Immunopathology

- As a branch of Immunology, **immunopathology** concerns disorders caused by alterations of the immune response

- 3 main categories of alterations:
  - excessive response ⟹ hypersensitivity reactions
  - inappropriate response ⟹ autoimmune diseases
  - defective response ⟹ immunodeficiencies

Four types of hypersensitivity

	Hypersensitivity Types and Their Mechanisms			
	Type I	**Type II**	**Type III**	**Type IV**
Immune reactant	IgE	IgG or IgM	IgG and IgM	T cells
Antigen form	Soluble antigen	Cell-bound antigen	Soluble antigen	Soluble or cell-bound antigen
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Hallmarks of type I hypersensitivity reaction

- **Allergy** is the **most common** disorder of immunity
- Exposure to an antigen (**allergen**)
- Production of **IgE** which bind to Fc receptors on **mast cells**
- **Basophils** and **eosinophils** also partake in allergic reactions

Allergens

- Antigens that elicit immediate sensitivity reaction
- Most individuals who encounter these allergens do not produce specific IgE
- There is a **strong genetic predisposition** for the development of type I hypersensitivity, known as **atopy**
- Typical allergens are common environmental proteins, such as those contained in pollen, house dust mites, animal dander, some foods and chemicals

Principali allergeni

POLLINI

Urticacee
Parietaria officinalis,Parietaria judaica
Ortica

Graminacee
Loglio, Coda di topo, Erba canina
Erba fierasta, Erba mazzolina
Paleo dei prati

Piante arboree
Olivo, Betulla, Quercia
Salice, Platano, Faggio, Olmo

Composite
Assenzio, Ambrosia
Dente di leone, Girasole
Margherita dei prati
Plantaginacee

Lanciuole

Chemopodiacee
Spinaico selvatico

ALIMENTI

Bianco d'uovo, Latte
Merluzzo, Frumento
Segale, orzo
Avena, Mais
Riso, Pisello
Arachide, Soia
Fagiolo, Noce
Nocciola, Castagna
Mandorla, Granchio
Pomodoro, Carne maiale
Carne bue, Banana
Carota, Limone
Aranci, Patata
Mitili, Tonno
Salmone, Fragola
Lievito ac. naturale
Aglio, Mela
Cacao, Caffe', Rosso d'uovo
Lattoalbumina, Lattoglobulina
Caseina, Glutine
Aragosta, Carne di pollo
Kiwi, Sedano, Prezzemolo
Melone, C. agnello
Senape, Pepe nero
Noce moscata, Lattuga
Cipolla, The, Spinacio
Cavolo, Pera, Pesca
Albicocca, Ciliegia, Lenticchia
Fava, Peperone, Melanzana
Carciofo, Uva, Mandarino
Basilico, Salvia, Cannella
Origano, Camomilla
Carne di coniglio

ARTROPODI

Dermatophagoides pter.
Dermatophagoides farinae
Acarus siro

EPITELI ANIMALI

Epitelio di gatto
Epitelio di cane
Forfora di cane
Forfore di cavallo
Epitelio di topo
Urina di topo
Epitelio di capra
Epitelio di pecora
Epitelio di coniglio
Epitelio di criceto
Piume di pappagallo
Forfore di gatto
Piume di colombo

VELENI DI IMENOTTERI

Api
Vespe
Calabroni

PARASSITI

Echinococco
Ascaridi

FARMACI

Penicillina G
Penicillina V
Insulina porcina
Insulina bovina
Insulina umana
Penicilline
Cefalosporina
Ampicillina
Amoxicillina
Acido Acetilsalicilico

MUFFE

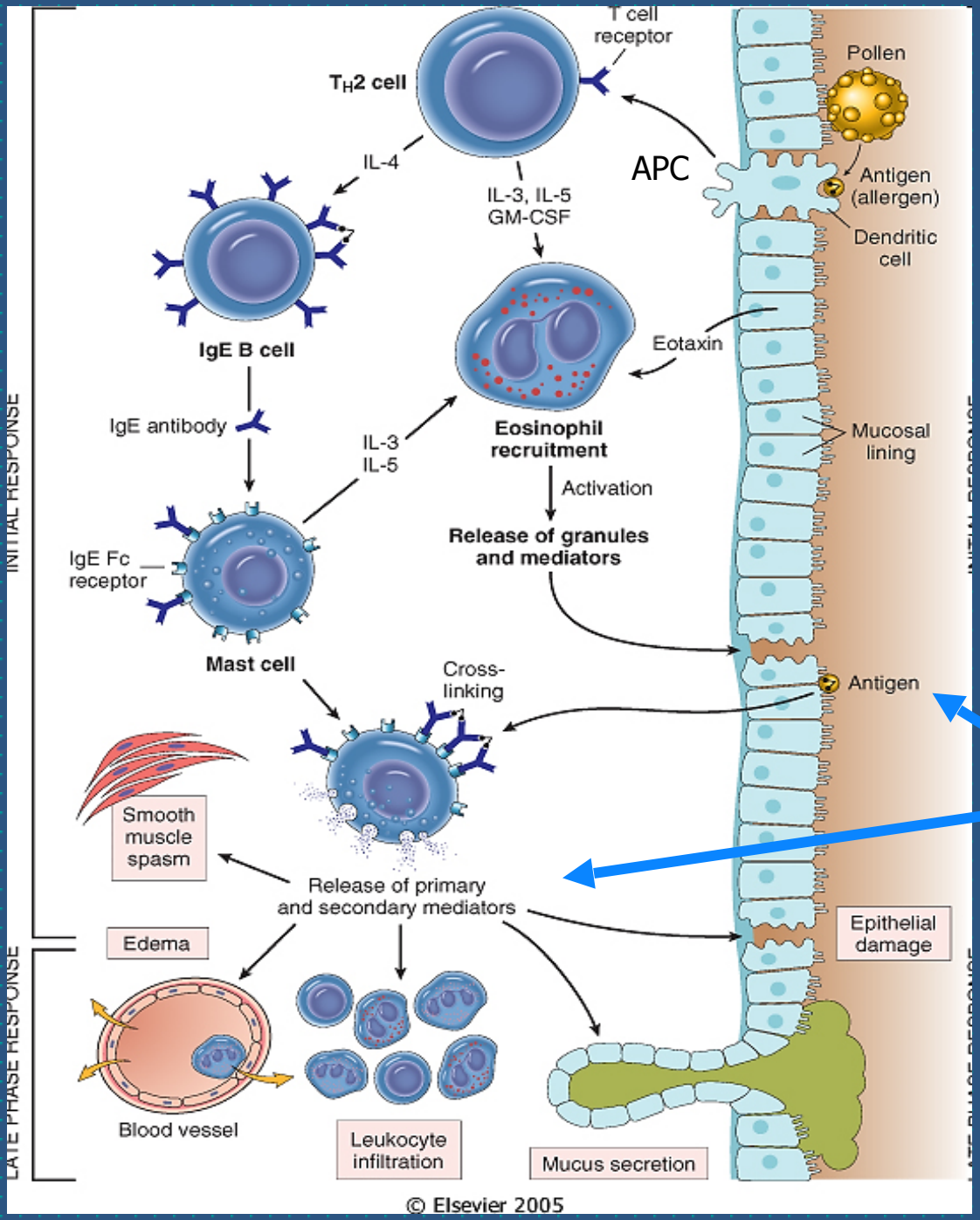
Cladosporium
Aspergillus fumigatus
Alternaria tenuis

VARIE

Seta cruda
Ficus benjamin
Latex
Cotone
Riso (polvere)
Polvere di mulino
Alcalase
Fieno
Juta
Kapok
Lino
Paglia
Polvere di tabacco
Polvere di legno Acero, Faggio, Quercia, Mogano, Noce, Obece, Ramin, Abete, Teak

Sequence of major events in type I hypersensitivity reaction

- First exposure to allergen (sensitization phase)
- **Activation of Th2 cells**
- Stimulation of IgE class switching in B cells
- Binding of released IgE to Fc receptors on mast cells and basophils
- Repeated exposure to allergen
- Release of mediators from mast cells



First exposure to allergen

sensitization phase

Second exposure to allergen

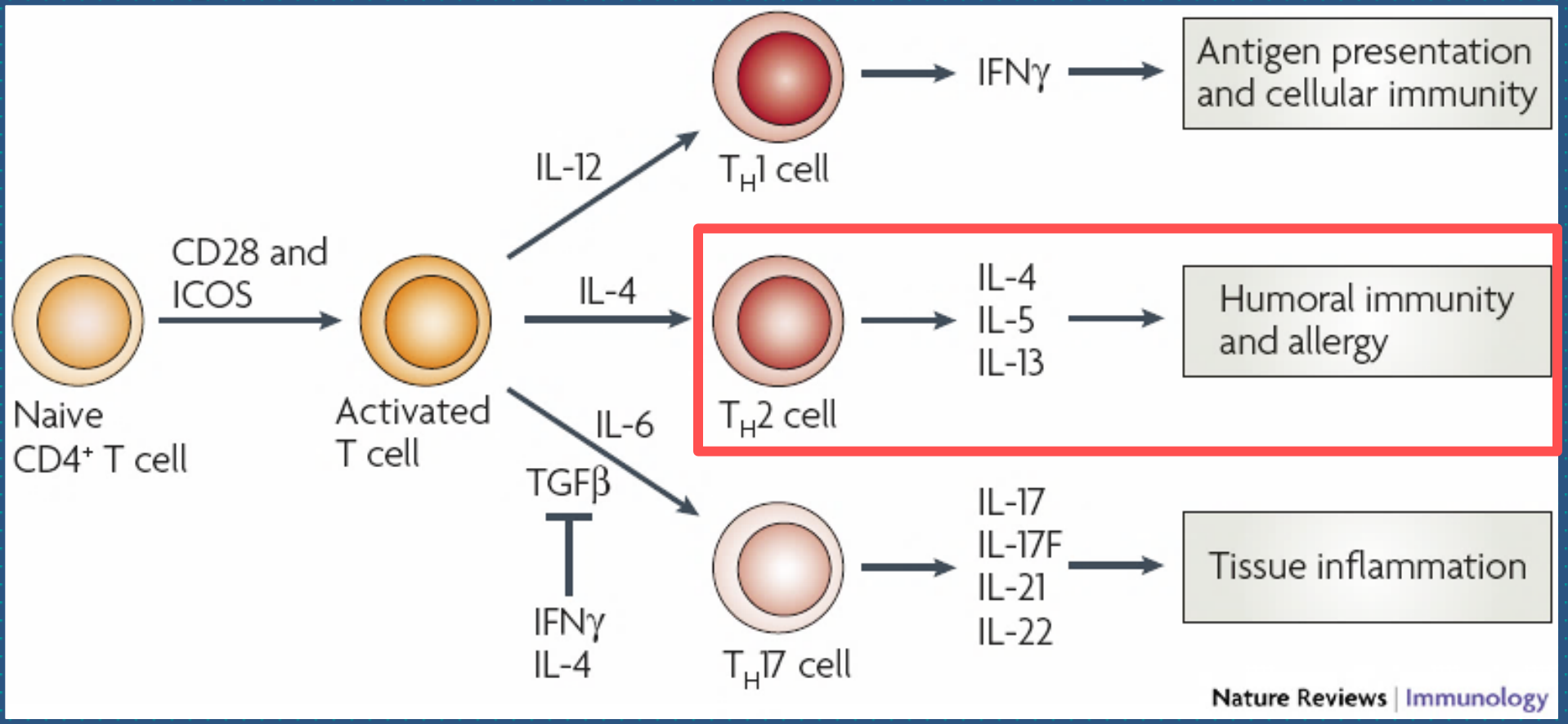
trigger phase (immediate and late-phase reactions

Reactions of type I hypersensitivity

- **Immediate** reaction (within **minutes**): immediate **degranulation** of mast cells and subsequent inflammation; vascular and smooth muscle responses are dominant

- **Late-phase** reaction (**2 to 4 hours** later): other inflammatory mediators such as **leukotrienes**, **chemokines** and **cytokines**; leukocyte recruitment, magnified inflammatory response

Origin of diverse **CD4+** (T helper) cell **subsets**



Naive CD4+ T cells, after activation by signalling through the T-cell receptor and co-stimulatory molecules such as CD28 and inducible T-cell co-stimulator (ICOS), differentiate into one of **three** lineages of effector T helper cells, **T_H1, T_H2 or T_H17**, which produce **different cytokines** and have **distinct immunoregulatory functions**

Central role of **Th2** cells in allergic reactions

- IgE synthesis is dependent on activation of Th2 cells and their secretion of **IL-4** and **IL-13**
- IL-4/IL-13-stimulated B cells undergo **heavy chain isotype switching** and **secrete IgE**
- Th2 also release **IL-5** that recruits and activate eosinophils
- **IL-13** released by Th2 also stimulates epithelial cells (e.g. in the airways) to secrete **increased amount of mucus**

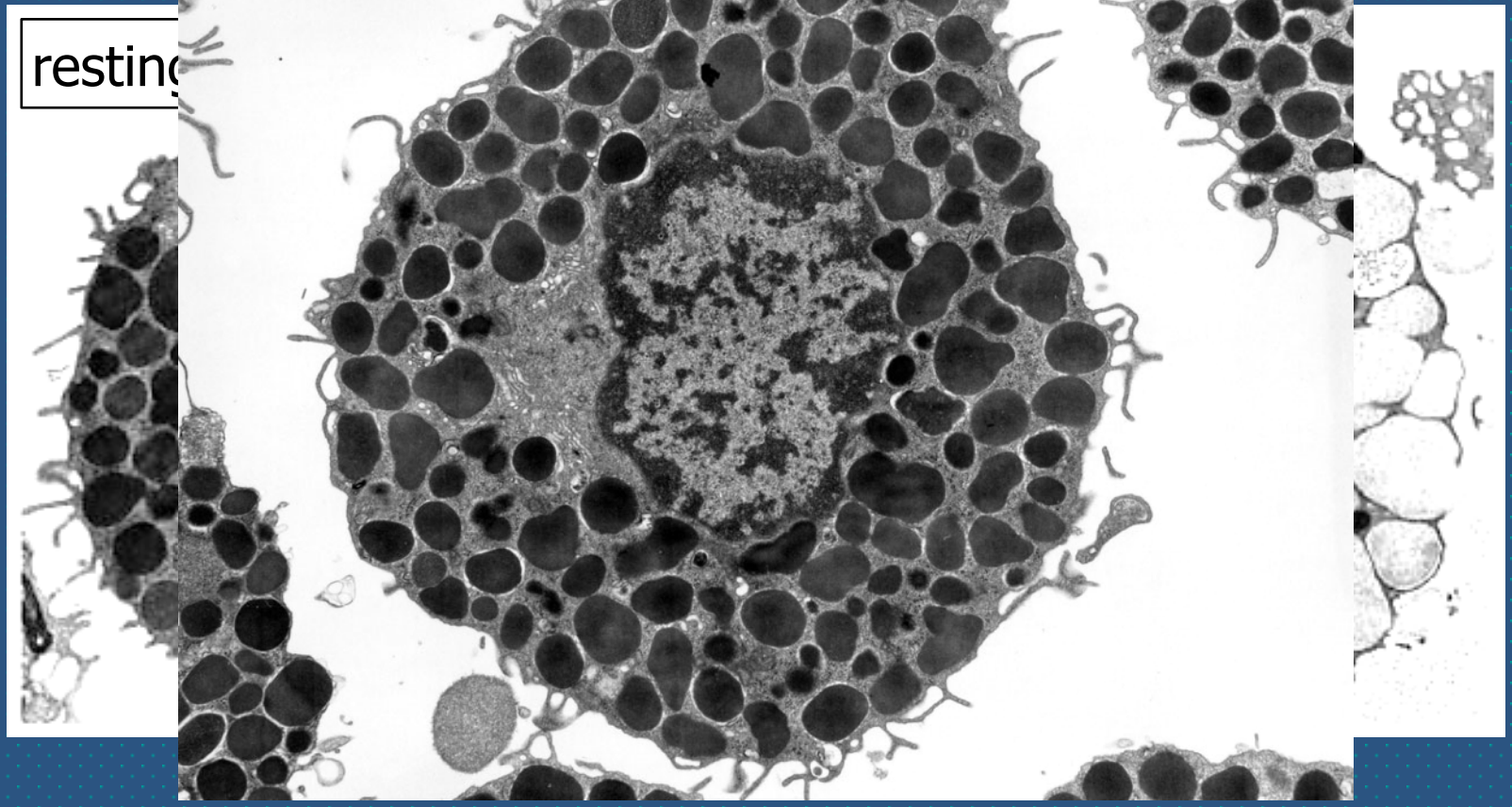
Genetic susceptibility to type I hypersensitivity

- The propensity to produce **high levels of IgE** (**atopy**) is influenced by a **multigenic pattern** of inheritance

- The **genes involved** code for several **proteins** which have a role in the **regulation of hypersensitivity**, such as:

  - modulators of T cell activation
  - IL-4 and IL-13 (IgE class switching)
  - IL-5 (eosinophil recruitment and activation)
  - stem cell factor (mast cell maturation)

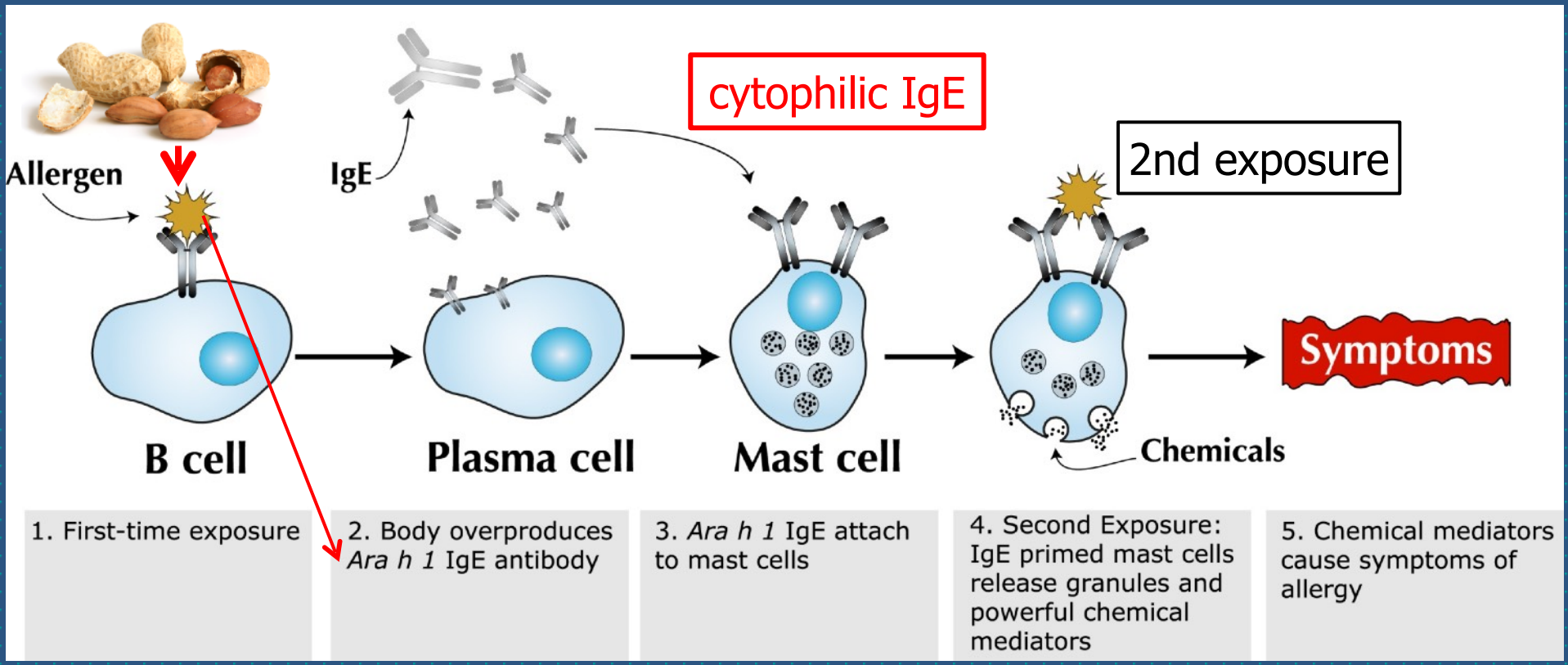
Mast cells



- Two major mast cell subsets are present in humans:
  - **Connective tissue** MC: skin, intestinal submucosa
  - **Mucosal** MC: airways, intestinal mucosa

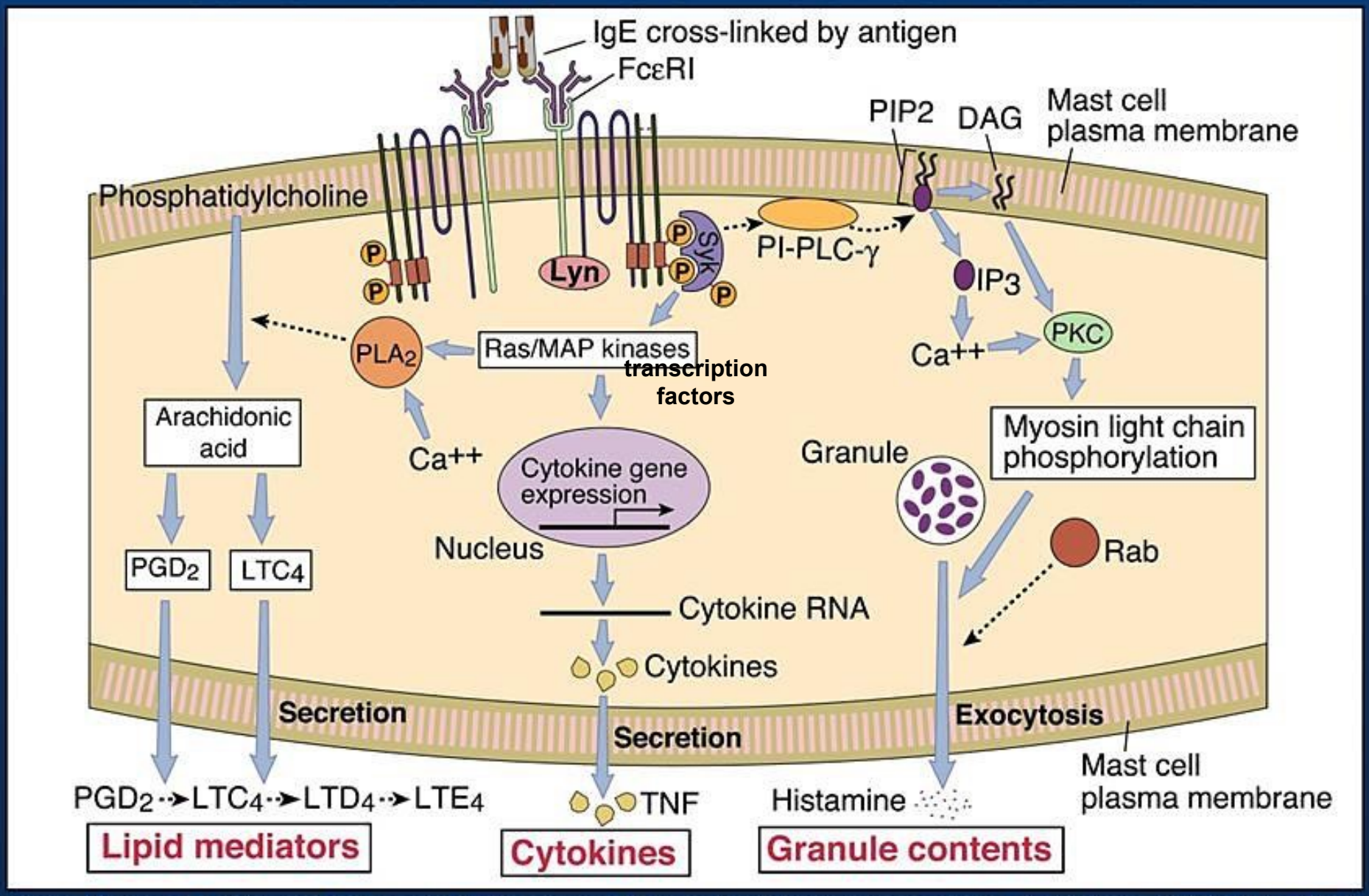
Crucial role of IgE in type I hypersensitivity

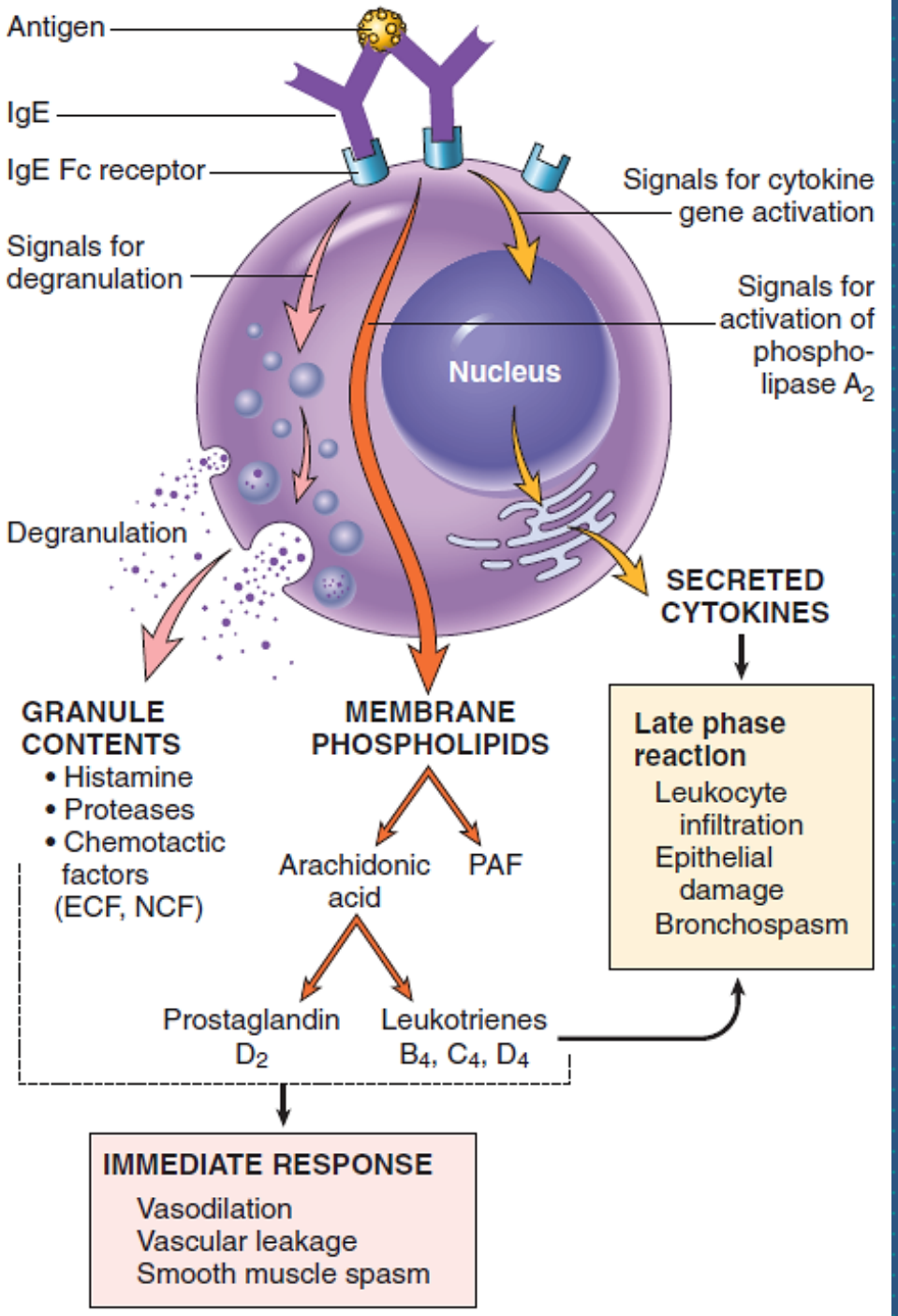
- Mast cells are primed with IgE bound to surface FcεRI



- Upon secondary exposure, allergen binds IgE and cross-links to activate FcεRI signals, such as **tyrosine phosphorylation**, **Ca++ influx** and others

Biochemical events of mast cell activation





Upon activation, mast cells release various classes of mediators that are responsible for the **immediate** and **late-phase** reactions.

ECF, eosinophil chemotactic factor; NCF, neutrophil chemotactic factor; PAF, platelet-activating factor.

Most common forms of atopic diseases

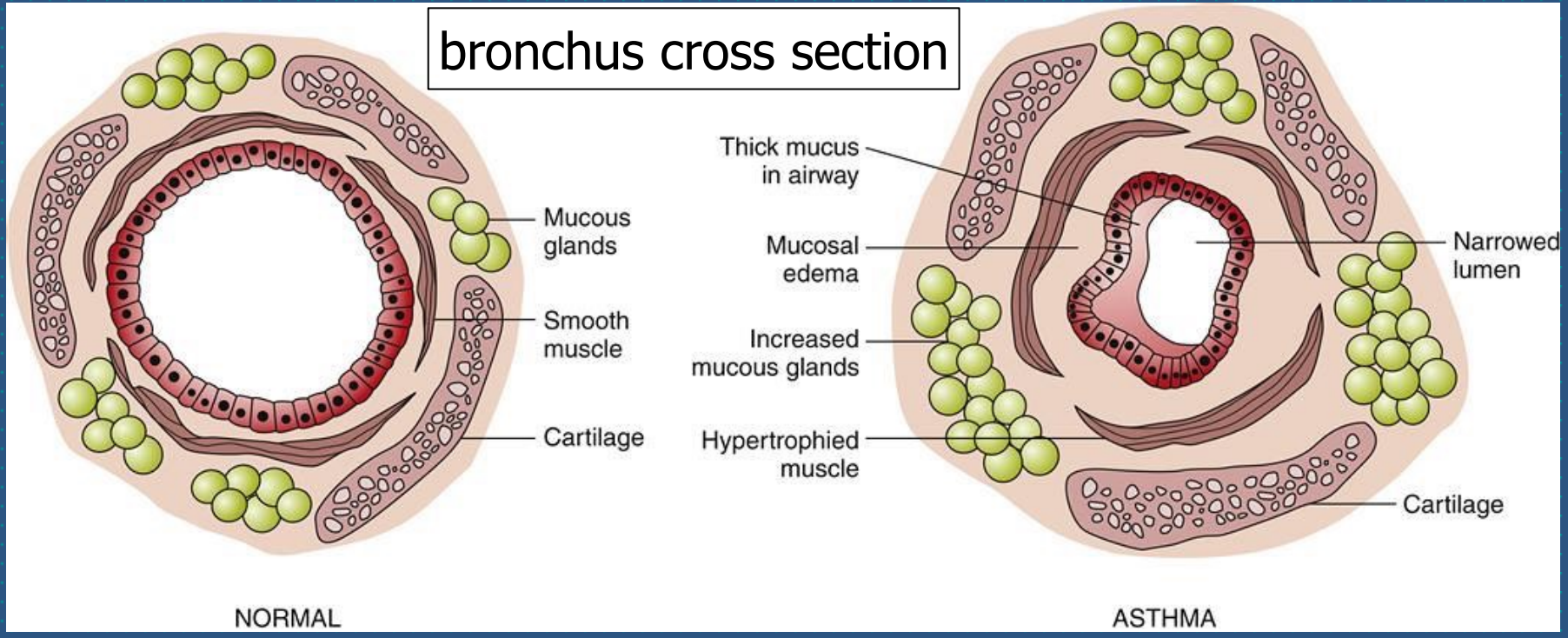
- The clinical and pathologic manifestations **depend on:**
  - **the tissues** in which the mediators released by mast cells, basophils and eosinophils have effects
  - **the chronicity of the resulting inflammatory reaction**

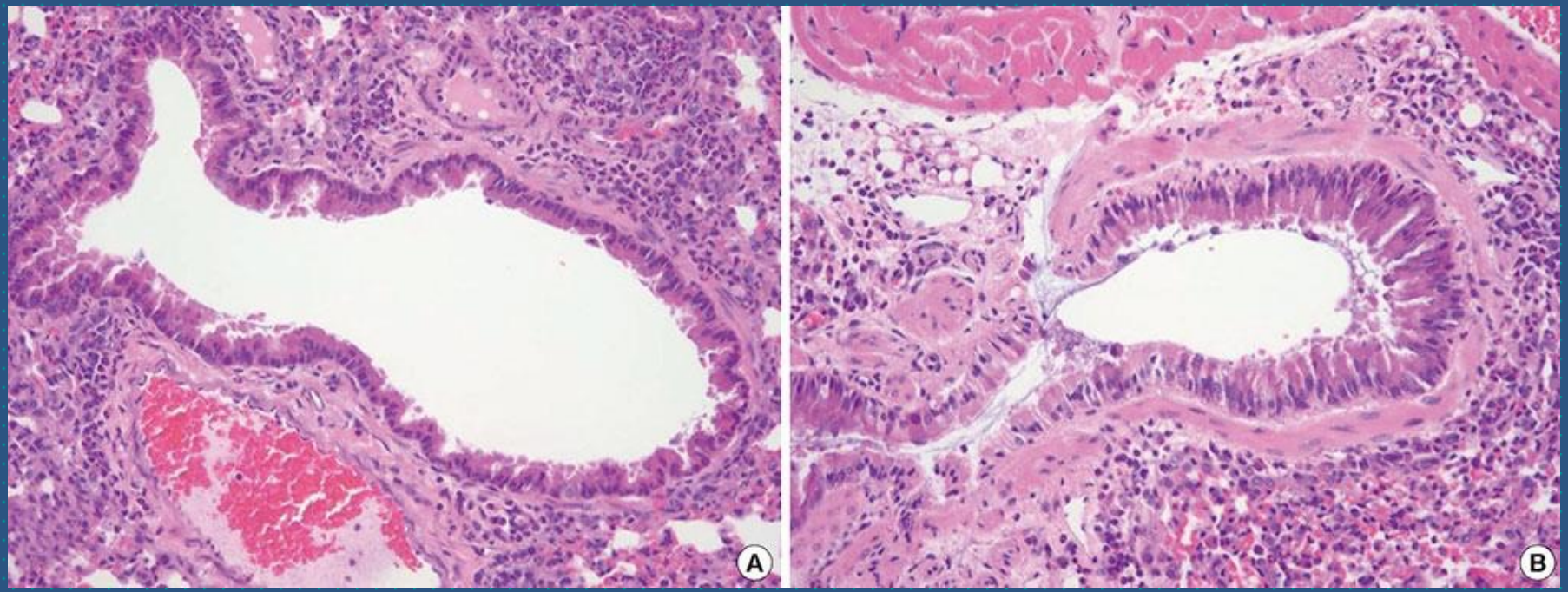
- Allergic rhinitis (hay fever)
- Bronchial asthma
- Atopic dermatitis (eczema)
- Food allergies

Bronchial asthma

- Inflammatory disease caused by **repeated** immediate and late-phase hypersensitivity reactions **in the lung**
- Affects 10 to 20% of childs and adults living in industrialized countries
- Major clinico-pathologic manifestations:
  - intermittent **airway obstruction**
  - chronic **bronchial inflammation**
  - bronchial **smooth muscle hypertrophy** and **hyperplasia**
  - **hyperreactivity** to **bronchoconstrictors** (products derived from arachidonic a., LTC4, LTD4)

bronchus cross section





Anaphylaxis: acute multiorgan systemic reaction

- A variety of sympthoms that may unevenly associate

- muco-cutaneous s. (generalized hive, hot flush, oedema of tongue, lips and throath) are almost **always** present

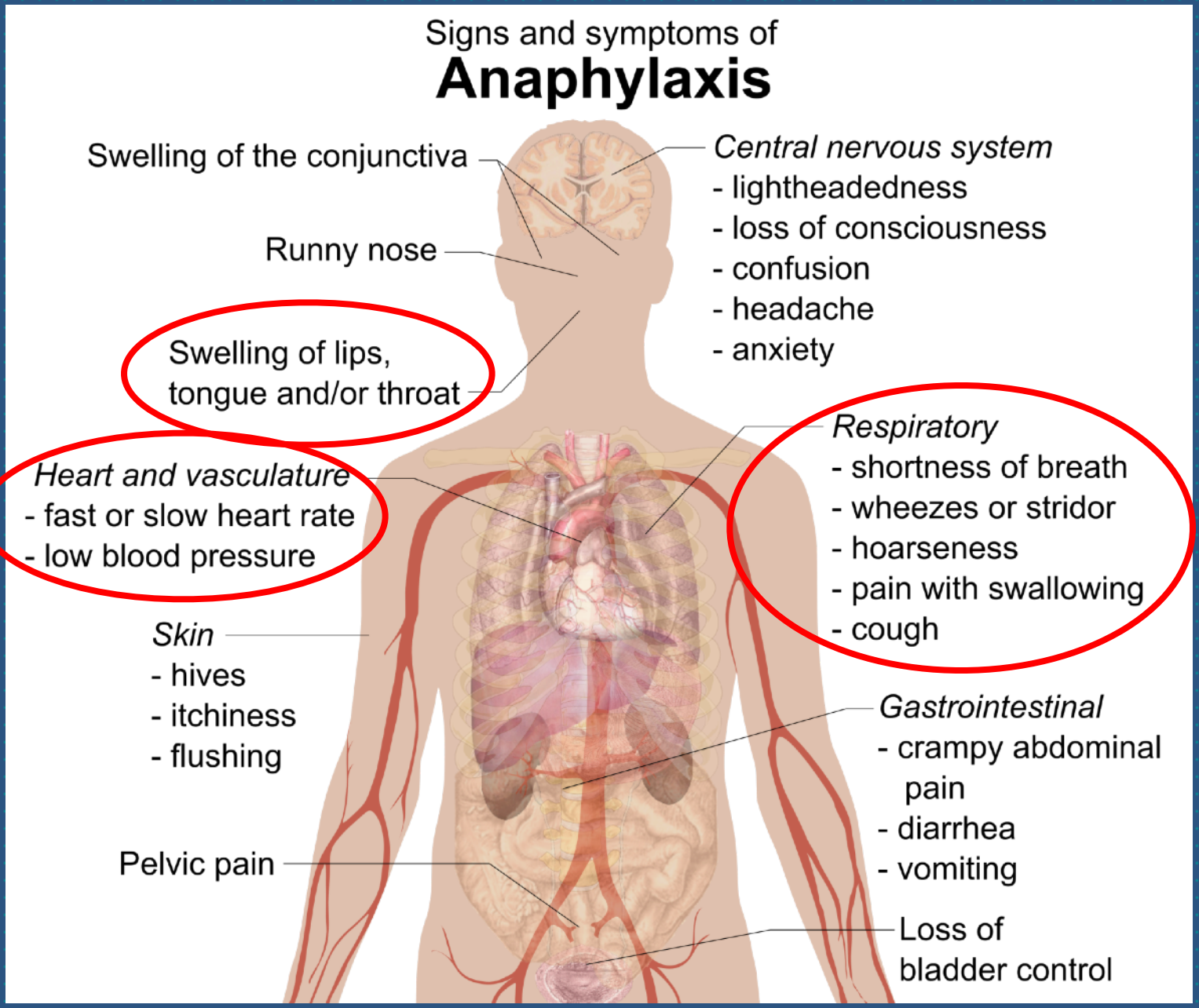
- The **diagnosis** of anaphylactic reaction is established when **at least two** of the following sympthoms occur

- respiratory s. (dyspnea, bronchospasm)
- cardiovascular s. (hypotension)
- gastroenteric s. (abdominal pain, vomiting)

Systemic anaphylaxis: a life-threatening condition

- Systemic exposure to protein antigens (e.g., bee venom) or drugs (e.g., penicillin) may result in systemic anaphylaxis
- Within **minutes** of the exposure in a sensitized host, itching, urticaria (hives), and **skin erythema** appear, followed by profound respiratory difficulty caused by pulmonary **bronchoconstriction**
- In addition, **laryngeal edema** may occur causing upper airway obstruction; the **musculature of the entire gastrointestinal tract** may be affected, with resultant vomiting, abdominal cramps, and diarrhea
- There may be systemic vasodilation with a fall in blood pressure (**anaphylactic shock**), and the patient may progress to circulatory collapse and death within few minutes

Systemic anaphylaxis



Four types of hypersensitivity reactions

	Hypersensitivity Types and Their Mechanisms			
	Type I	**Type II**	**Type III**	**Type IV**
Immune reactant	IgE	IgG or IgM	IgG and IgM	T cells
Antigen form	Soluble antigen	Cell-bound antigen	Soluble antigen	Soluble or cell-bound antigen
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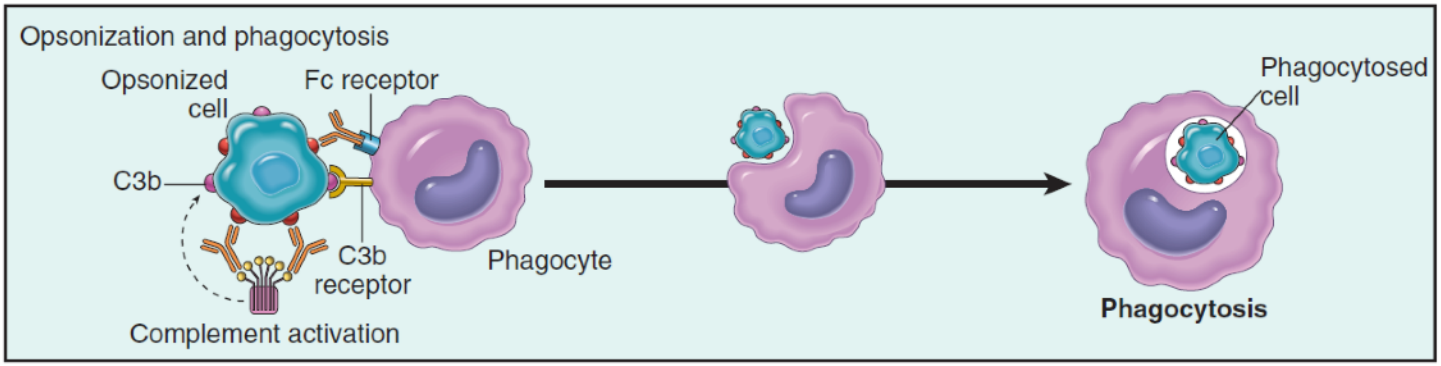
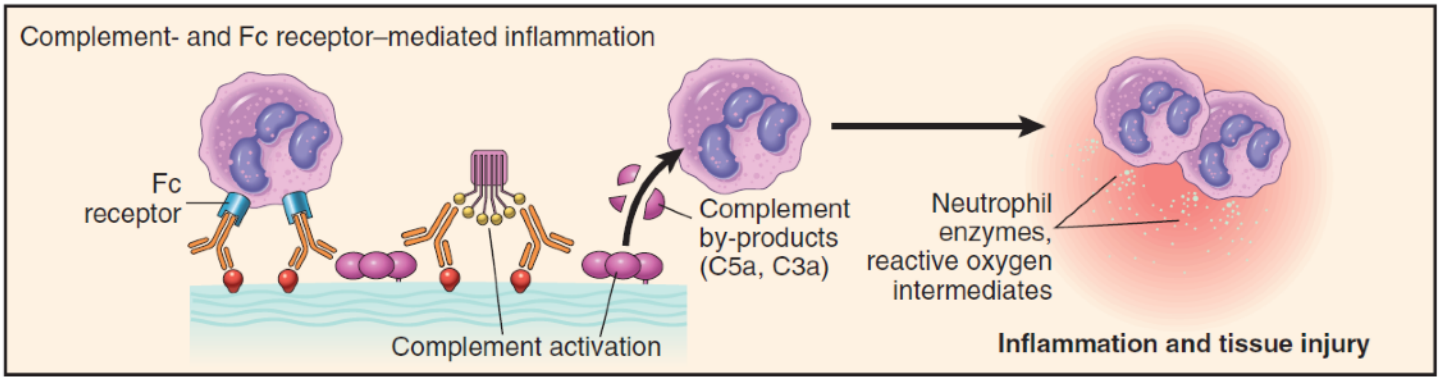
Antibody mediated hypersensitivity (type II)

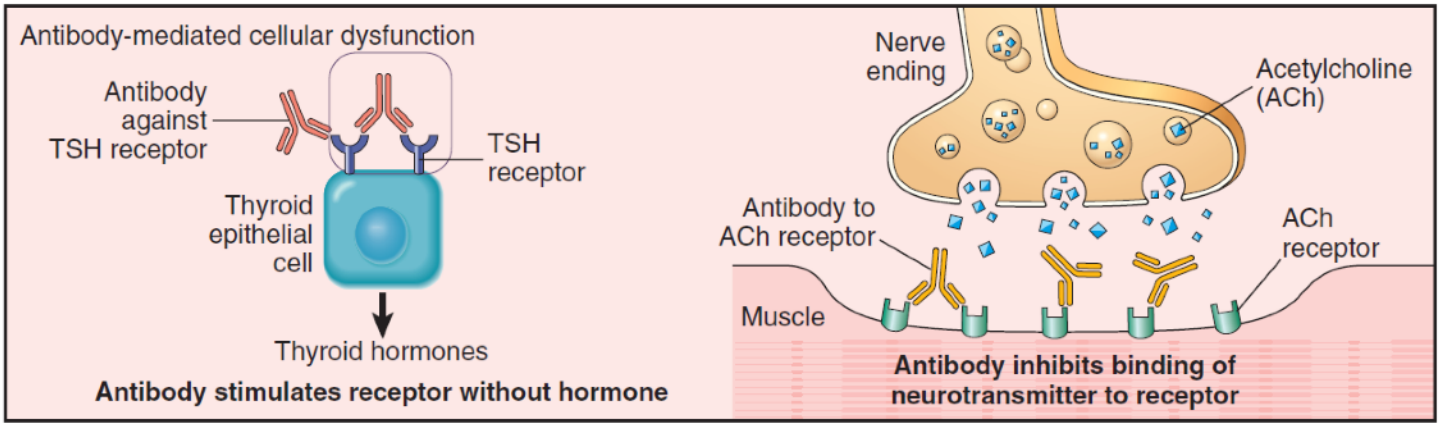
- Antibodies against **cellular or matrix antigens** cause tissue-specific diseases
- In **most cases** such antibodies are **auto-antibodies**
- Occasionally, these antibodies may be produced against **foreign antigens** that are **immunologically cross-reactive** with components of **self tissue**
- Antibodies against tissue antigens cause **diseases** by **three main mechanisms** (next slide)

Mechanisms of antibody-mediated injury



cytotoxic





non cytotoxic

Examples of Antibody-Mediated Diseases (Type II Hypersensitivity)

Table 4–3 Examples of Antibody-Mediated Diseases (Type II Hypersensitivity)

Disease	Target Antigen	Mechanisms of Disease	Clinicopathologic Manifestations
Autoimmune hemolytic anemia	Red cell membrane proteins (Rh blood group antigens, I antigen)	Opsonization and phagocytosis of erythrocytes	Hemolysis, anemia
Autoimmune thrombocytopenic purpura	Platelet membrane proteins (GpIIb/IIIa integrin)	Opsonization and phagocytosis of platelets	Bleeding
Pemphigus vulgaris	Proteins in intercellular junctions of epidermal cells (epidermal desmoglein)	Antibody-mediated activation of proteases, disruption of intercellular adhesions	Skin vesicles (bullae)
Vasculitis caused by ANCA	Neutrophil granule proteins, presumably released from activated neutrophils	Neutrophil degranulation and inflammation	Vasculitis
Goodpasture syndrome	Noncollagenous protein (NC1) in basement membranes of kidney glomeruli and lung alveoli	Complement- and Fc receptor–mediated inflammation	Nephritis, lung hemorrhage
Acute rheumatic fever	Streptococcal cell wall antigen; antibody cross-reacts with myocardial antigen	Inflammation, macrophage activation	Myocarditis
Myasthenia gravis	Acetylcholine receptor	Antibody inhibits acetylcholine binding, downmodulates receptors	Muscle weakness, paralysis
Graves disease (hyperthyroidism)	TSH receptor	Antibody-mediated stimulation of TSH receptors	Hyperthyroidism
Insulin-resistant diabetes	Insulin receptor	Antibody inhibits binding of insulin	Hyperglycemia, ketoacidosis
Pernicious anemia	Intrinsic factor of gastric parietal cells	Neutralization of intrinsic factor, decreased absorption of vitamin B_{12}	Abnormal myelopoiesis, anemia

ANCA, antineutrophil cytoplasmic antibodies; TSH, thyroid-stimulating hormone.

Four types of hypersensitivity

immune complexes

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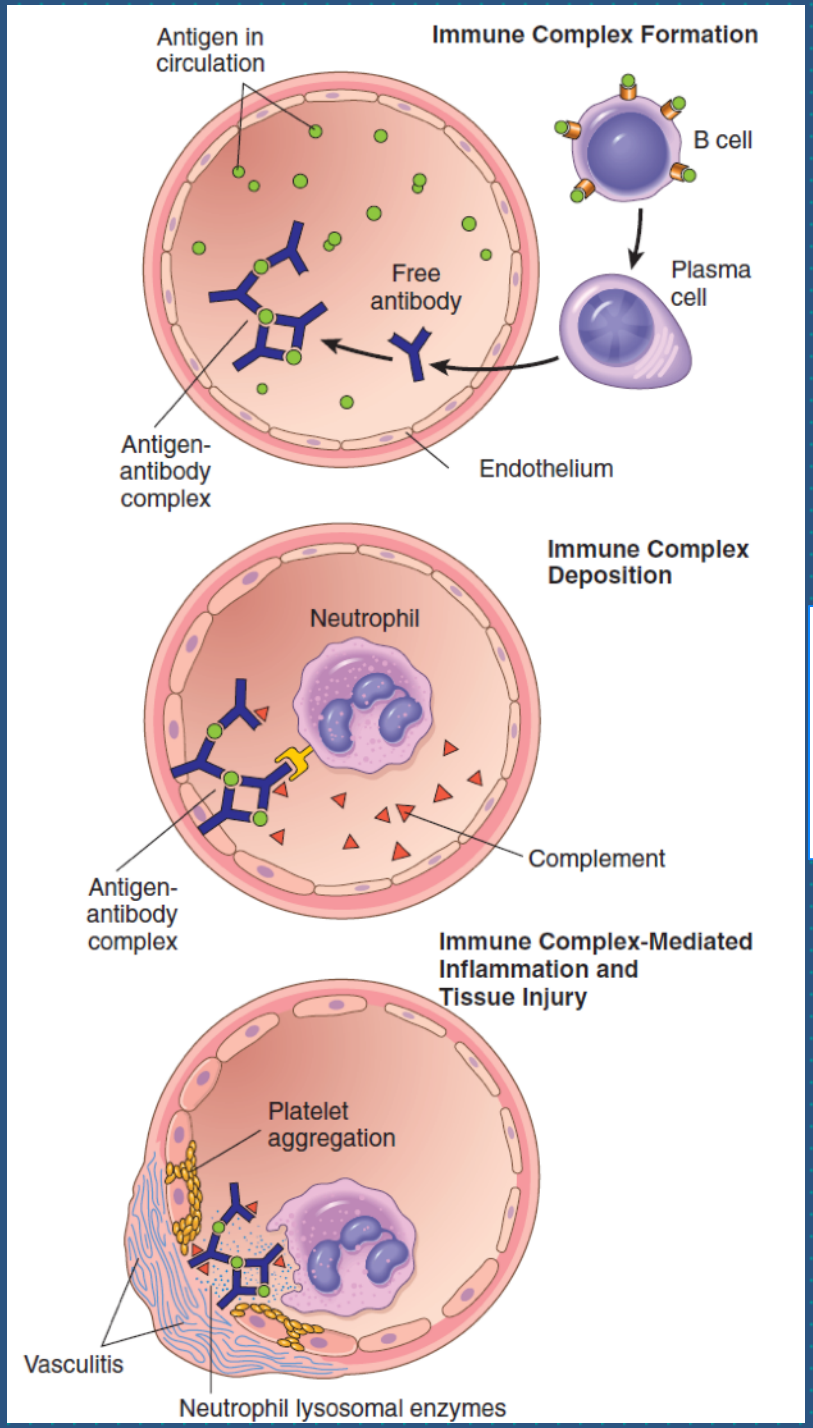
Patterns of immune complexes related diseases

- The antigens in IC may be exogenous (e.g., microbial proteins) or endogenous (e.g., nucleoproteins). Antibodies are either IgG or IgM
- Immune complex (IC)–mediated **injury** is **systemic** when complexes are formed in the circulation and are deposited in **several** organs
- If IC are formed and deposited in a **specific site**, injury may be **localized** to particular organs (e.g., kidneys, joints, skin)
- The mechanism of tissue injury is the same regardless of the pattern of distribution



Mechanisms of tissue damage in type III hypersensitivity: **complement** and **neutrophils**

If not eliminated, IC mostly **deposit in capillaries** or **joints** and trigger inflammation

Immune Complex Diseases

Examples of **localized disease**

- IC deposited in **joints** causing local inflammation = acute arthritis (bacterial antigens)
- IC deposited in **kidneys** = glomerulonephritis (streptococcal cell wall antigens)

Example of **systemic disease**

Systemic lupus erythematosus: associated with an enormous array of **autoantibodies**; commonly, IC with anti-nuclear **auto-antibodies** deposit in **heart**, **joints**, **skin**, **kydneys**, lungs, blood vessels, liver, nervous system)

Examples of human IC–mediated diseases

Table 4–4 Examples of Immune Complex–Mediated Diseases

Disease	Antigen Involved	Clinicopathologic Manifestations
Systemic lupus erythematosus	Nuclear antigens	Nephritis, skin lesions, arthritis, others
Poststreptococcal glomerulonephritis	Streptococcal cell wall antigen(s); may be "planted" in glomerular basement membrane	Nephritis
Polyarteritis nodosa	Hepatitis B virus antigens in some cases	Systemic vasculitis
Reactive arthritis	Bacterial antigens (e.g., *Yersinia*)	Acute arthritis

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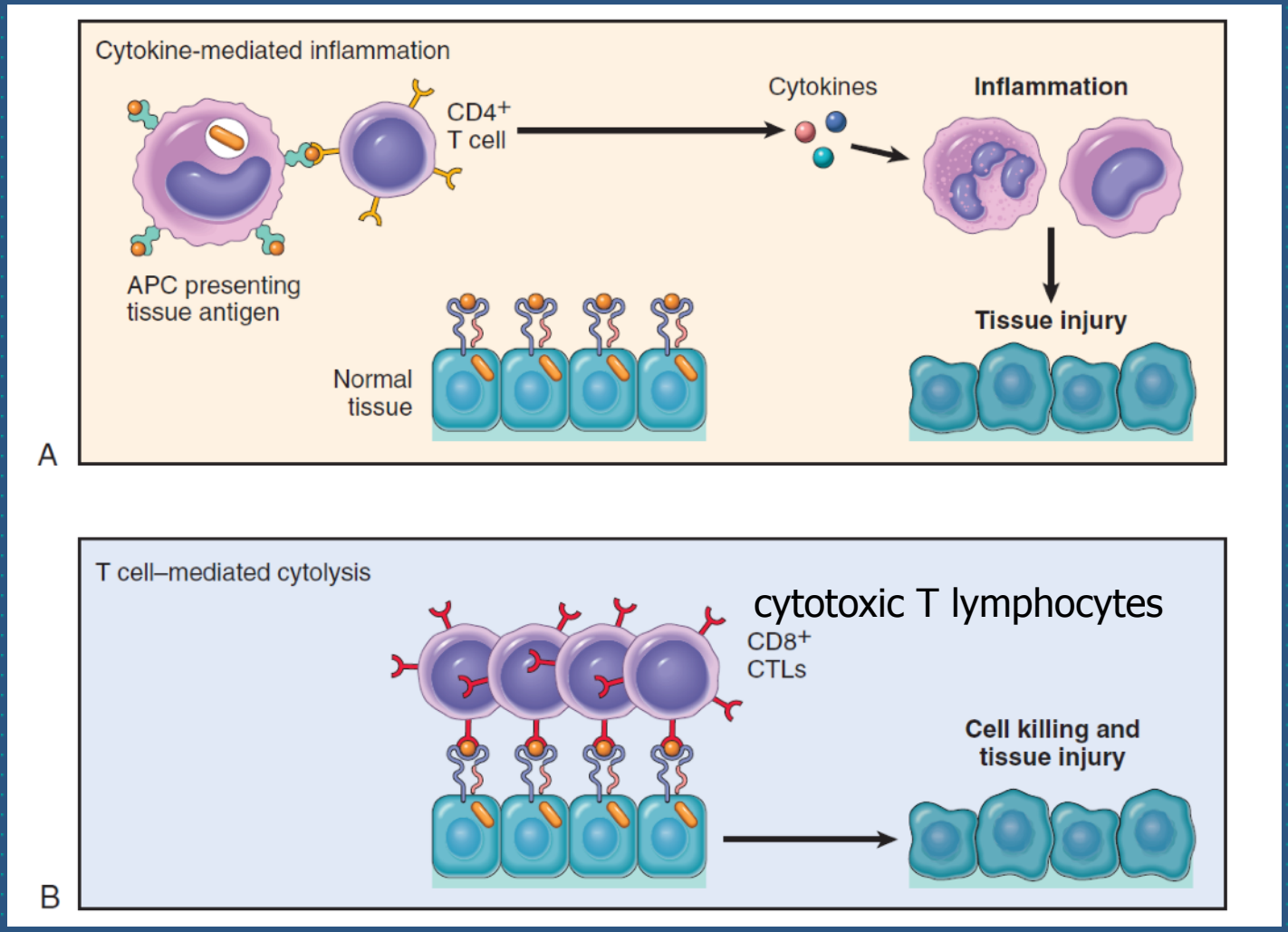
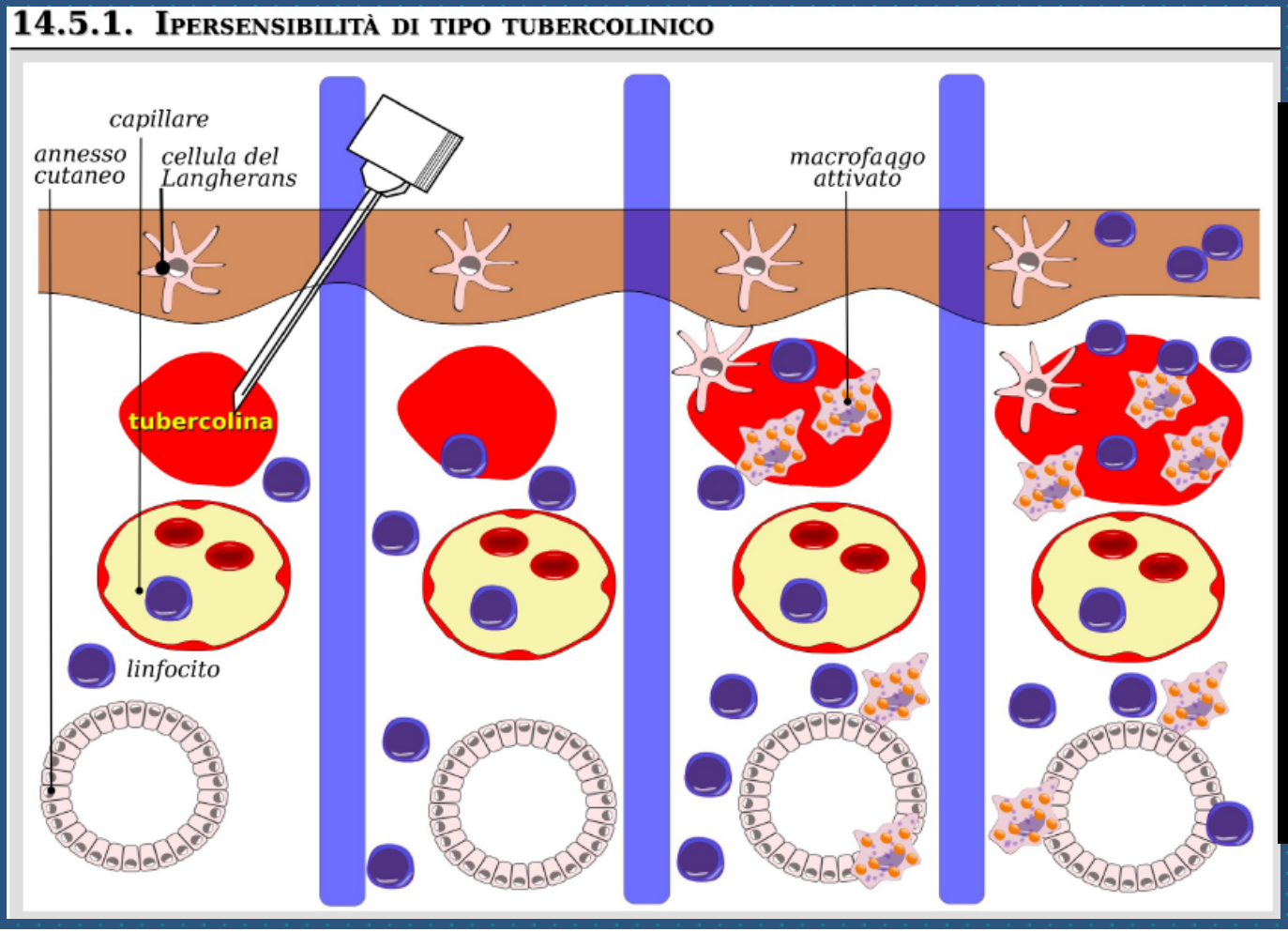
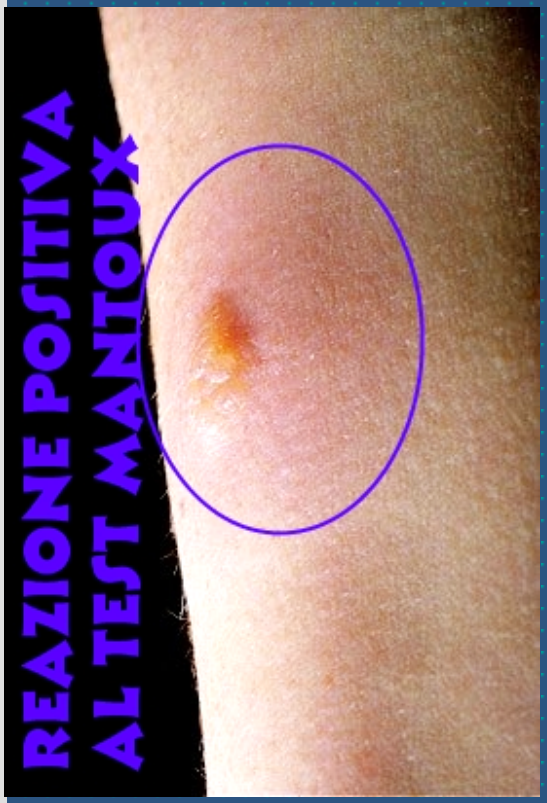


Mechanisms of T cell–mediated (type IV) hypersensitivity reactions. **A,** In cytokine-mediated inflammatory reactions, **CD4+ T cells** respond to tissue antigens by secreting **cytokines** that stimulate inflammation and activate phagocytes, leading to tissue injury. **B,** In some diseases, **CD8+ CTLs** directly kill tissue cells.

Examples of human T cell–mediated diseases

Disease	Specificity of Pathogenic T Cells	Principal Mechanisms of Tissue Injury	Clinicopathologic Manifestations
Rheumatoid arthritis	Collagen?; citrullinated self proteins?	Inflammation mediated by T_H17 (and T_H1?) cytokines; role of antibodies and immune complexes?	Chronic arthritis with inflammation, destruction of articular cartilage and bone
Multiple sclerosis	Protein antigens in myelin (e.g., myelin basic protein)	Inflammation mediated by T_H1 and T_H17 cytokines, myelin destruction by activated macrophages	Demyelination in CNS with perivascular inflammation; paralysis, ocular lesions
Type I diabetes mellitus	Antigens of pancreatic islet β cells (insulin, glutamic acid decarboxylase, others)	T cell–mediated inflammation, destruction of islet cells by CTLs	Insulitis (chronic inflammation in islets), destruction of β cells; diabetes
Hashimoto thyroiditis	Thyroglobulin, other thyroid proteins	Inflammation, CTL-mediated killing of thyroid epithelial cells	Hypothyroidism
Inflammatory bowel disease	Enteric bacteria; self antigens?	Inflammation mediated mainly by T_H17 cytokines	Chronic intestinal inflammation, ulceration, obstruction
Autoimmune myocarditis	Myosin heavy chain protein	CTL-mediated killing of myocardial cells; inflammation mediated by T_H1 cytokines	Cardiomyopathy
Contact sensitivity	Various environmental chemicals (e.g., urushiol from poison ivy or poison oak)	Inflammation mediated by T_H1 (and T_H17?) cytokines	Epidermal necrosis, dermal inflammation with skin rash and blisters





Tuberculin skin test is the classic **clinical demonstration** of the function of DTH response. When an antigen, i.e protein purified derivative (PPD) of mycobacterium, is injected intradermally in an individual, immune response of **person who has been exposed to the bacteria** is expected to mount within 48-72 hrs leading to the **formation of induration** (a raised bump in the area of injection) which is due to the **influx and activation of macrophages**