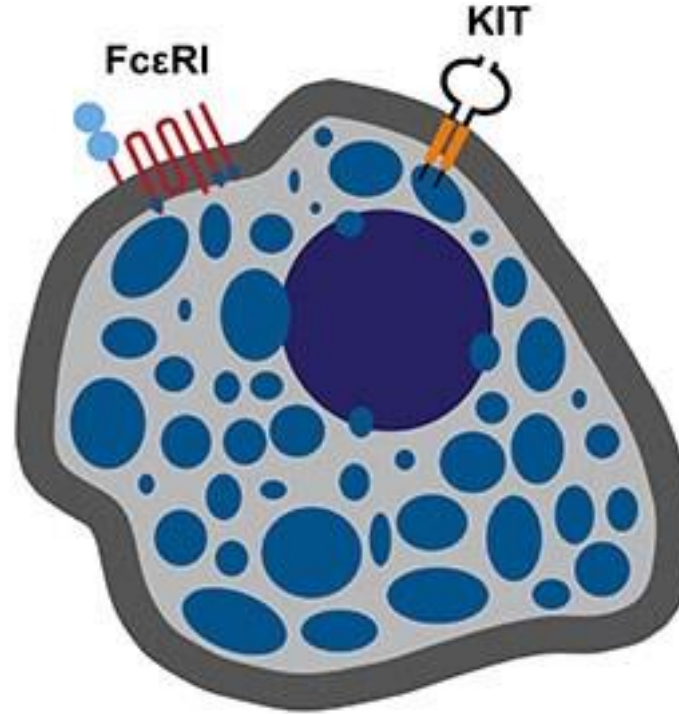
Cell-cell contact

OX40 / OX40L
CD40 / CD40L
TCR / MHCII



Priming Factors

SCF
IL-4
IL-6



Mast Cell

Effector Functions

Preformed mediators



Histamine
Proteases
Serotonin
Heparin
IL-4, TNF, GM-CSF

T and B cell ligands



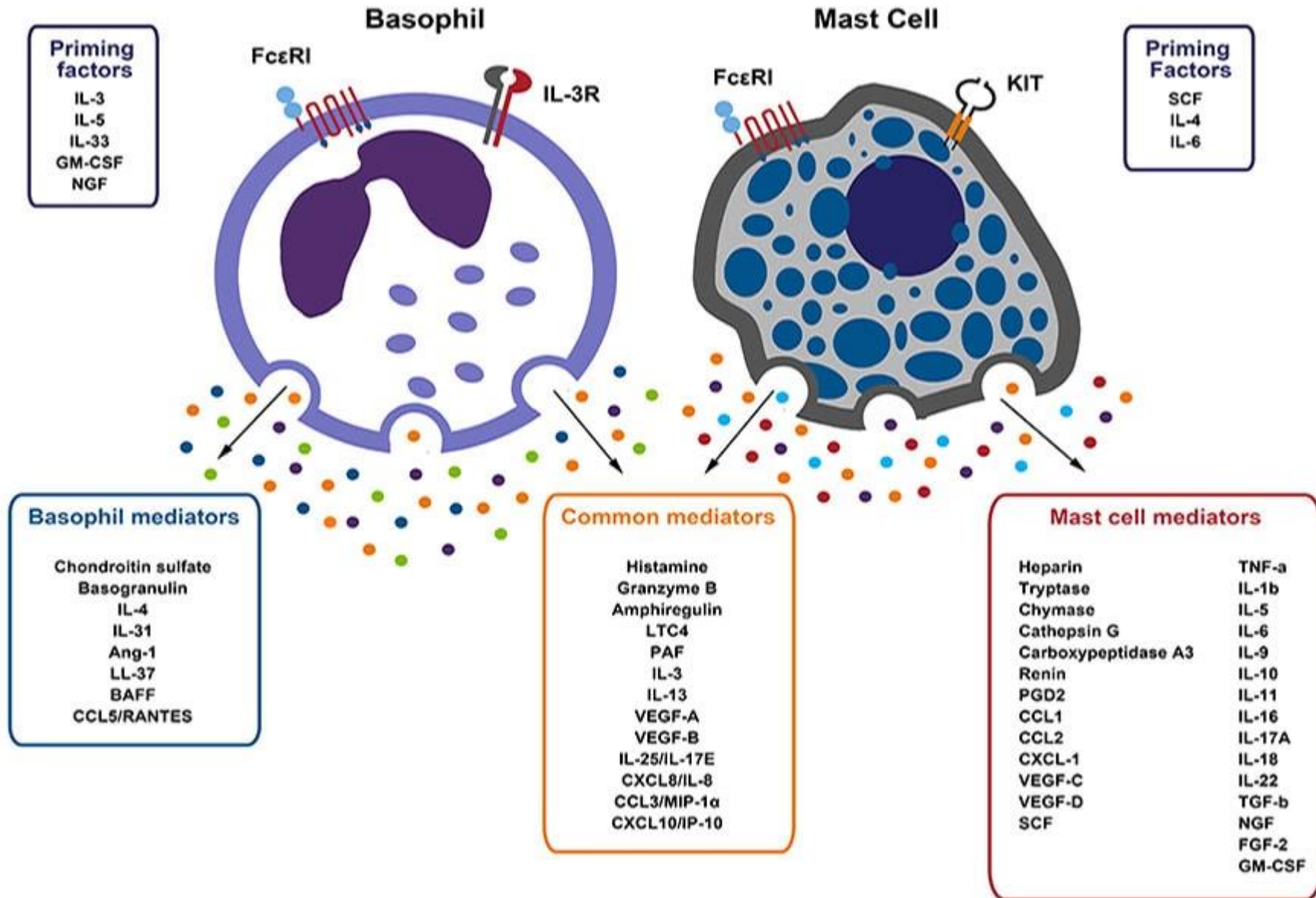
PD-1, OX40L, CD30L,
CD40L, CCL19, 4-1BB

Newly synthesized mediators

Lipid derived: prostaglandins
Leukotrienes
PAF



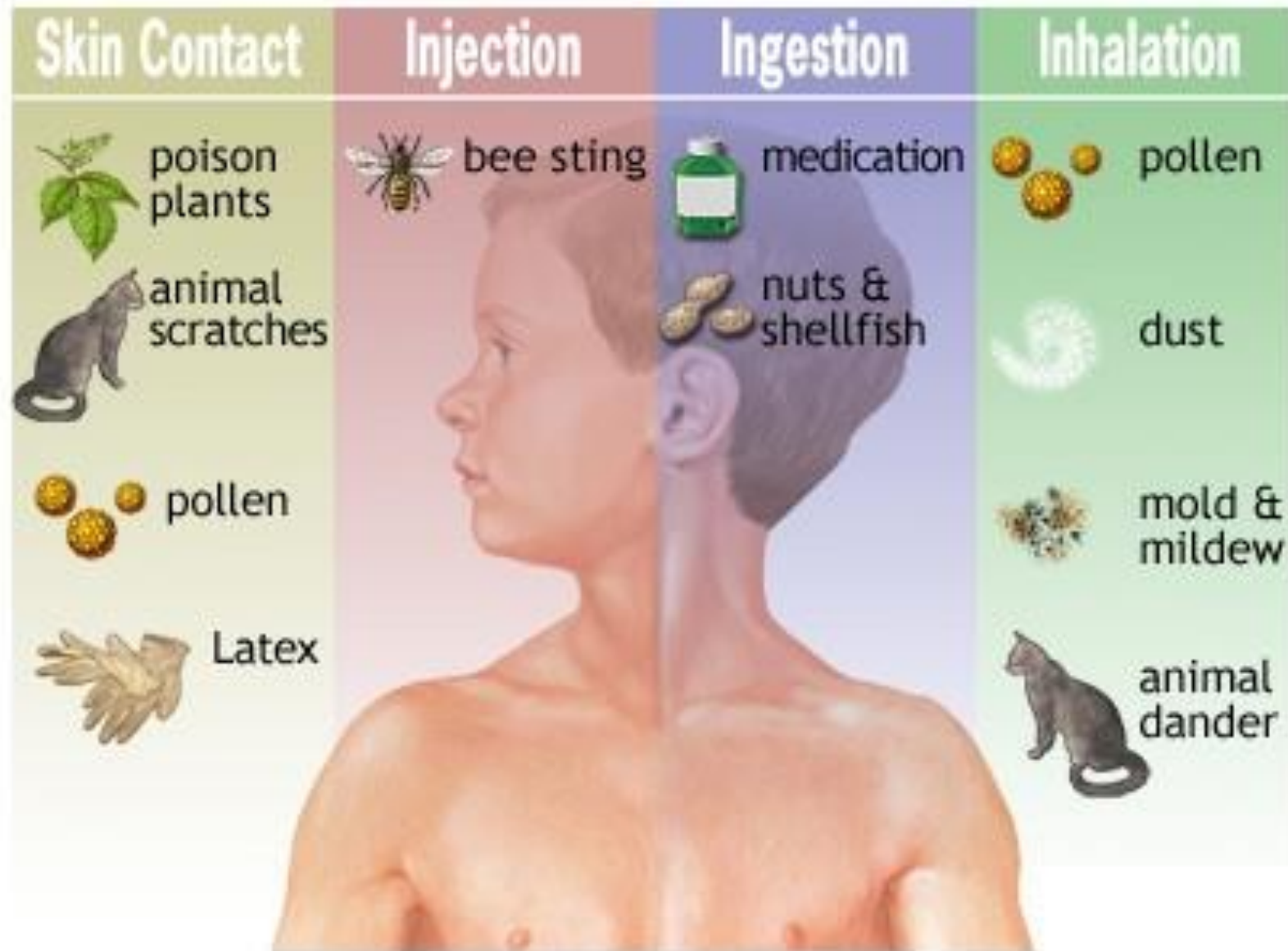
Cytokines
Growth factors
Chemokines
Free radicals



Clinically manifestation of type I hypersensitivity

- one or more clinical forms of this type of hypersensitivity may occur in the same person who has a genetic predisposition to the occurrence of type I hypersensitivity reactions
- which clinical form of type I hypersensitivity will occur depends on:
 - the nature of the allergen
 - **ways of allergen entry**
 - the number, localization and characteristics of mast cells and other cells in the target organ
 - the sensitivity of the target organ to the effect of the mediator

Entry Routes of Allergen

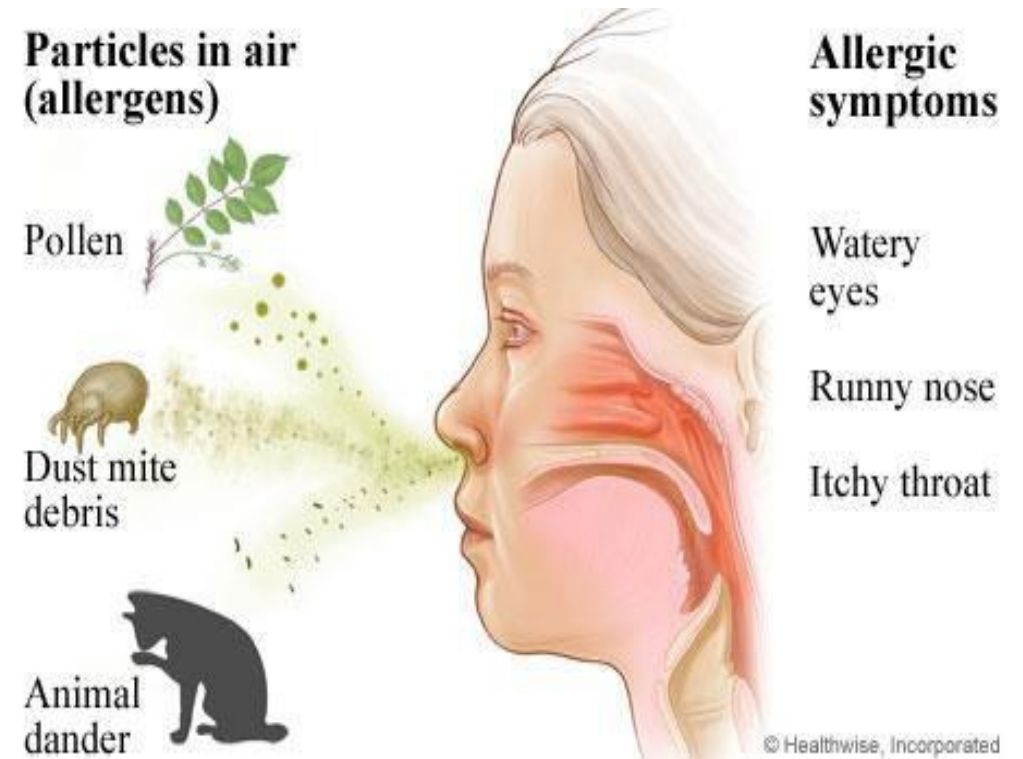


IgE-mediated allergic reactions			
Syndrome	Common allergens	Route of entry	Response
Systemic anaphylaxis	Drugs Serum Venoms Food, e.g. peanuts	Intravenous (either directly or following oral absorption into the blood)	Edema Increased vascular permeability Laryngeal edema Circulatory collapse Death
Acute urticaria (wheal-and-flare)	Animal hair Insect bites Allergy testing	Through skin Systemic	Local increase in blood flow and vascular permeability
Seasonal rhinoconjunctivitis (hay fever)	Pollens (ragweed, trees, grasses) Dust-mite feces	Inhalation	Edema of nasal mucosa Sneezing
Asthma	Danders (cat) Pollens Dust-mite feces	Inhalation	Bronchial constriction Increased mucus production Airway inflammation
Food allergy	Tree nuts Shellfish Peanuts Milk Eggs Fish Soy Wheat	Oral	Vomiting Diarrhea Pruritis (itching) Urticaria (hives) Anaphylaxis (rarely)

Figure 13-2 Immunobiology, 7ed. (© Garland Science 2008)

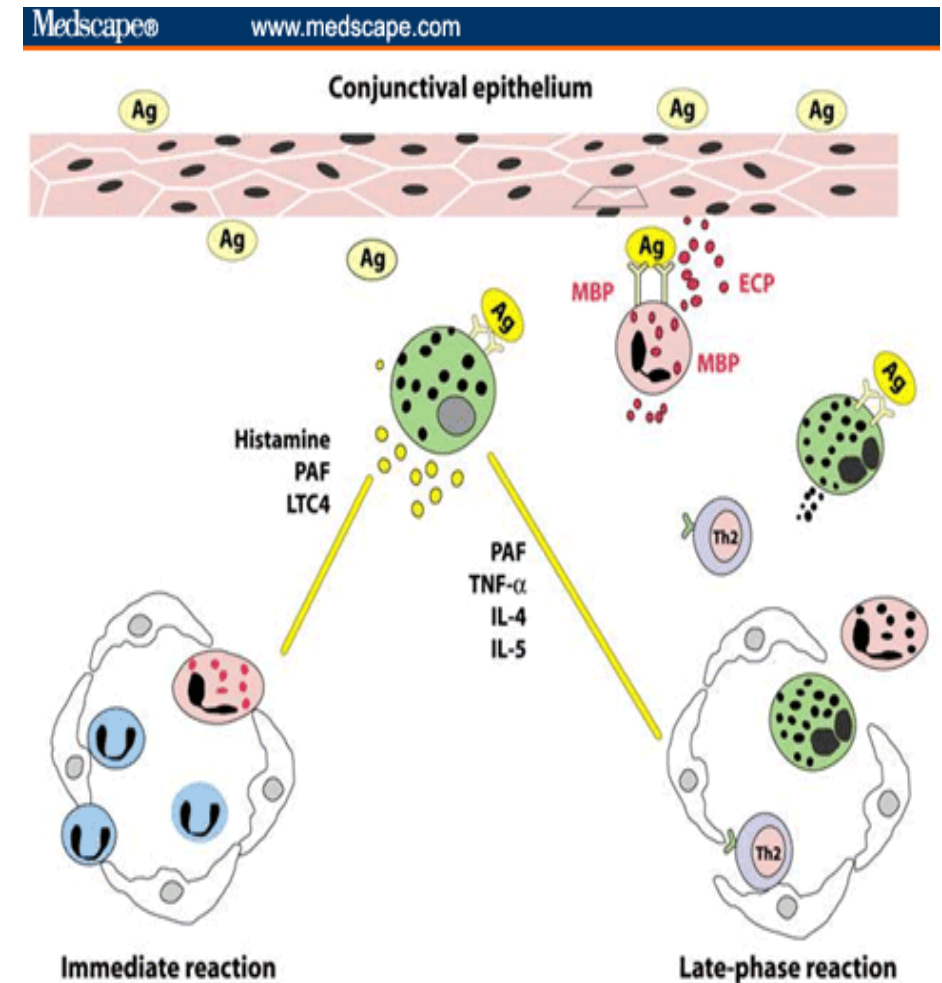
Allergic rhinitis

- allergic rhinitis is clinical manifestation of type I hypersensitivity
- occurs seasonally (pollen) or throughout the year (house dust, dust mites)
- allergic rhinitis is a consequence of the activation of **mast cells** in the nasal mucosa by allergens
- manifested by increased secretion, sneezing and obstruction of the nasal cavity after exposure to the allergen (key mediators - **histamine**)



Allergic conjunctivitis

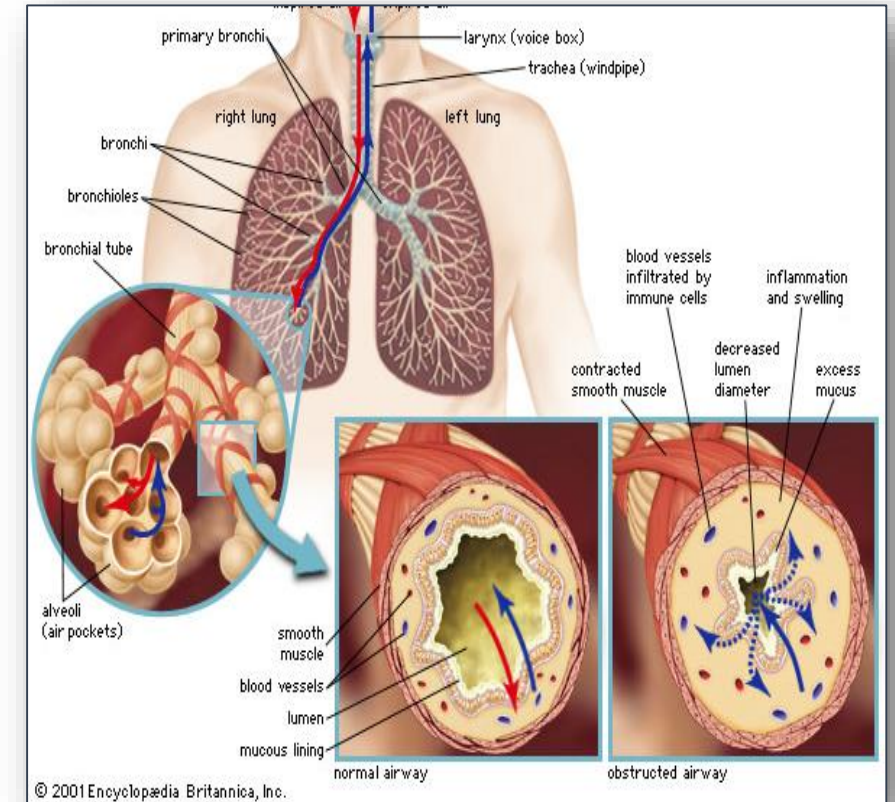
- allergic conjunctivitis is also called seasonal conjunctivitis
- occurs seasonally (pollen) or throughout the year (house dust, dust mites)
- allergic conjunctivitis is a consequence of the activation of mast cells in the conjunctiva by allergens
- it is manifested by increased secretion, redness, irritation and itching, so frequent touching is a risk for eye infection



Bronchial asthma

Bronchial asthma is a disease characterized by:

- intermittent and reversible airway obstruction
- chronic bronchial inflammation by eosinophilic leukocytes as well as a population of CD4+ NKT cells that recognize glycolipid antigens
- hyperactivity of bronchial smooth muscles to bronchoconstriction stimulation



Bronchial asthma-pathogenesis

EARLY PHASE: consequence of the release of mediators

- histamine causes vasodilation
- prostaglandins lead to bronchoconstriction
- leukotrienes leads to increased production of mucus

LATE PHASE: it is the result of local infiltration by eosinophils, neutrophils and Th2 cells

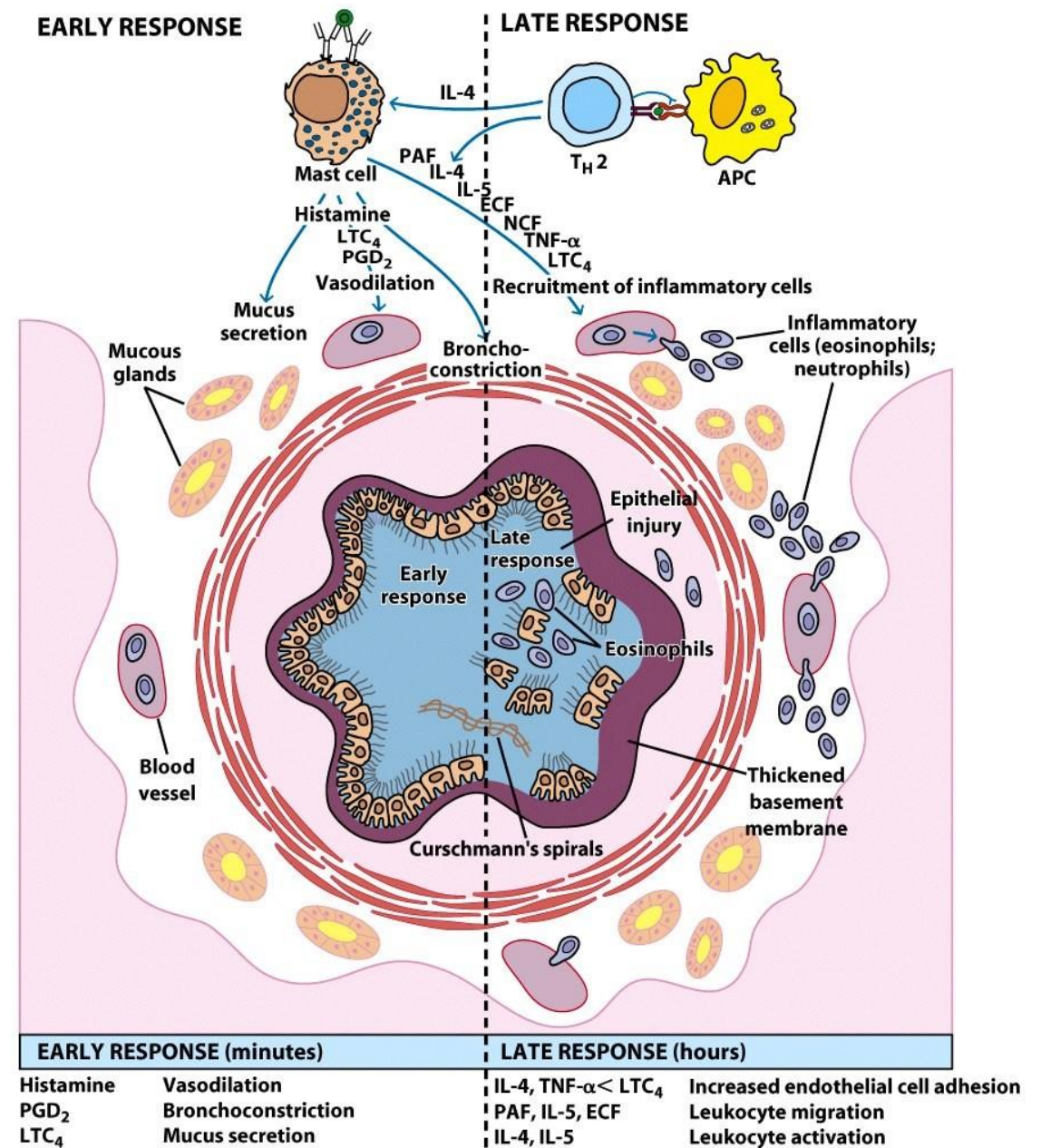
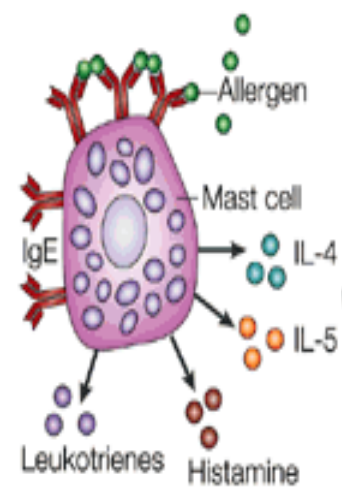
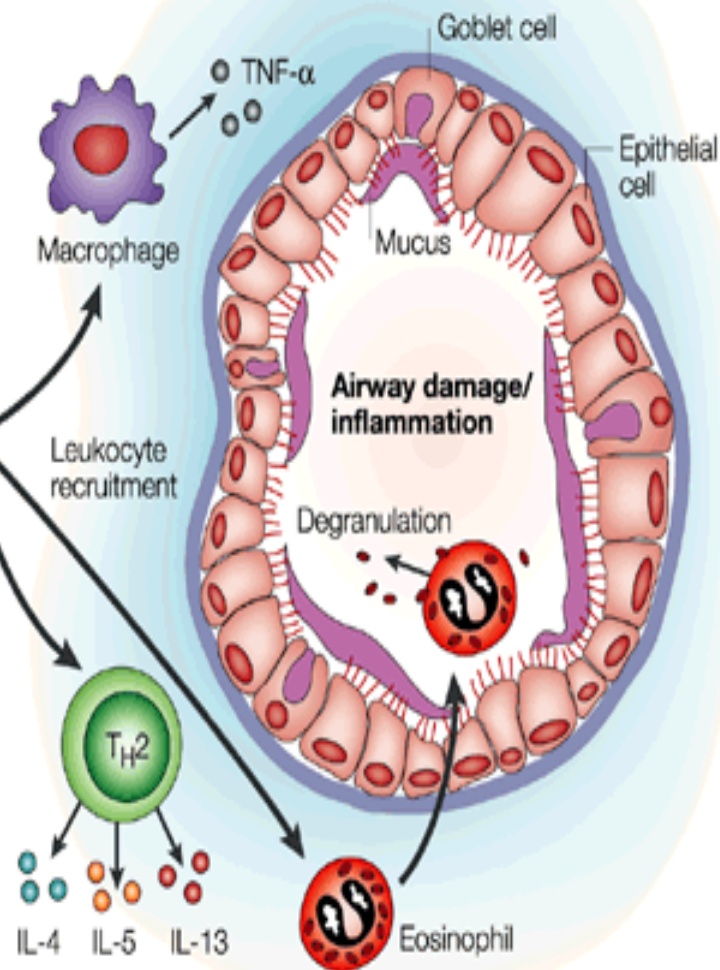


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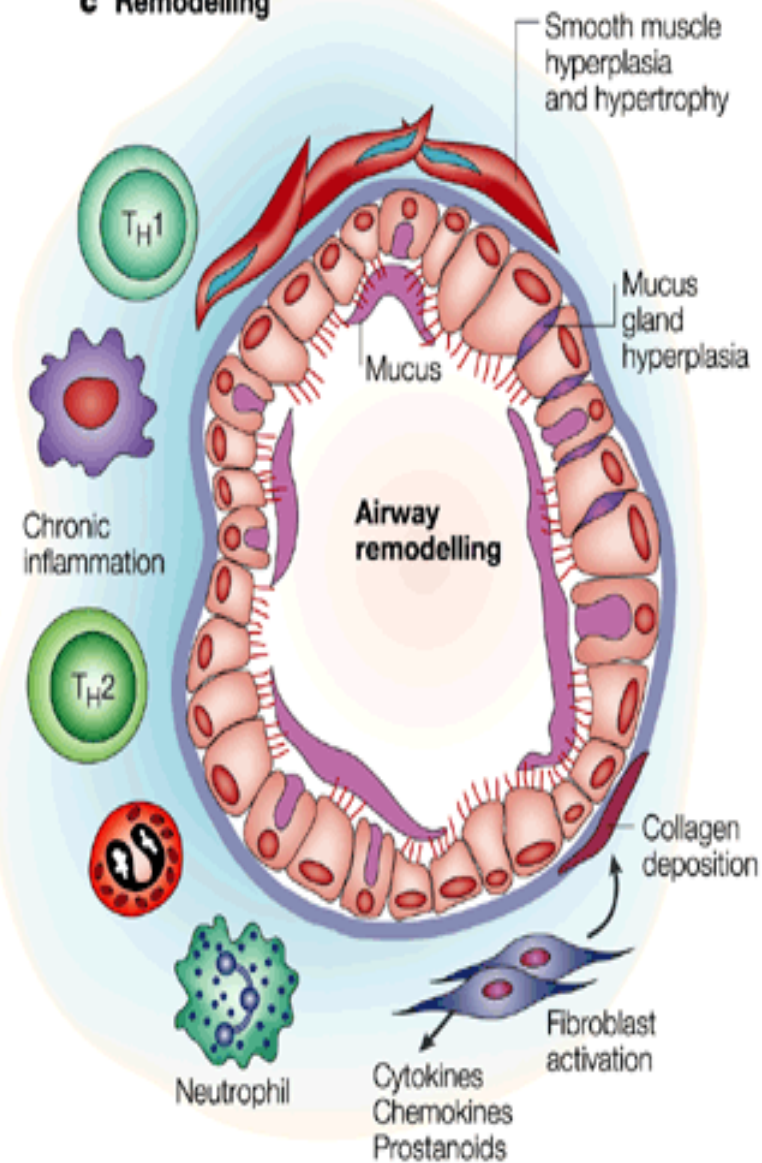
a Acute phase



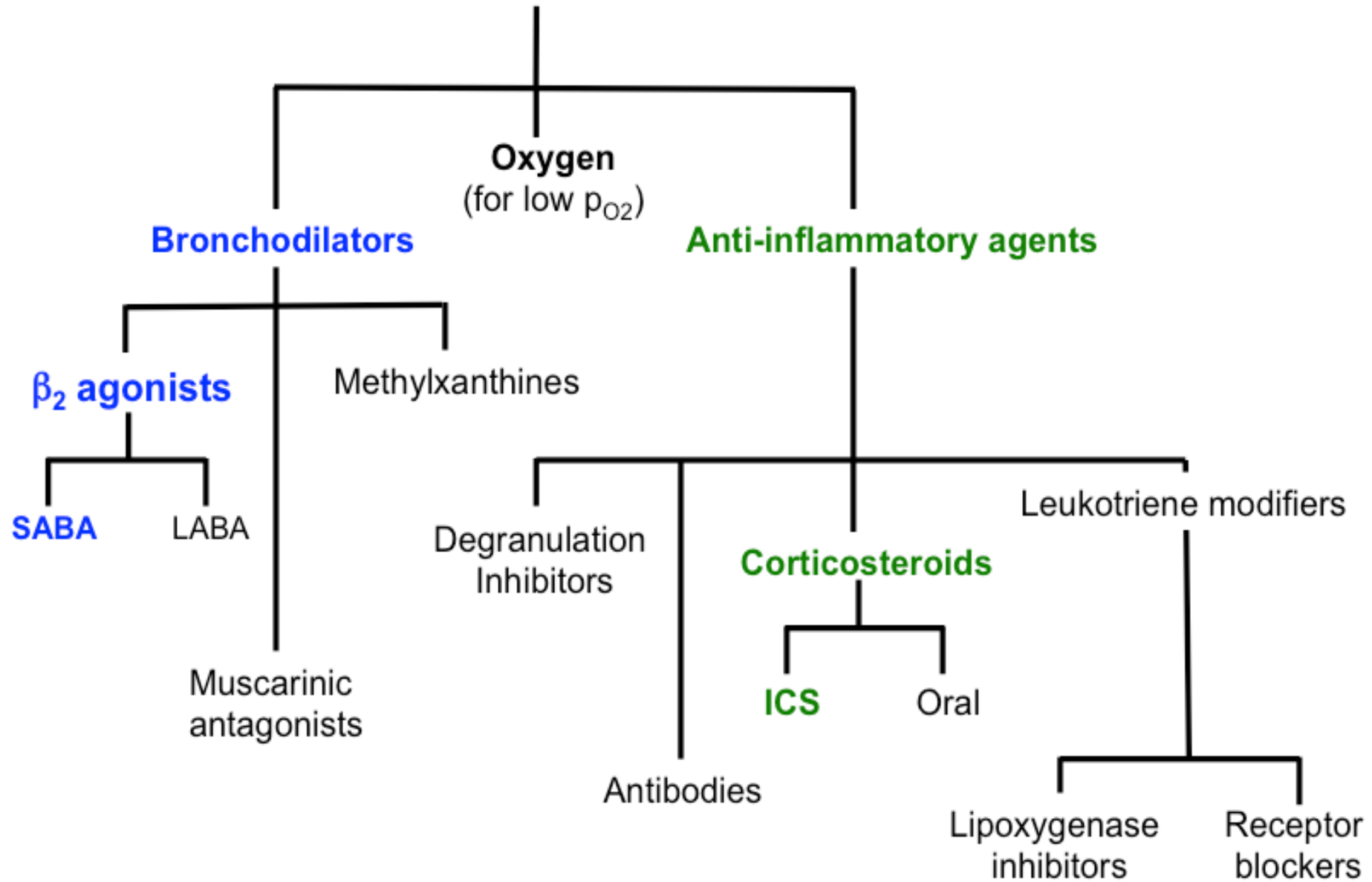
b Chronic phase

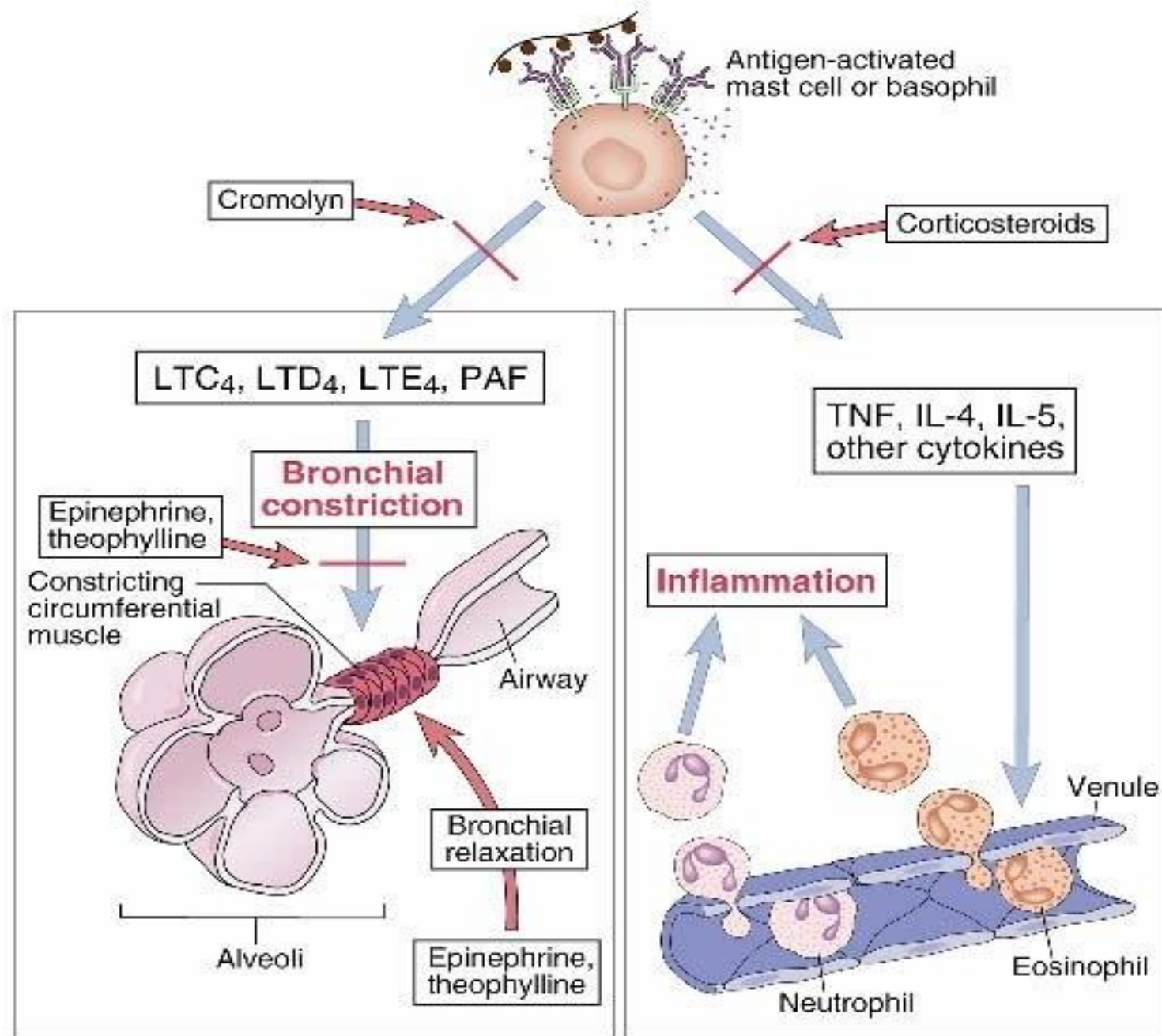


c Remodelling



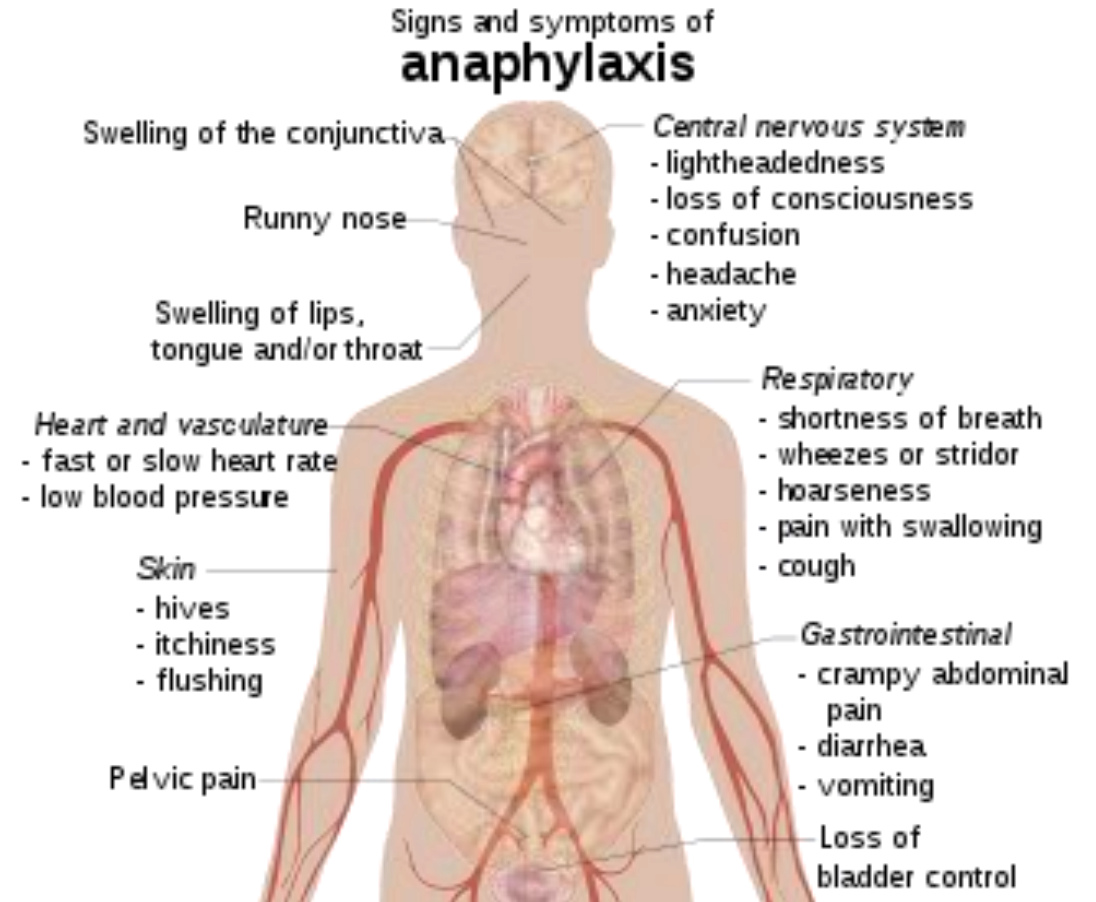
Drugs Used In Asthma





Anaphylaxis

- systemic form of type I hypersensitivity that occurs due to the presence of allergens in the circulation:
 - after injection,
 - insect sting
 - absorption through epithelial surfaces
 - may be due to:
 - anaphylactic reactions
 - anaphylactoid reactions

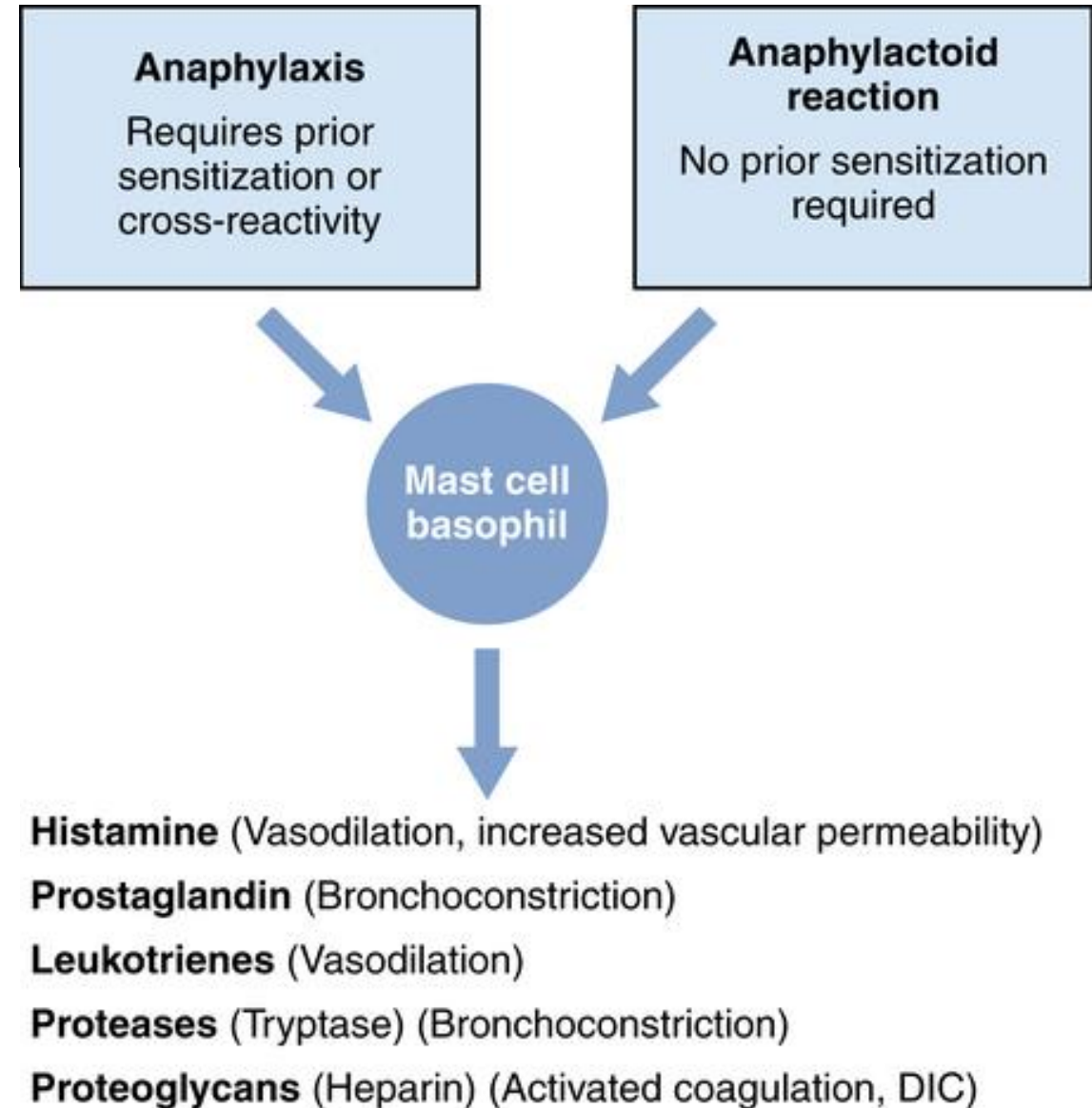


Anaphylactic reaction

- It is an immune-mediated reaction.
- IgE antibody plays an important role.
- The allergen[antigen] reacts with the IgE antibody and the complex causes degranulation of the mast cells and hence release of histamine and other mediators.

Anaphylactoid reaction

- It is a non-immune mediated reaction.
- No relation with IgE antibody.
- The allergen[antigen] causes direct release of histamine and other mediators from the mast cell and does not cause degranulation.



Urticaria and angioedema

Urticaria:

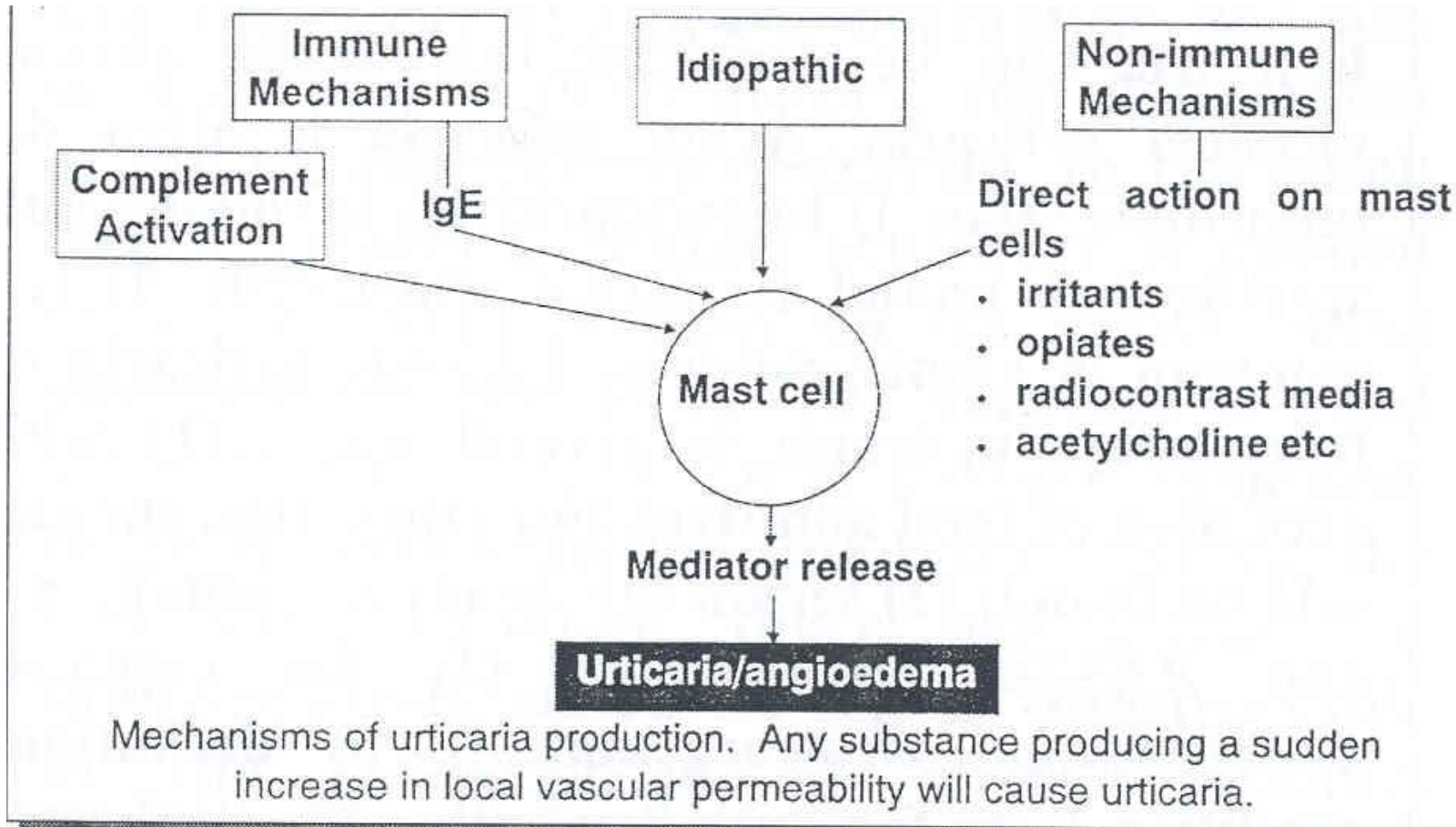
- is a physical sign, not a disease
- the term urticaria refers to transient episodes of circumscribed, edematous, and erythematous lesions with raised edges that are accompanied by pruritus
- it occurs as a result of a sudden, local accumulation of fluid in the skin

Angioedema:

- is a similar process that involves the deeper structures of the dermis, subcutaneous tissue or mucous membranes.

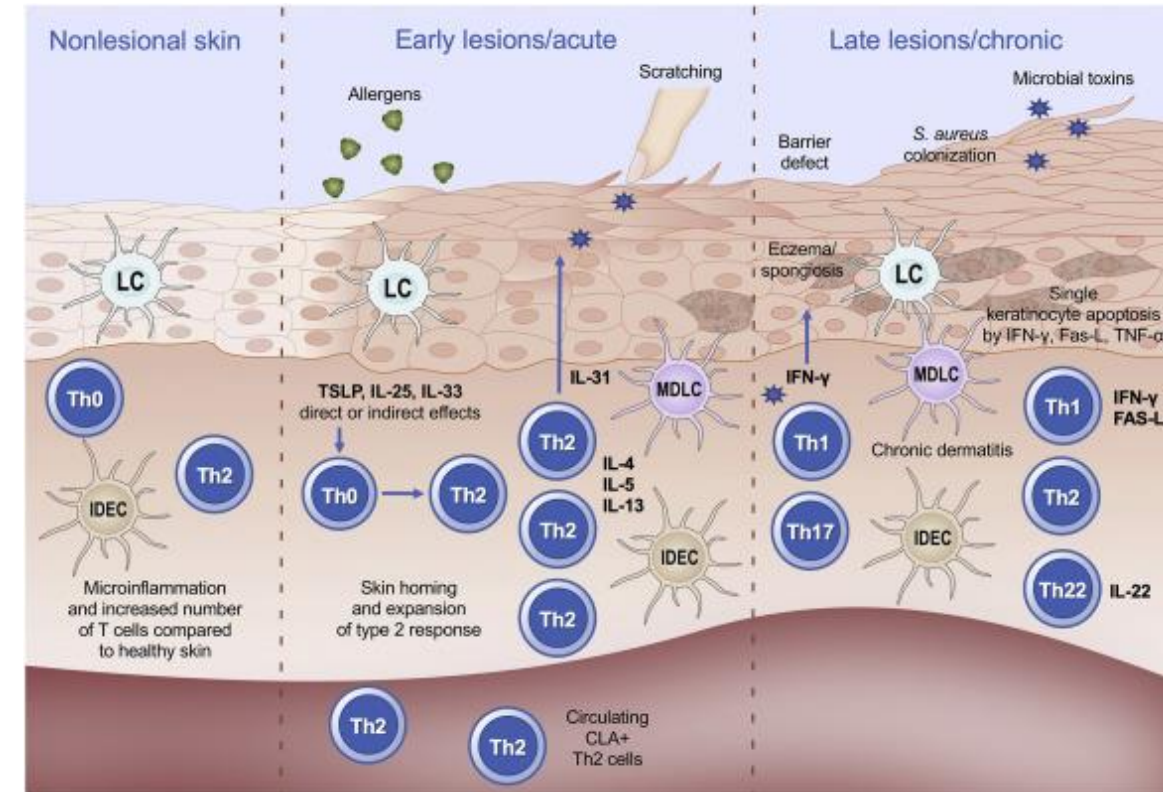
Urticaria and angioedema usually coexist

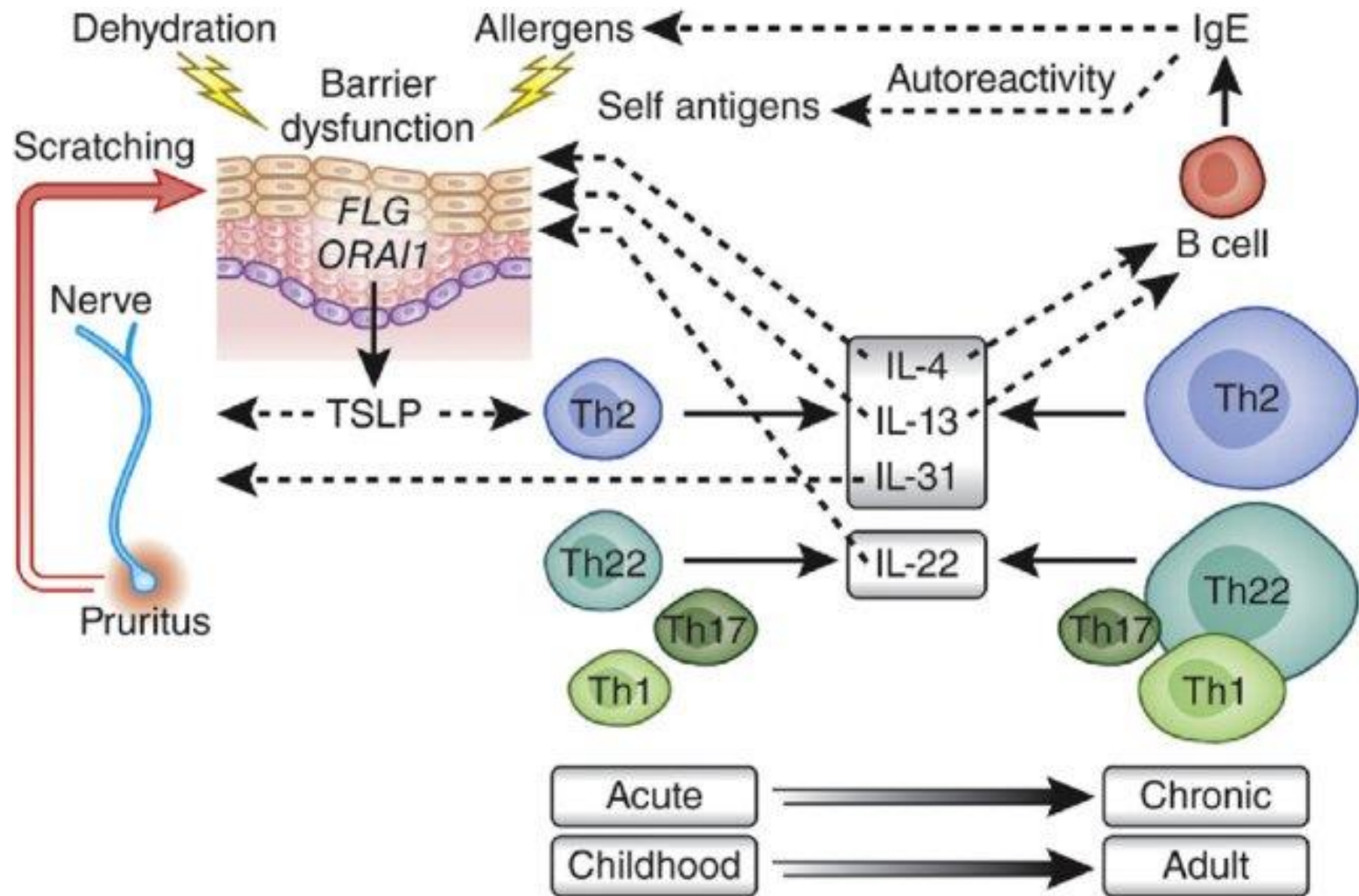
Urticaria and angioedema



Atopic dermatitis

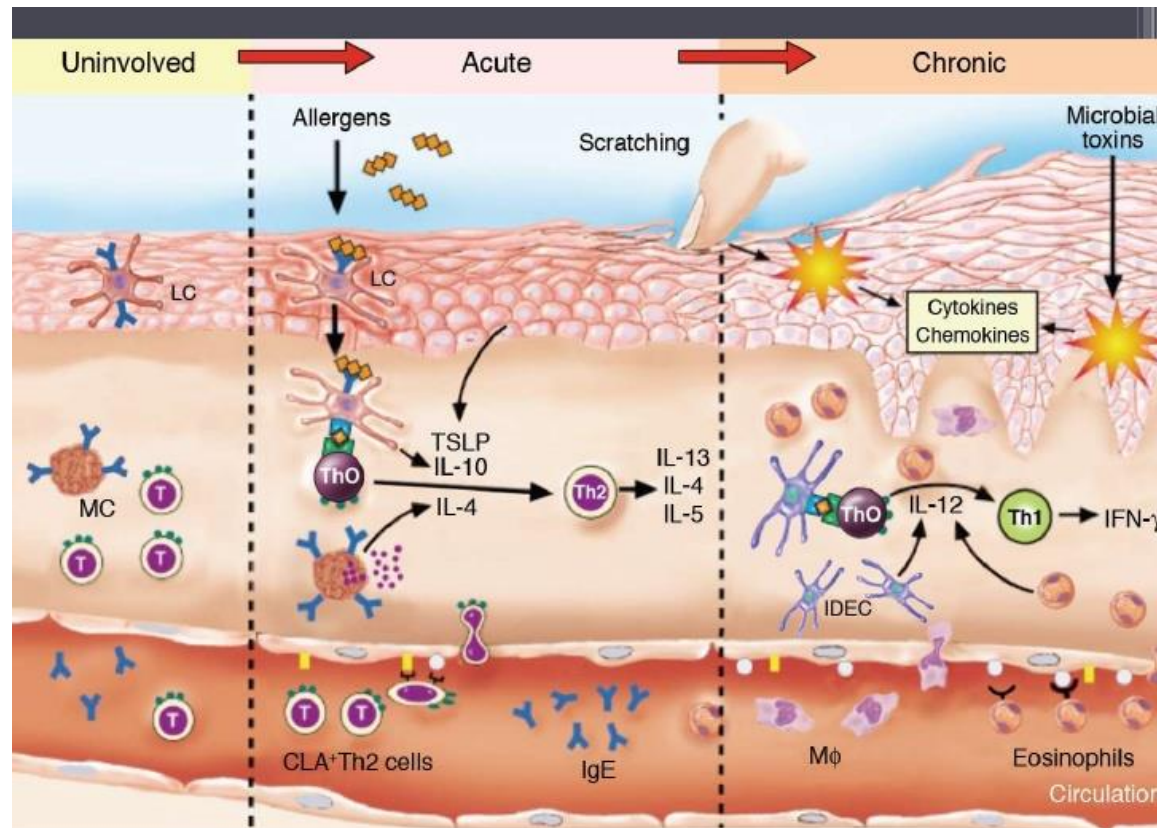
- Type I hypersensitivity reaction localized in the skin, which can be acute or chronic
- acute reactions (acute eczema) are more common
- they occur after local contact with an allergen on the skin surface
- after allergen binding to IgE antibodies on the mast cell membrane, histamine is released → vasodilation and increased vascular permeability
- the effects can be blocked by antihistamines





Atopic dermatitis

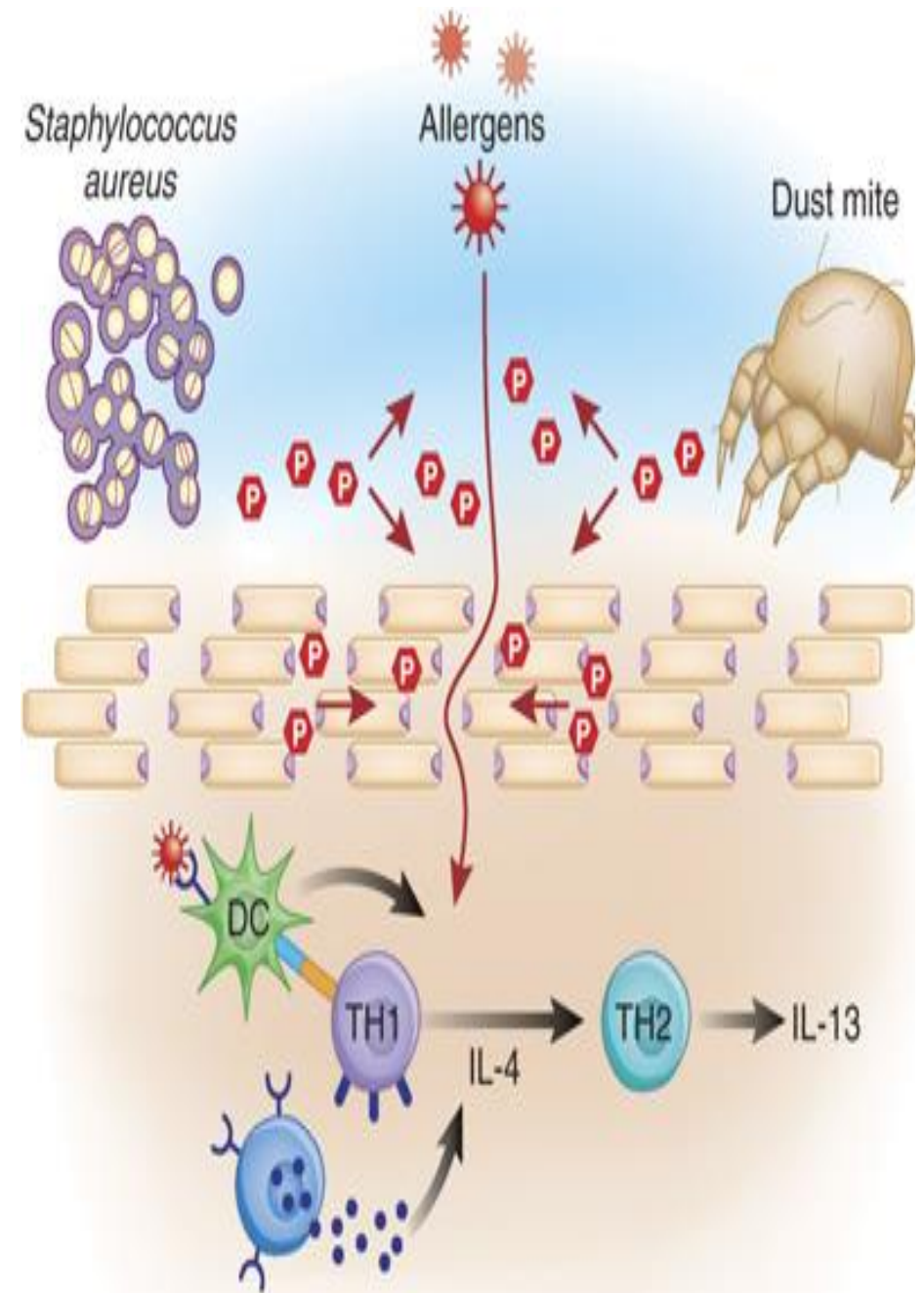
The basis of this skin disease is a **biphasic** inflammation with an initial **Th2 phase**, while **Th1 lymphocytes** dominate in chronic lesions...



J. Clin. Invest.2004;113:651-657

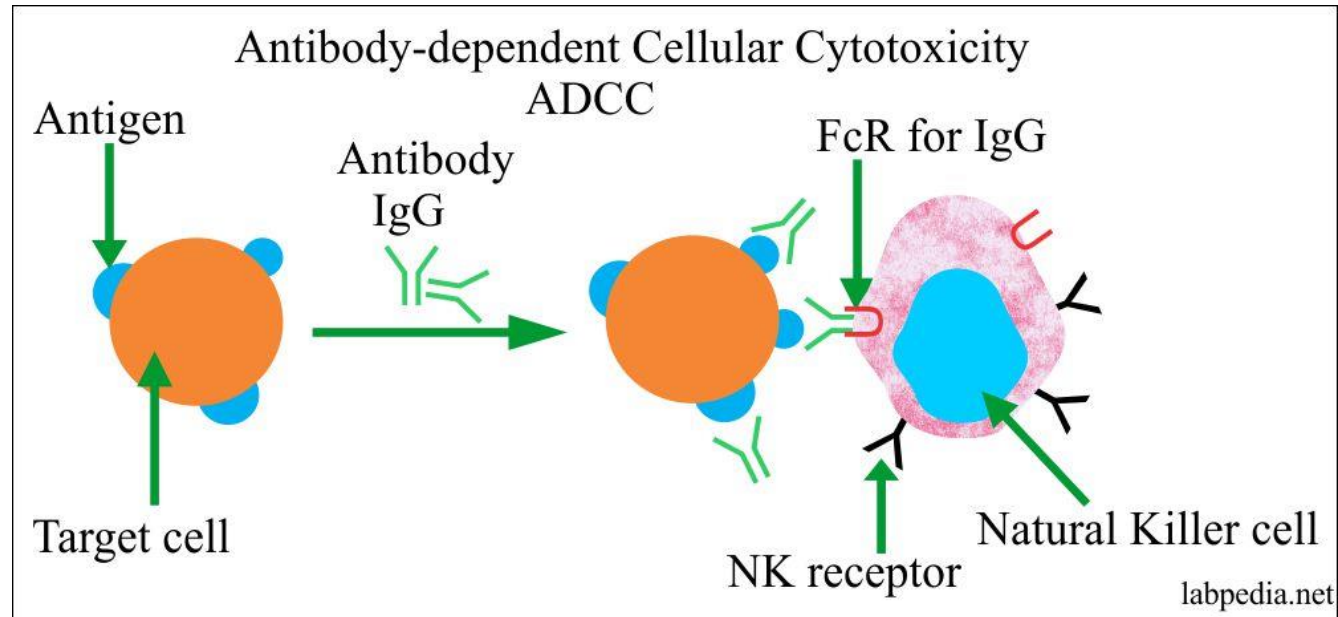
Atopic dermatitis

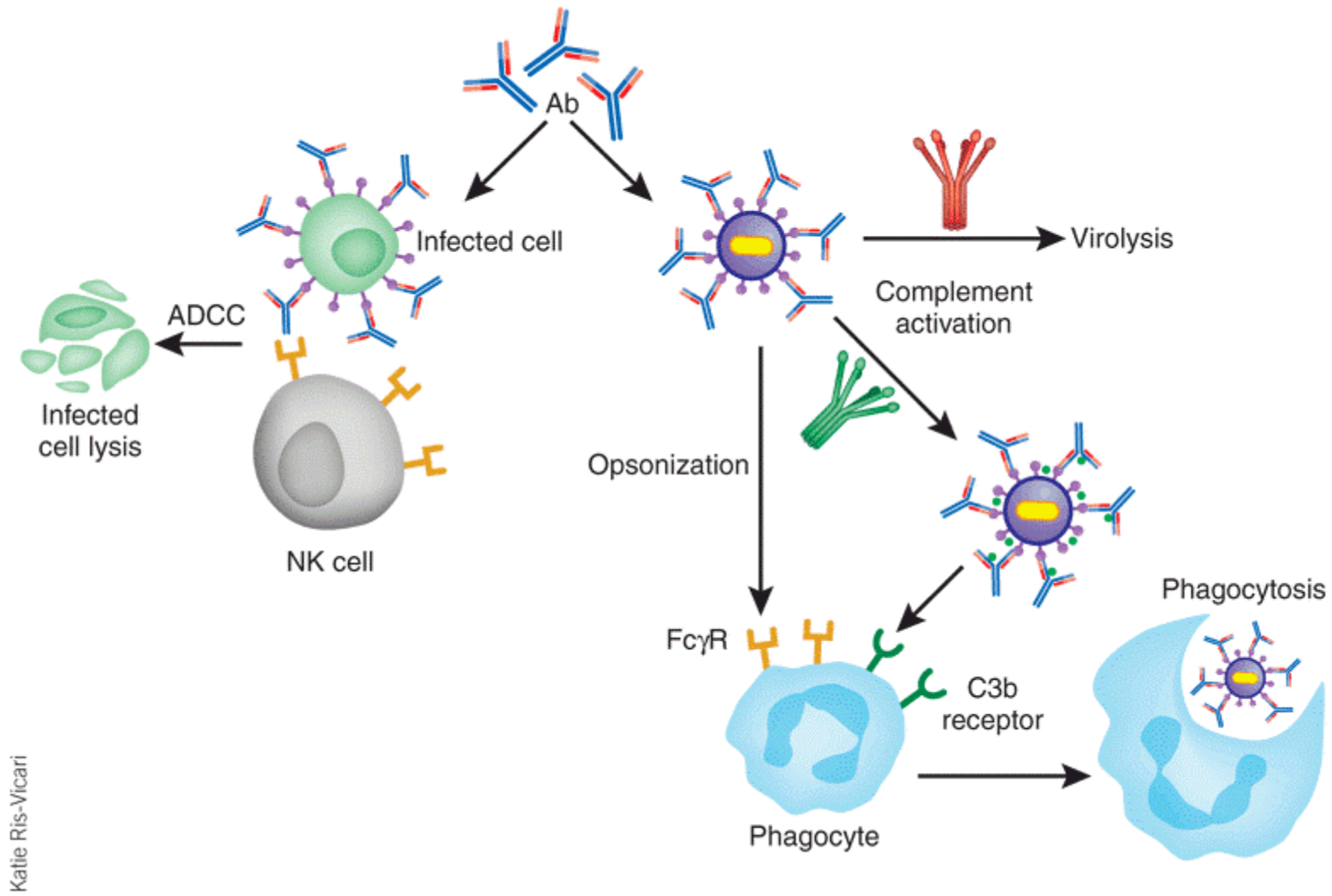
- the diagnosis of atopic dermatitis (eczema) is made based on the **clinical picture** and on the basis of personal and family history - strong **genetic predisposition** for the development of atopic eczema is essential
- environmental factors also play a significant role:
 - house mite as a provocative factor,
 - food intolerance,
 - *Staphylococcus aureus* infections exacerbate skin inflammation by releasing toxins that act as super-antigens

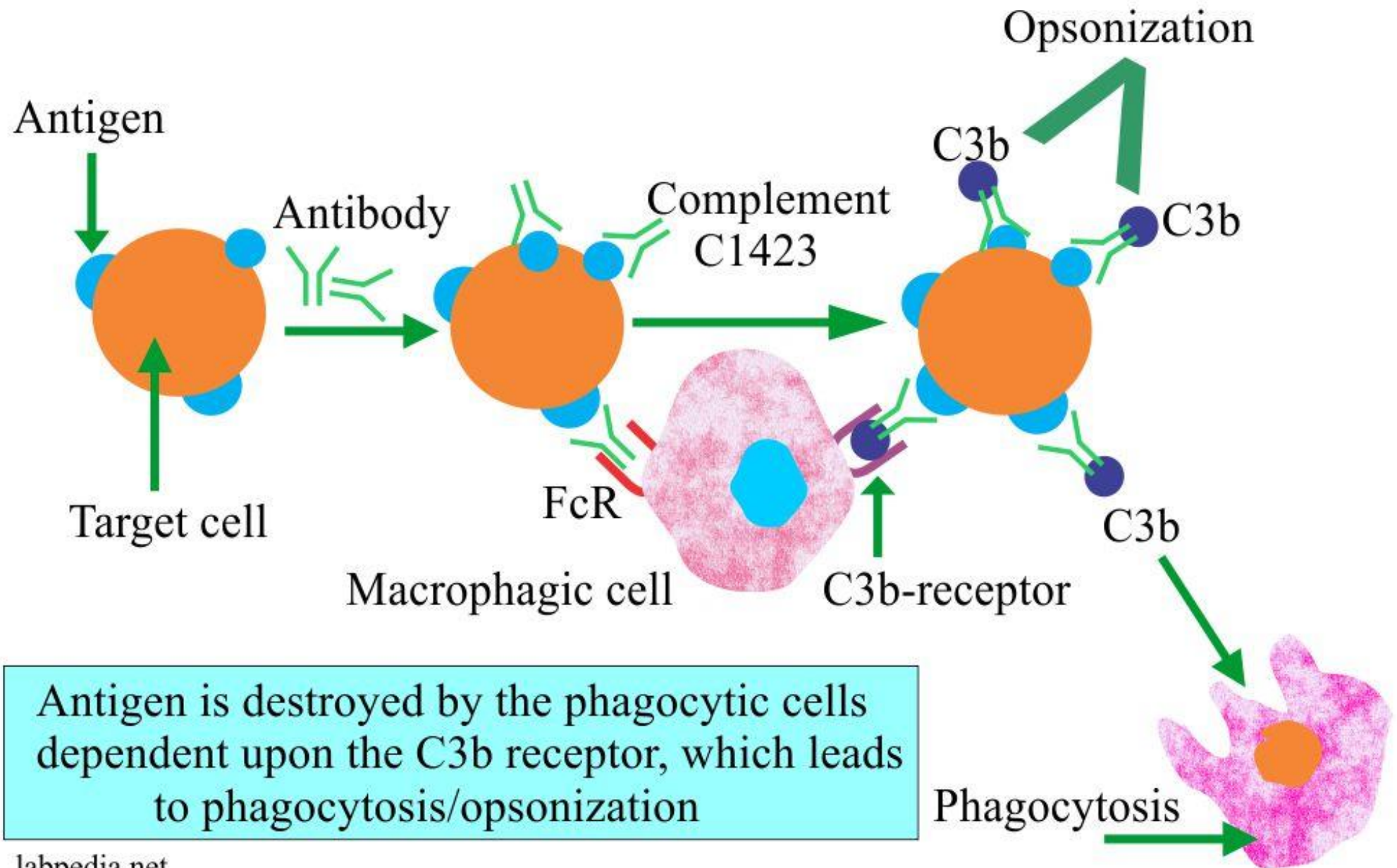


Type II hypersensitivity

- lymphocytes are activated by antigens that are expressed on the cell membrane → activated B lymphocytes synthesize antibodies (IgG and/or IgM) that bind to membrane receptors → the effector phase of the response begins (activation of the complement system, phagocytosis, ADCC reaction)







Type II hypersensitivity

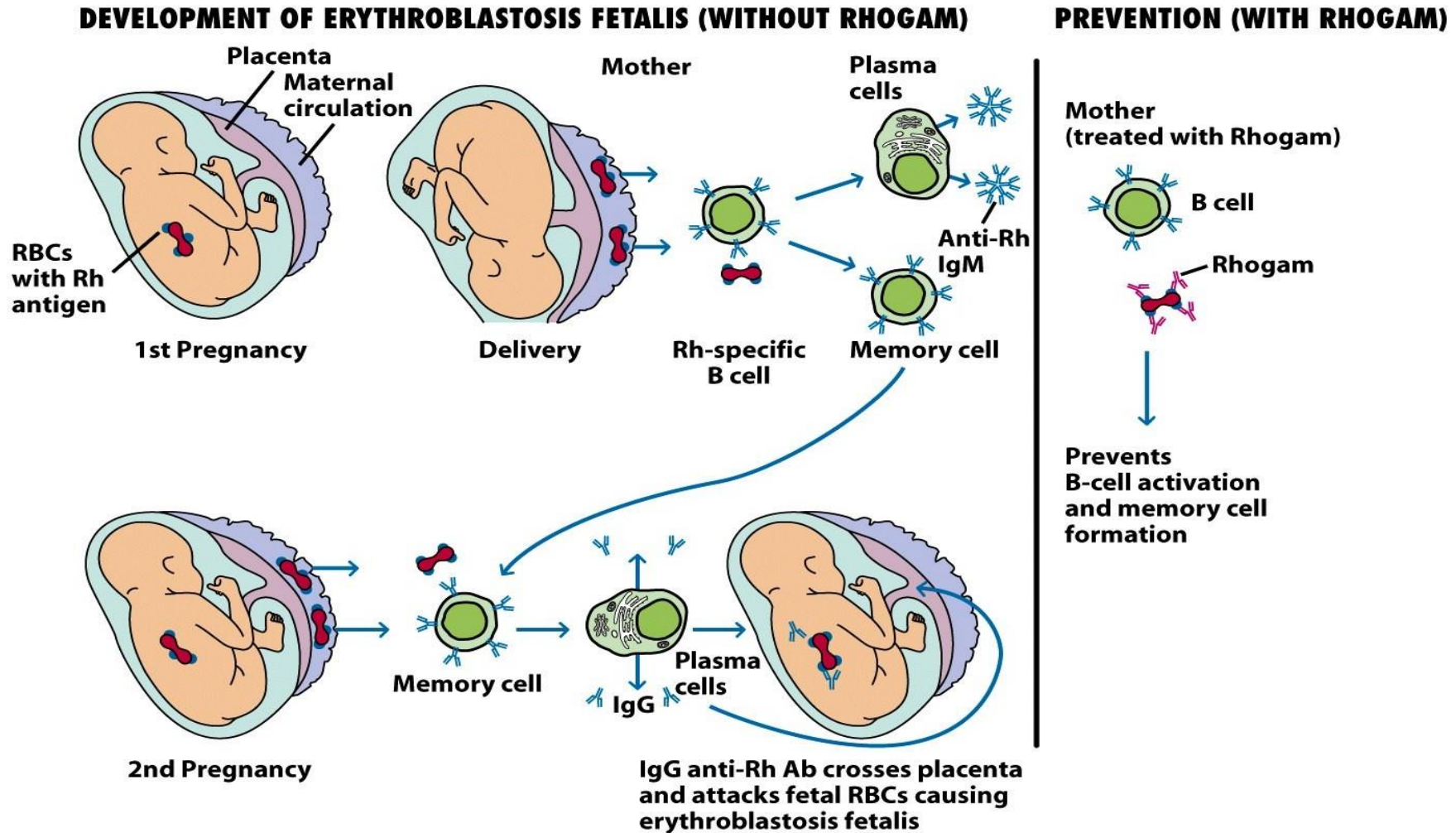
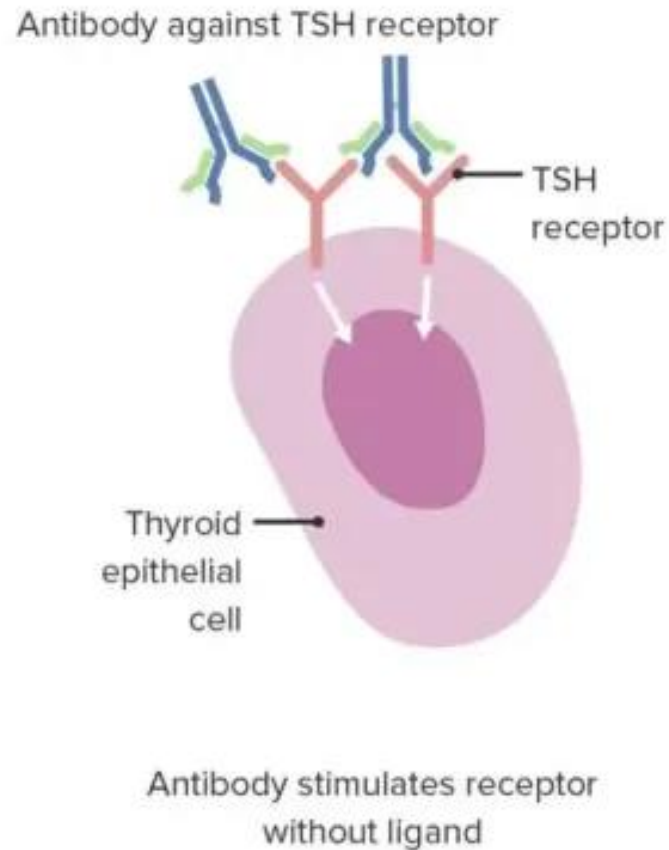


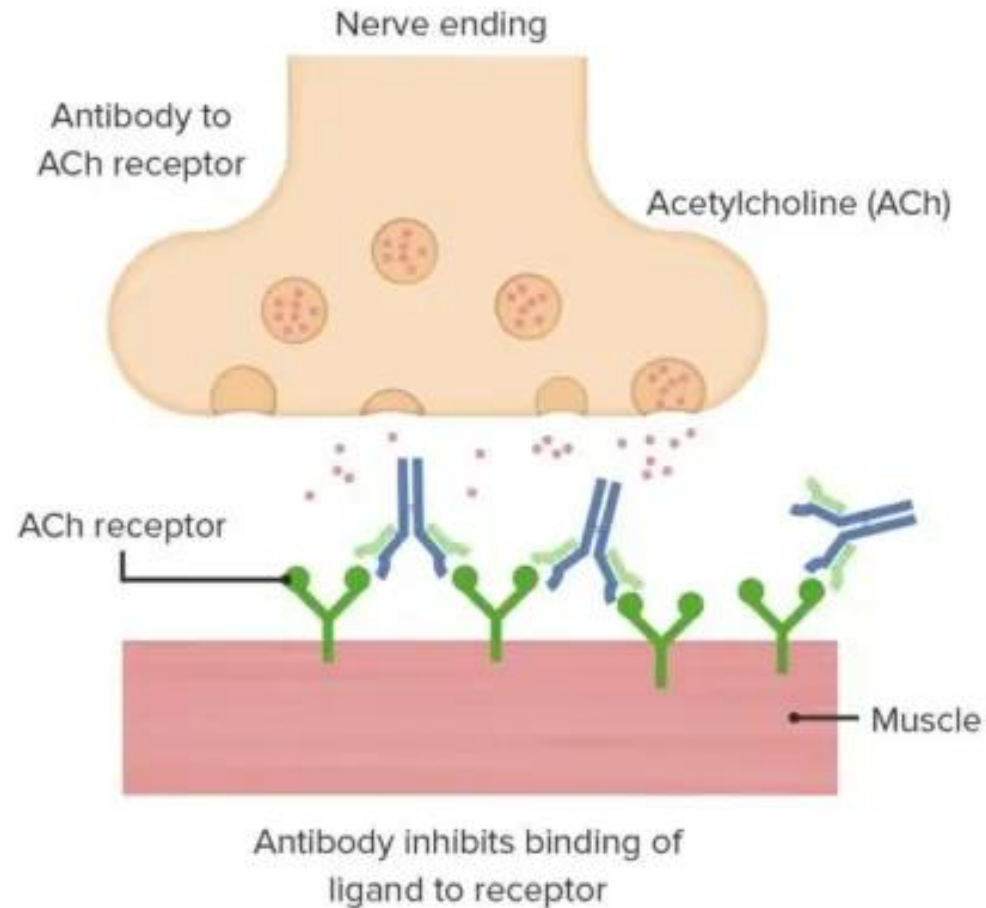
Figure 15-14
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Type II hypersensitivity

Graves' disease

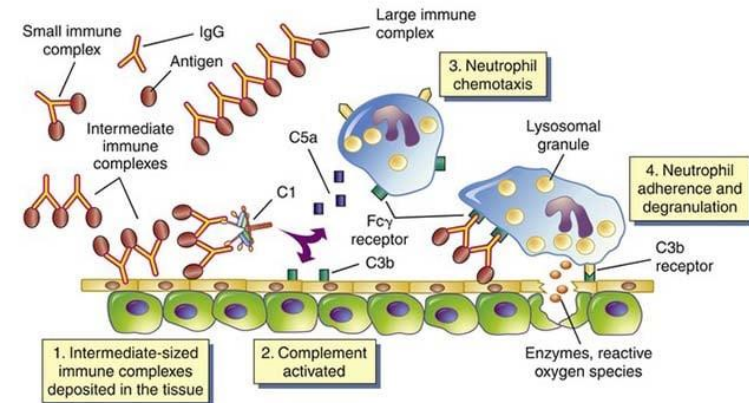


Myasthenia gravis



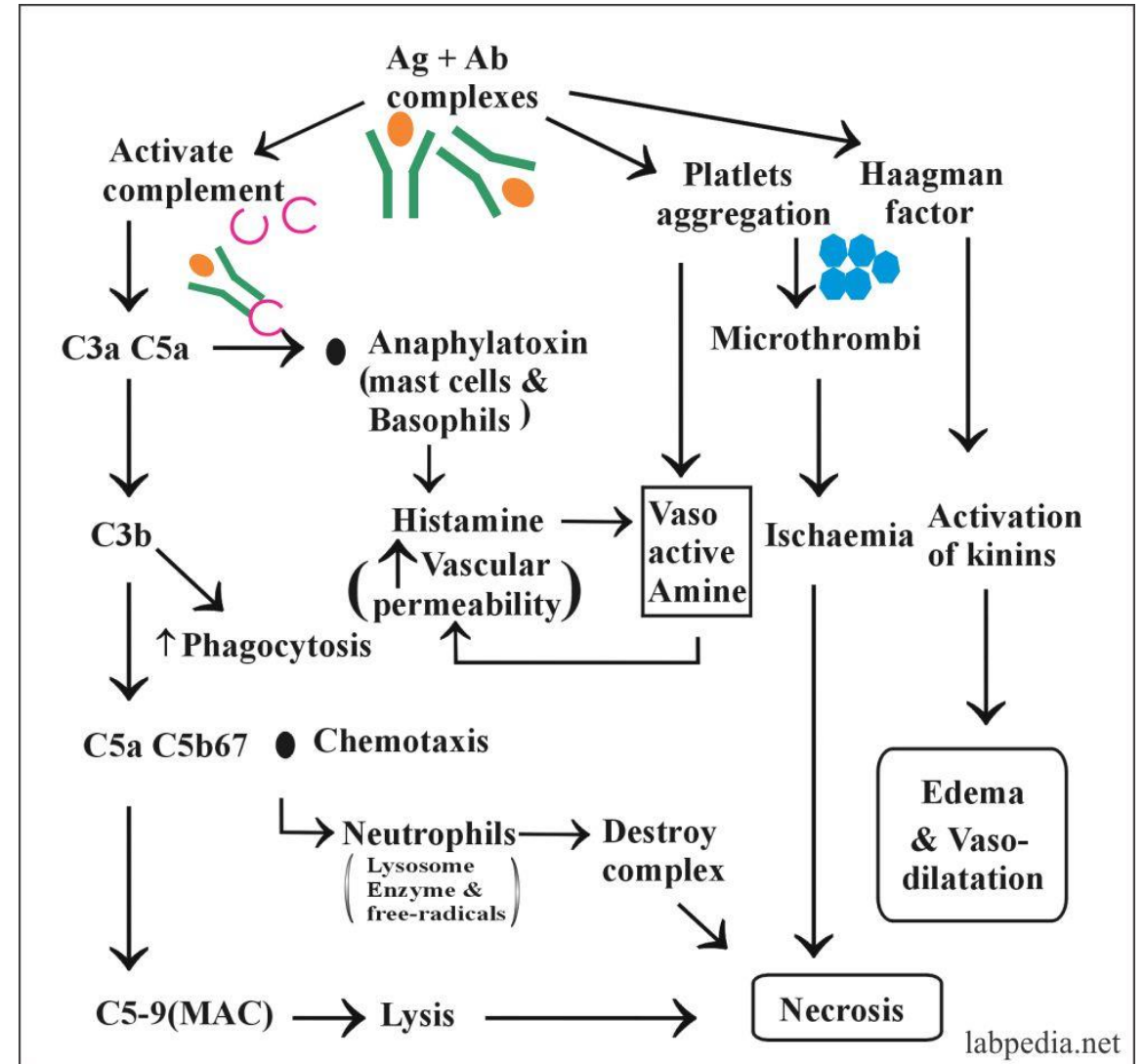
Type III hypersensitivity

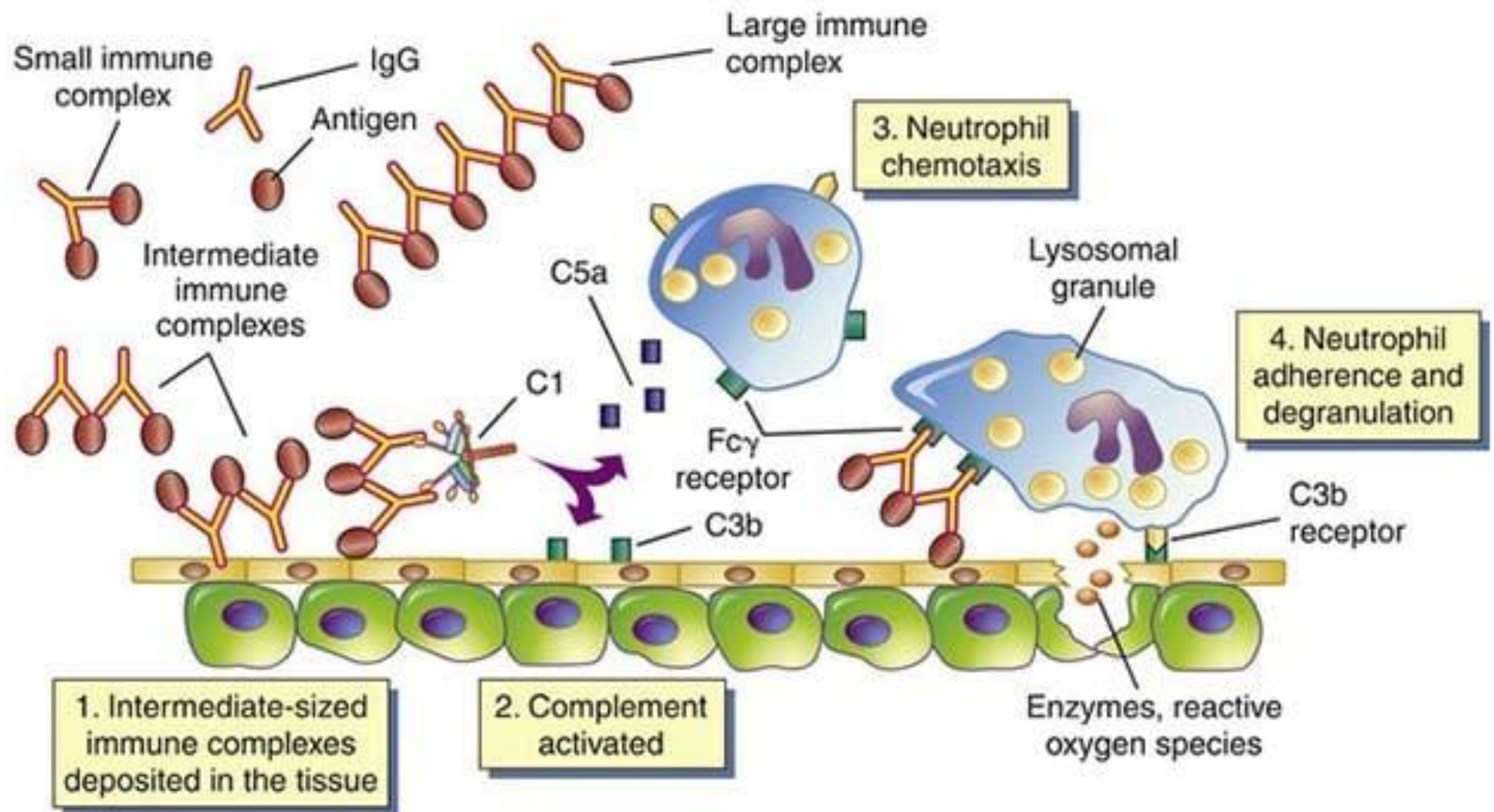
- diseases caused by immune complexes arise as a result of excessive production of immune complexes, which cannot be removed from the circulation, so they are deposited in the tissues
- since the complexes are primarily deposited in small arteries, glomeruli and joint synovium, the pathological and clinical manifestations of these diseases are vasculitis, nephritis and arthritis
- these diseases are usually systemic



Type III hypersensitivity

- antigen-antibody complexes exert their pathogenic effect after deposition in tissues
- after deposition in tissues, immune complexes trigger numerous effector mechanisms
- activation of effector mechanisms can cause tissue damage





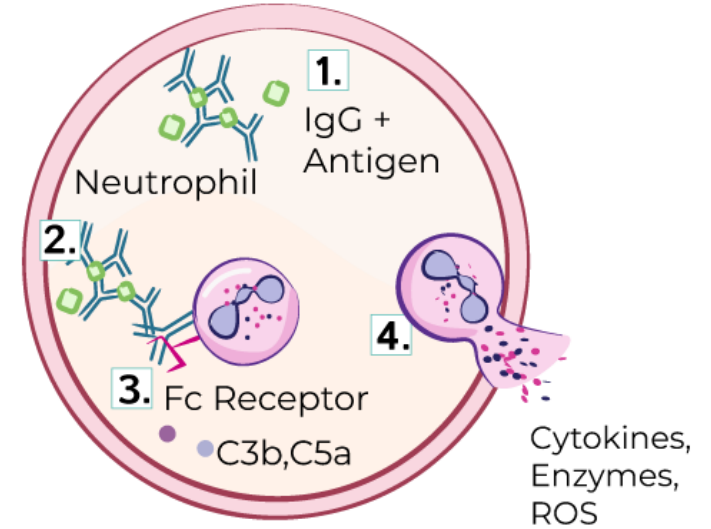
Type III hypersensitivity

Hypersensitivity Type III

IMMUNE COMPLEX-MEDIATED *IgG Antibody-Antigen Complexes*

PATHOPHYSIOLOGY

1. IMMUNE COMPLEXES FORM
2. COMPLEXES DEPOSIT ON VESSEL WALL (OR TISSUES)
3. COMPLEMENT & NEUTROPHIL ACTIVATION, INFLAMMATION
4. INC. PERMEABILITY → TISSUE DAMAGE



CLINICAL PATHOLOGY

VASCULITIS

FIBRINOID NECROSIS - IMMUNE COMPLEXES
& FIBRIN IN VESSEL WALL

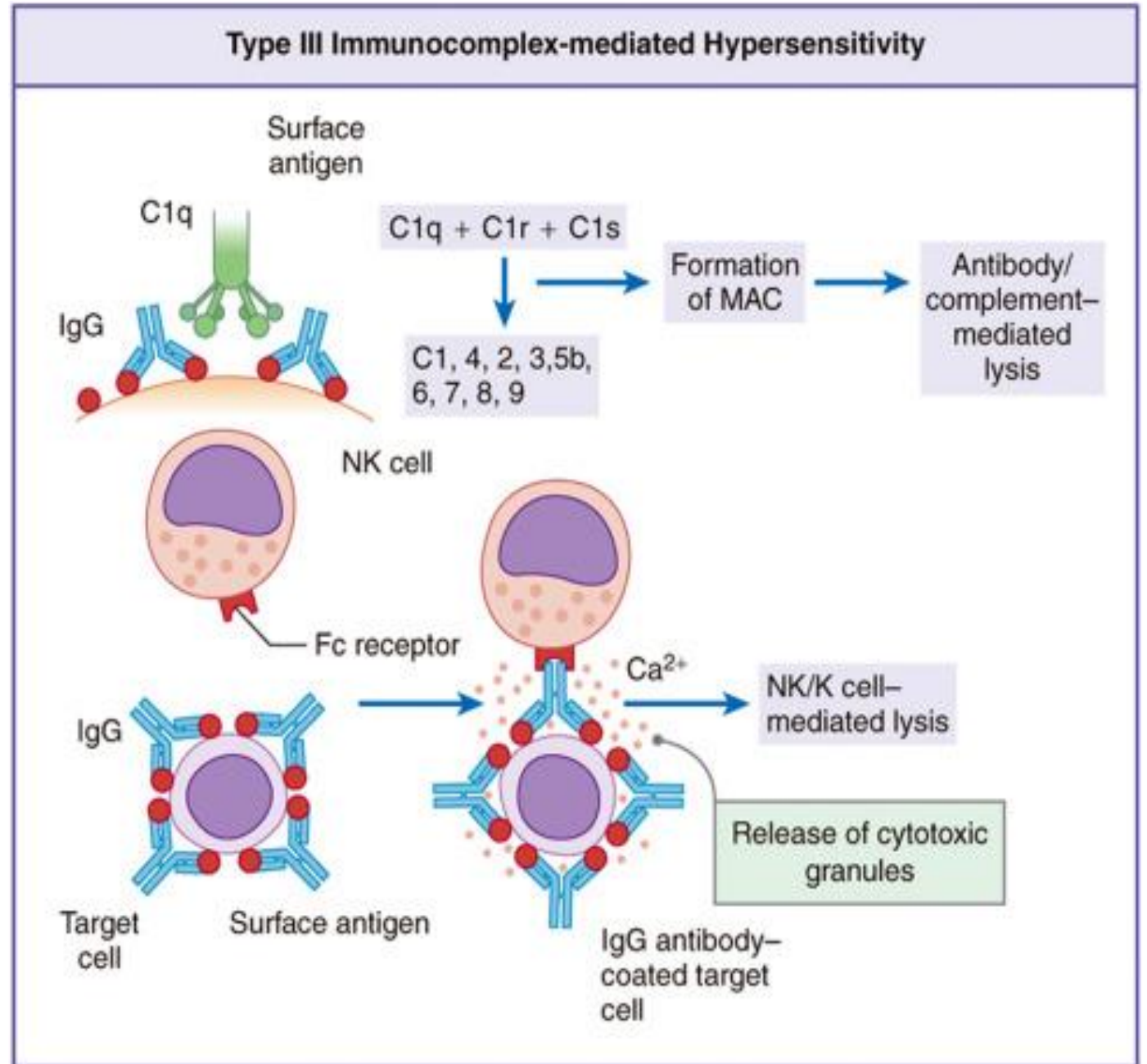
ARTHRITIS

COMPLEX PRECIPITATION & INFLAMMATION IN THE SYNOVIAL JOINT

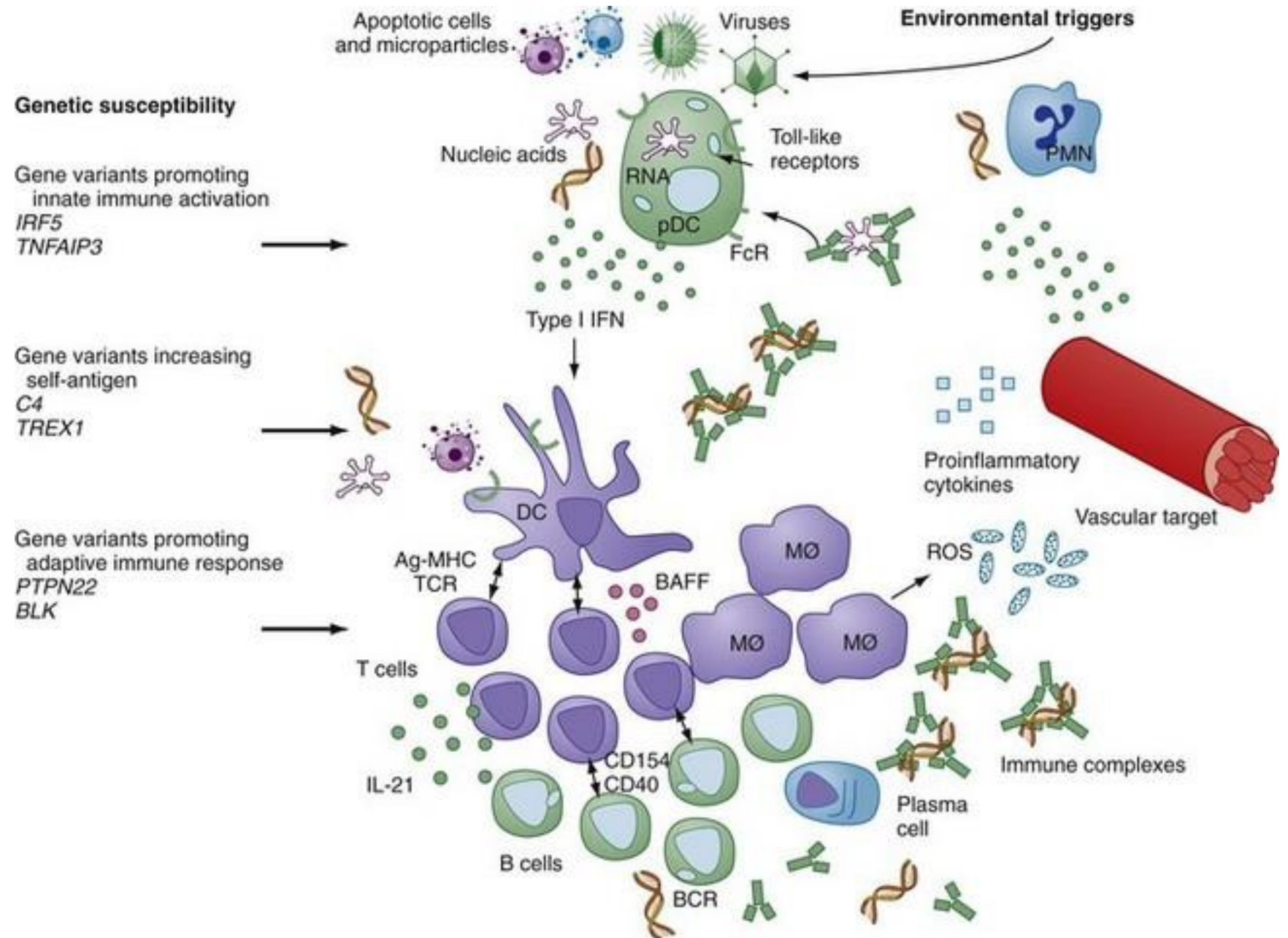
POST-INFECTION GLOMERULONEPHRITIS

ANTIGEN-ANTIBODY COMPLEXES IN BASEMENT MEMBRANE

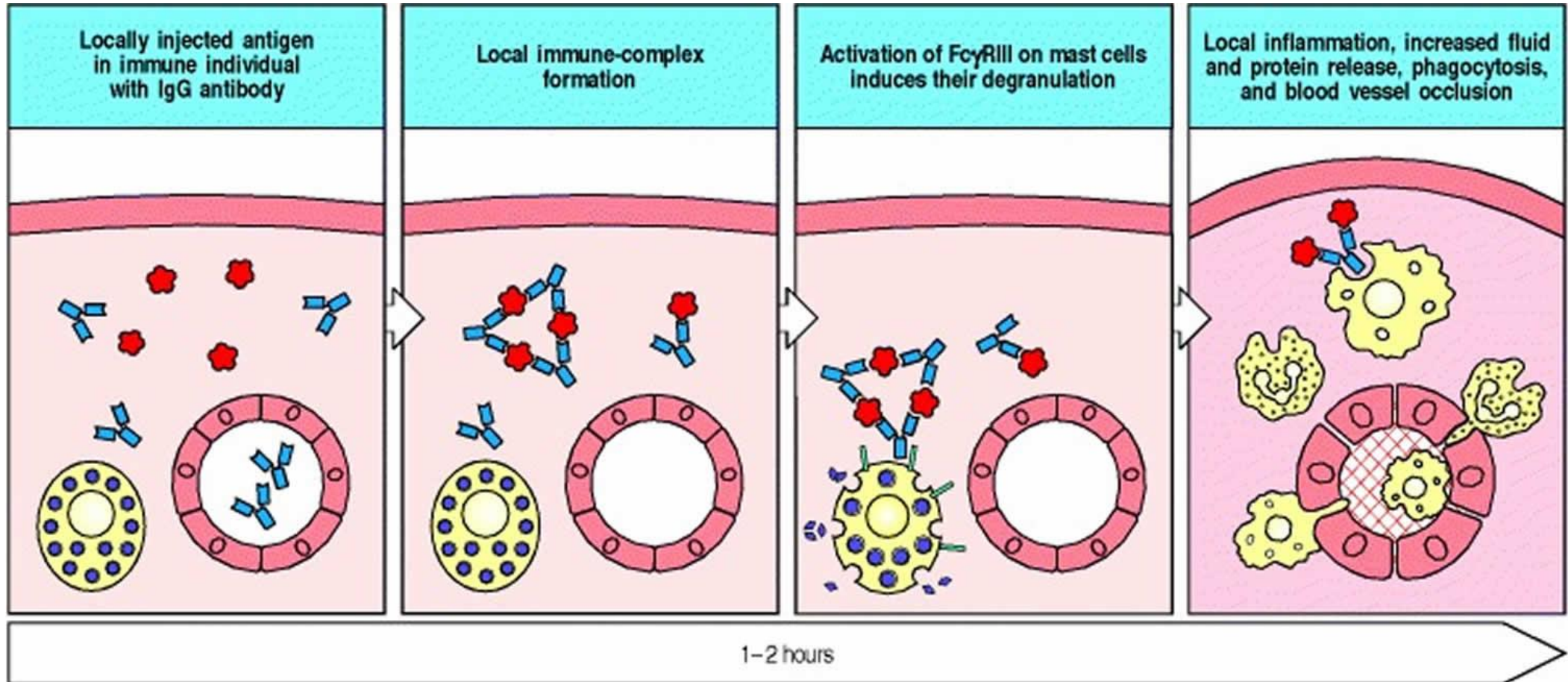
Type III hypersensitivity



SLE



Arthus reaction



Arthus reaction

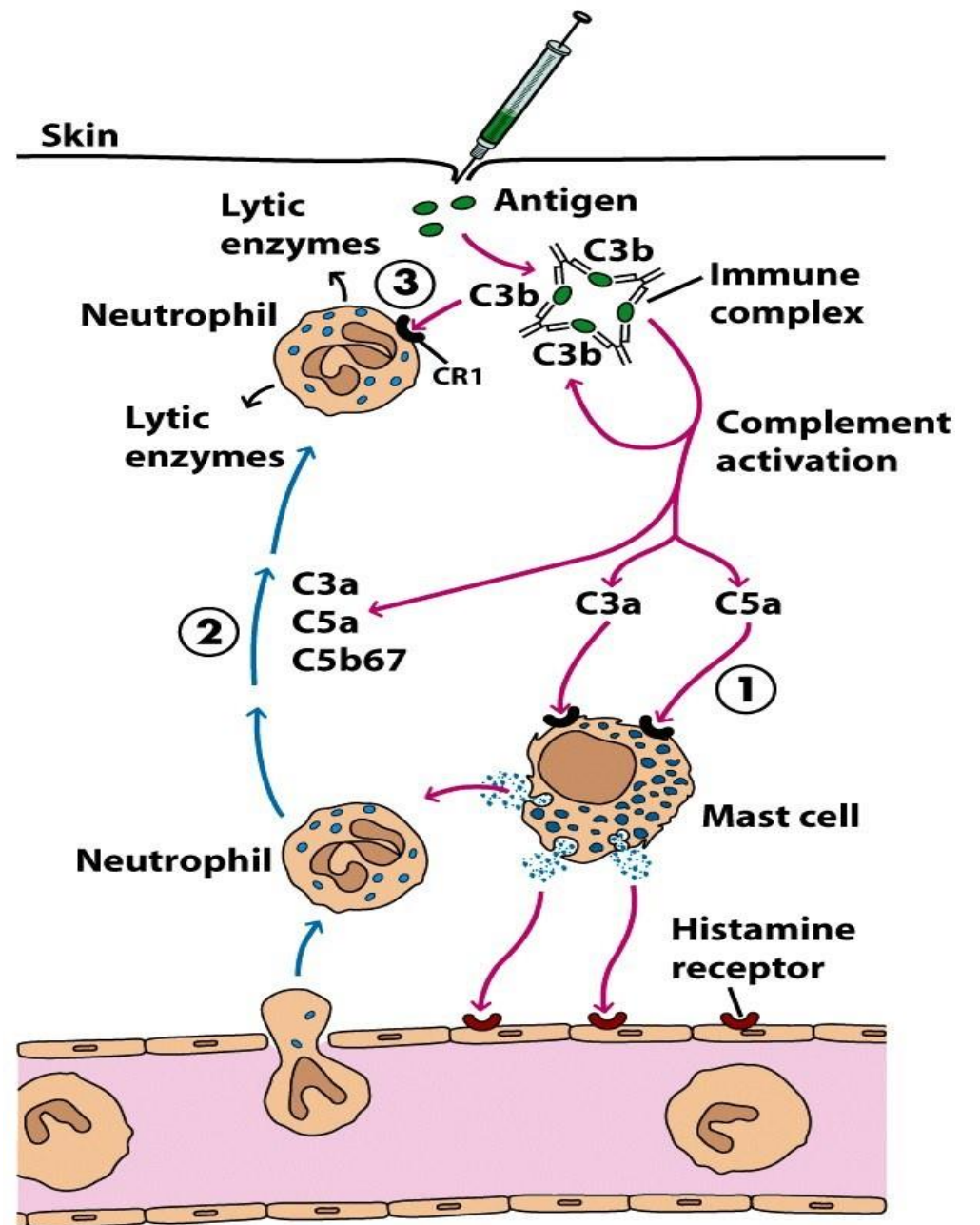


Figure 15-15
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Type IV hypersensitivity

- is mediated by **T lymphocytes** and not antibodies
- it can occur as a consequence of an autoimmune process or an excessive, persistent response to environmental antigens
- autoimmune reactions are usually directed against cellular antigens that have limited tissue distribution (usually not systemic)

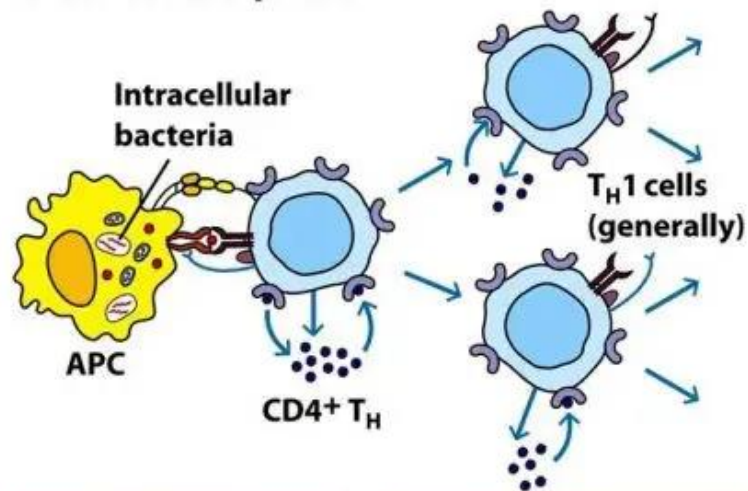
Type IV hypersensitivity reactions:

- contact hypersensitivity
- tuberculin form (body's response to microorganisms)
- granulomatous form (granulomatous inflammation)

Type IV hypersensitivity

Type IV - Hypersensitivity

Sensitization phase



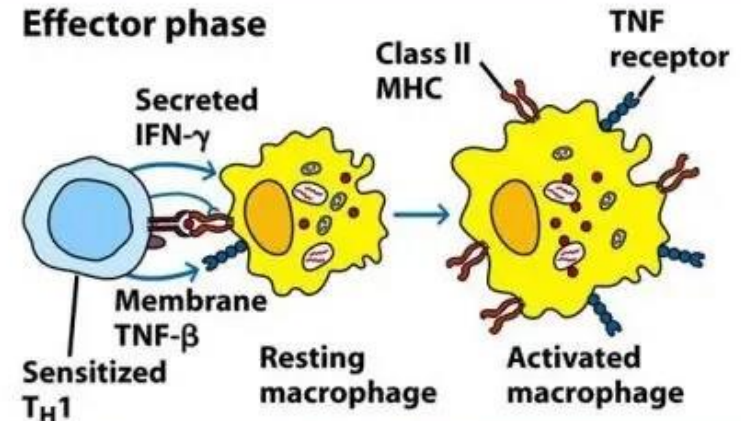
Antigen-presenting
cells: Macrophages
Langerhans cells

DTH-mediating cells:
T_H1 cells generally
CD8 cells occasionally

Figure 15-17a
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Type IV - Hypersensitivity

Effector phase



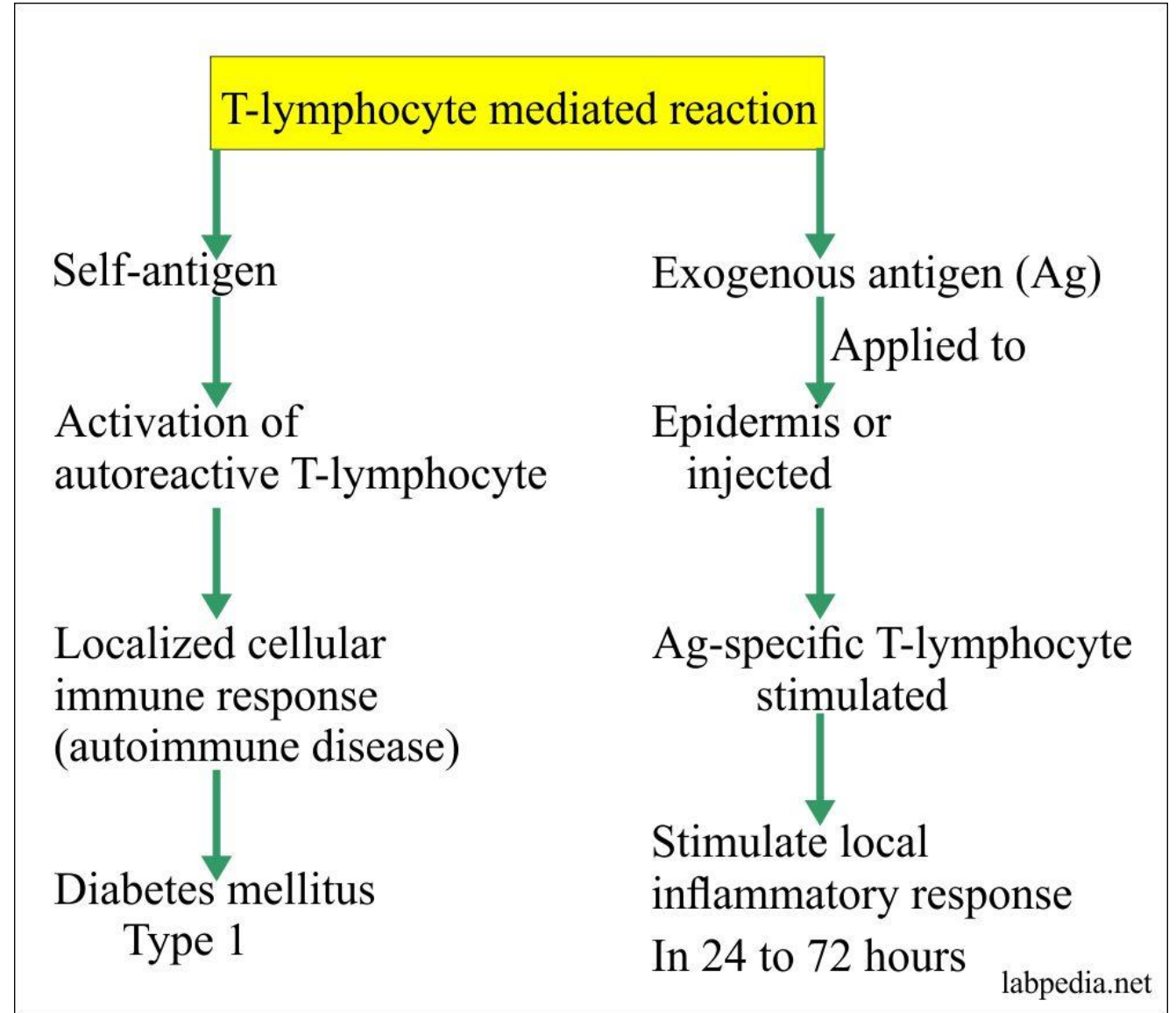
T_H1 secretions:
Cytokines: IFN-γ, TNF-β,
IL-2,
IL-3, GM-CSF, MIF
Chemokines: IL-8/CXCL8,
MCP-1/CCL2

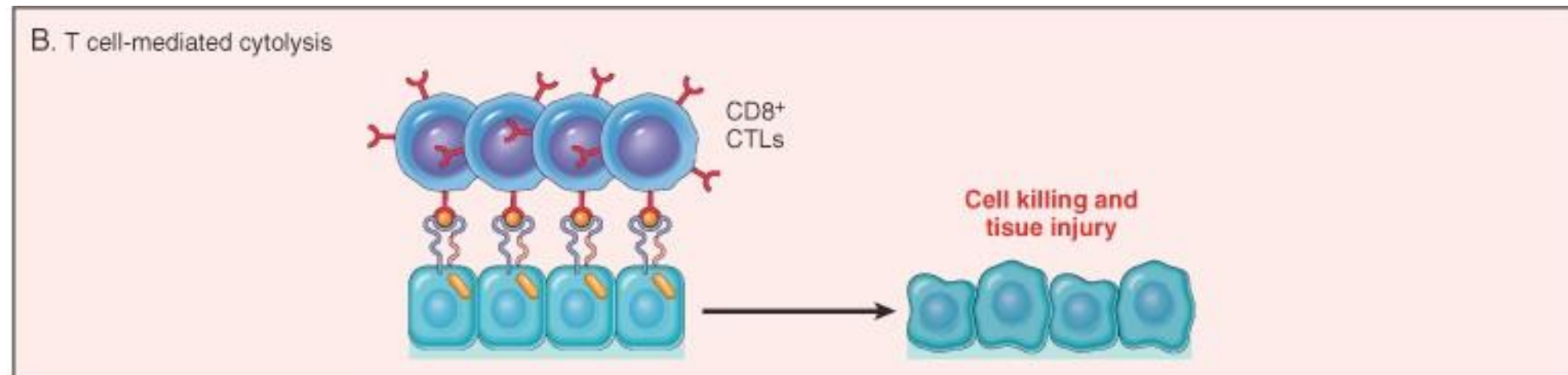
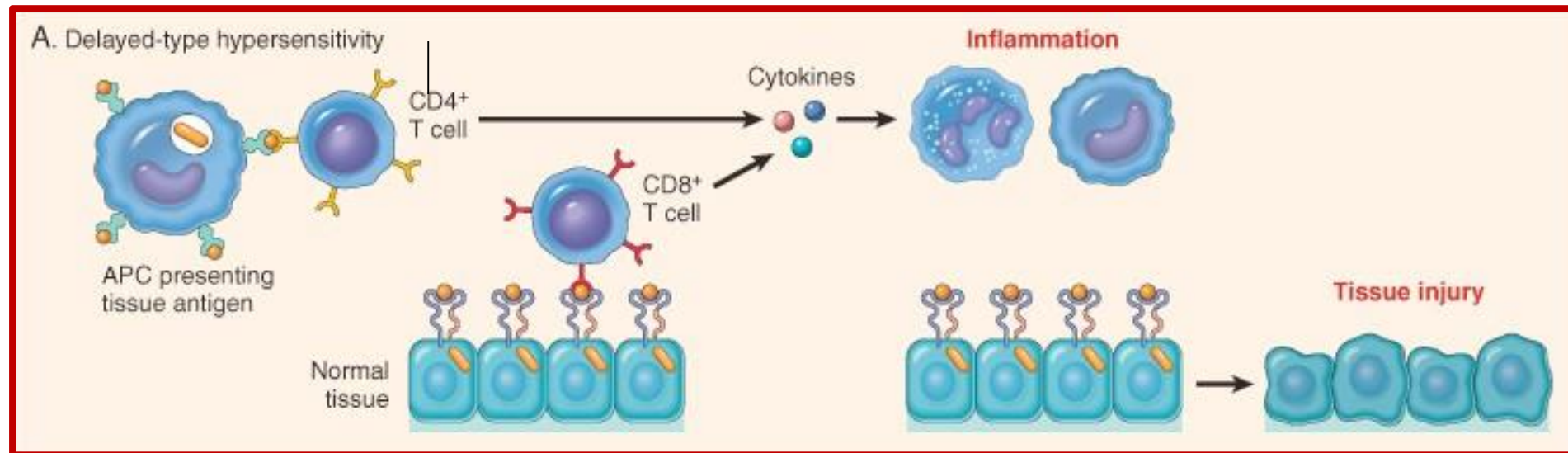
Effects of macrophage
activation:
↑ Class II MHC
molecules
↑ TNF receptors
↑ Oxygen radicals
↑ Nitric oxide

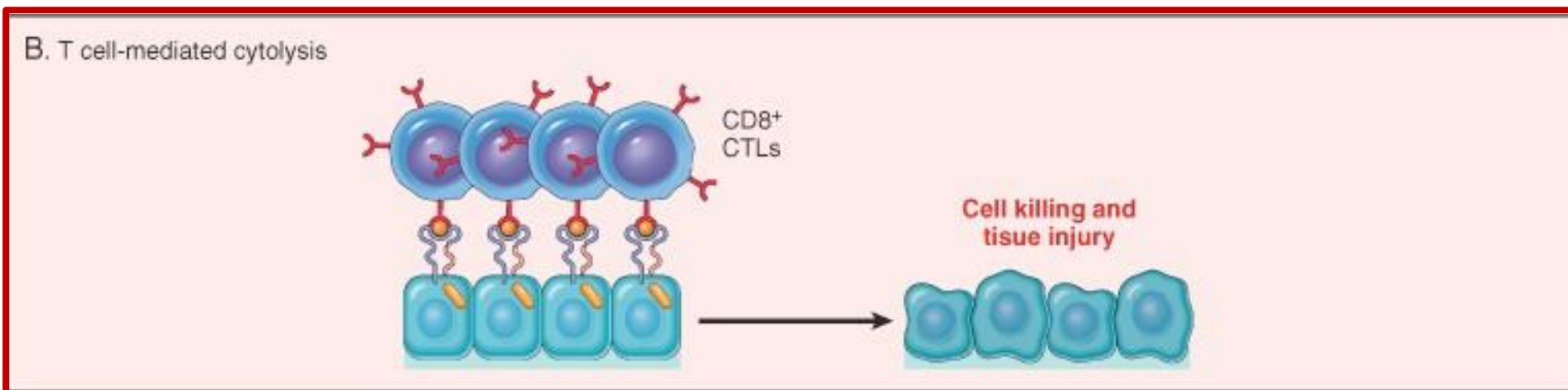
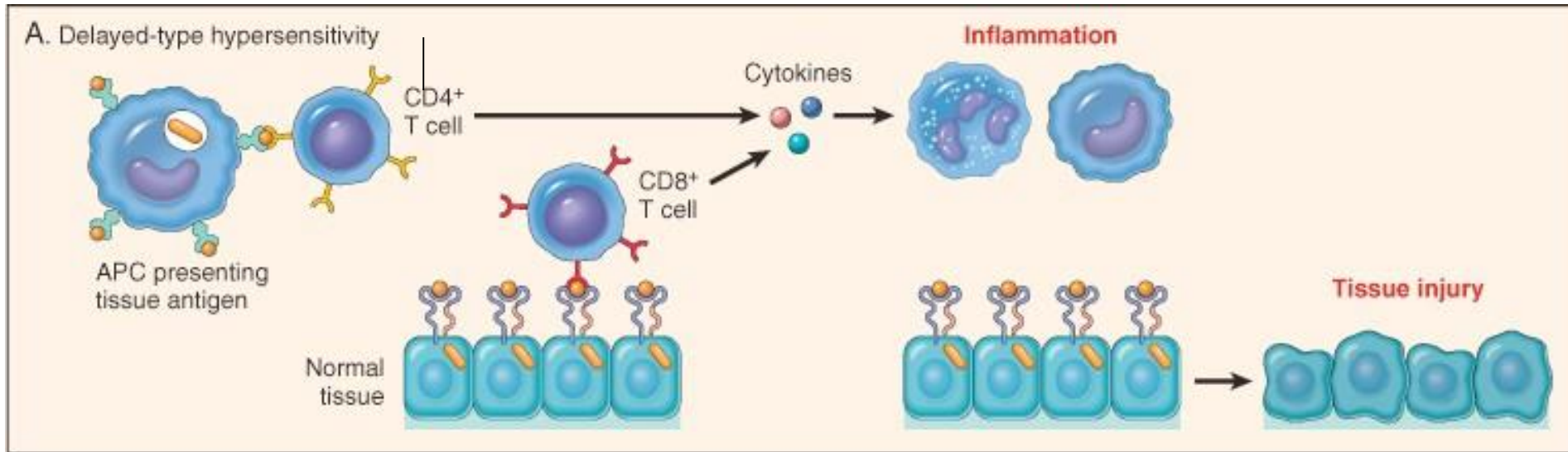
Figure 15-17b
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Type IV hypersensitivity

- in various T cell-mediated diseases
- tissue damage is caused by inflammation under the influence of cytokines mainly produced by CD4+ T lymphocytes or by killing of host cells by CD8+ cytotoxic T lymphocytes.







Contact dermatitis

- in this form of type IV hypersensitivity, very small molecules, which are not immunogenic in themselves (haptens), pass through the epidermis and form complexes with body proteins
- after the activation of specific T lymphocytes (sensitization), memory cells are formed
- during the next contact with the same allergen, memory T lymphocytes are activated with the onset of infiltration and damage

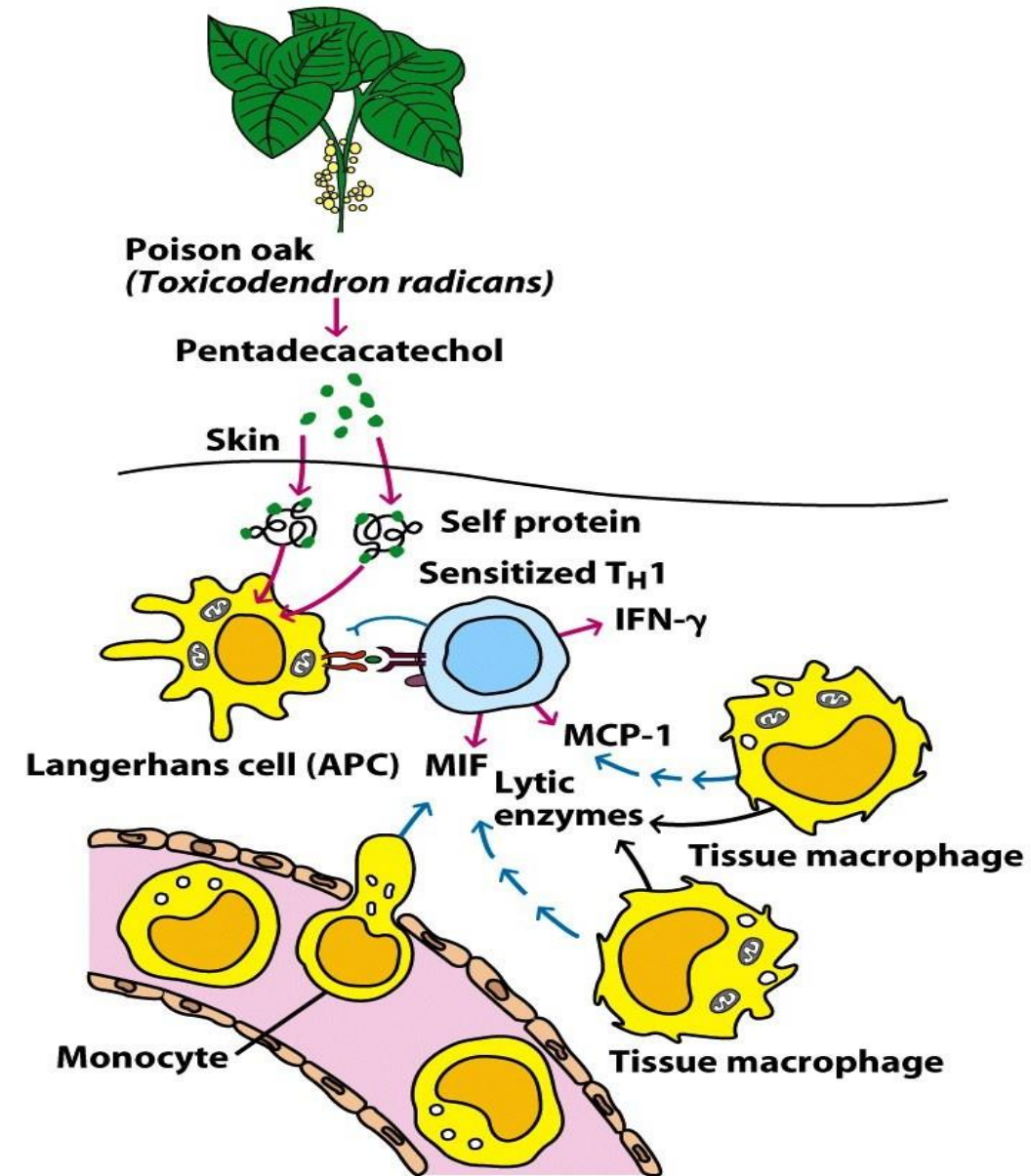


Figure 15-20
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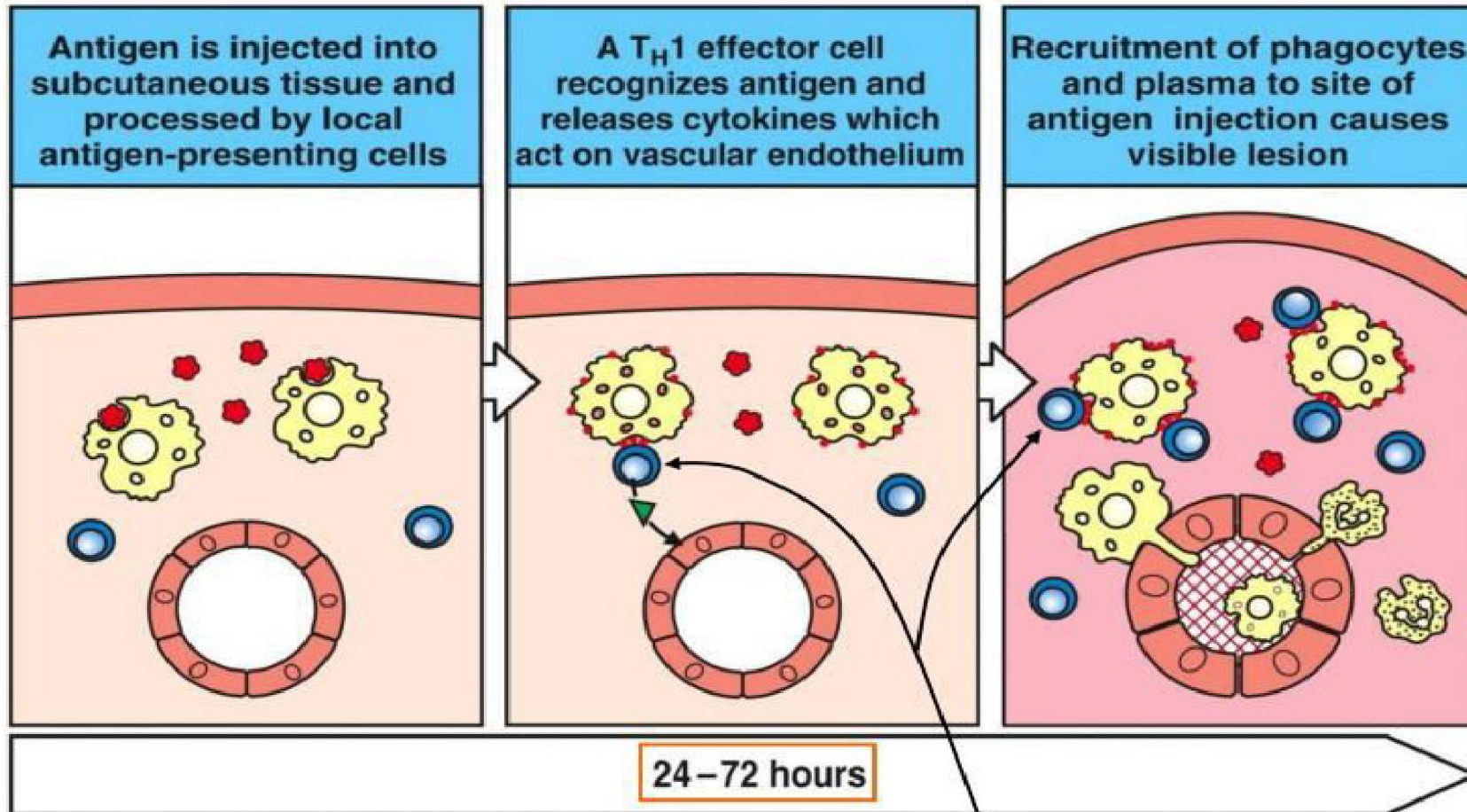


Figure 12-25 Immunobiology, 6/e. (© Garland Science 2005)

THANKS

