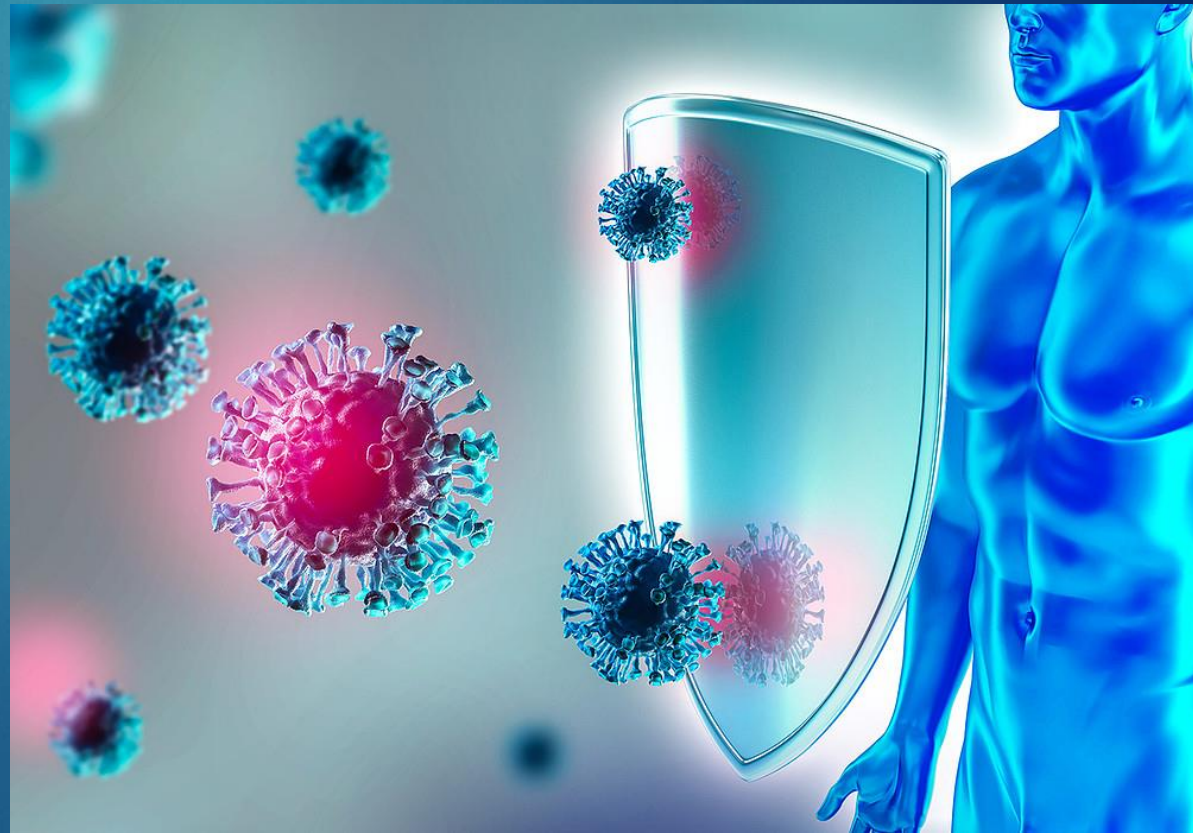


Immunopathology

Dr. Methaq Mueen

Lec 1



The Normal Immune Response

The function of the immune system is to protect individual from invasion by foreign and potentially harmful agents.

Immune responses can be elicited by a wide range of agents (termed antigens) including:

- ▶ infectious agents (bacteria, viruses, parasites),
- ▶ Non infectious :chemicals, toxins, drugs and transplanted tissues .



There are two mechanisms for this protection:

- ▶ Innate (natural or native) immunity
- ▶ Adaptive immunity

▶ 1. Innate immunity (also called Natural, or Native, Non specific immunity)

▶ IN:INSIDE

▶ NATE: born

▶ Already present before birth

▶ the immediate, first line defense mechanisms

▶ This form of immunity is always present, even before infection , ready to provide defense against microbes

▶ it protect individual against infection.

▶ And eliminate damaged cells

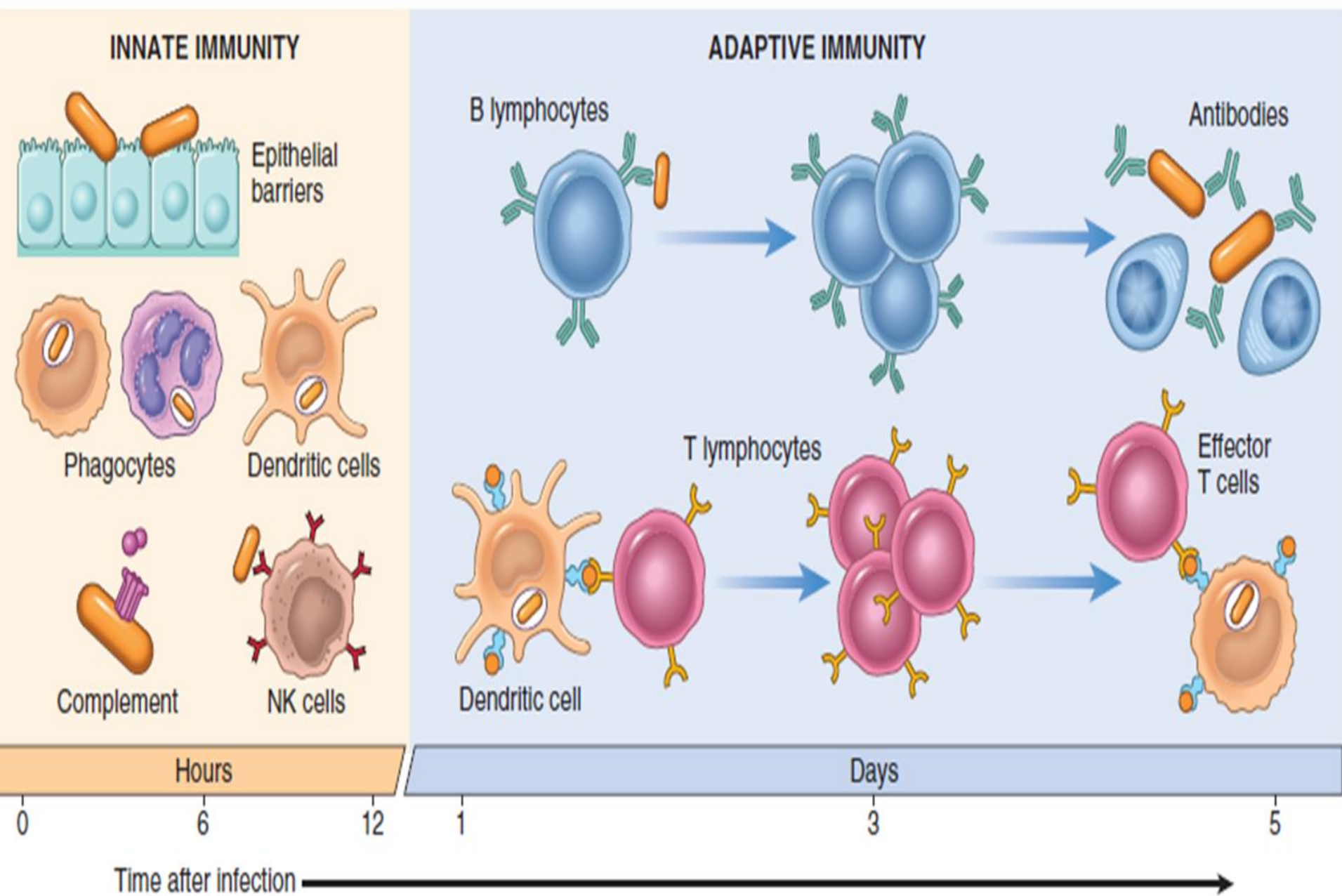


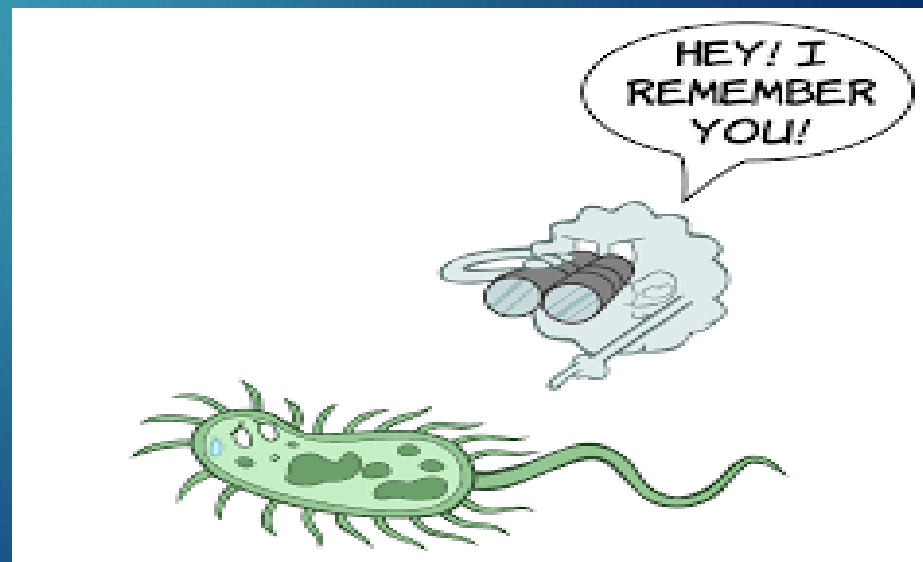
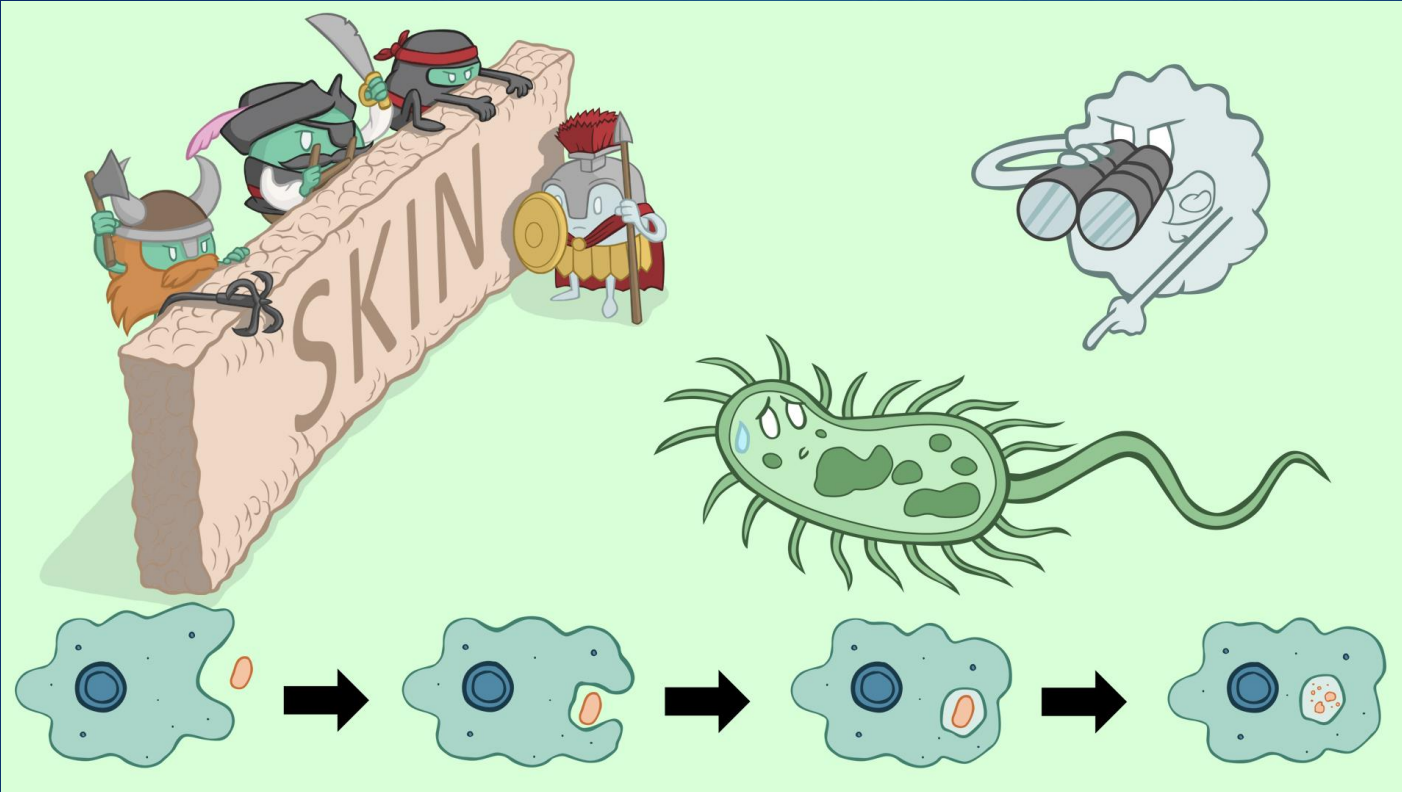
Fig. 5.1 The principal components and kinetics of response of the innate and adaptive immune systems. NK cells, Natural killer cells.

▶ The major components of innate immunity are :

- ▶ Anatomical epithelial barriers and secretions (like skin, mucosa, mucous and cilia in resp., acid and mucin in GIT, acidic secretion in vagina.
- ▶ Cellular components like phagocytic cells (mainly neutrophils and macrophages), dendritic cells, natural killer (NK) cells,
- ▶ several plasma proteins, including the proteins of the complement system.

▶ Advantages of innate immunity:

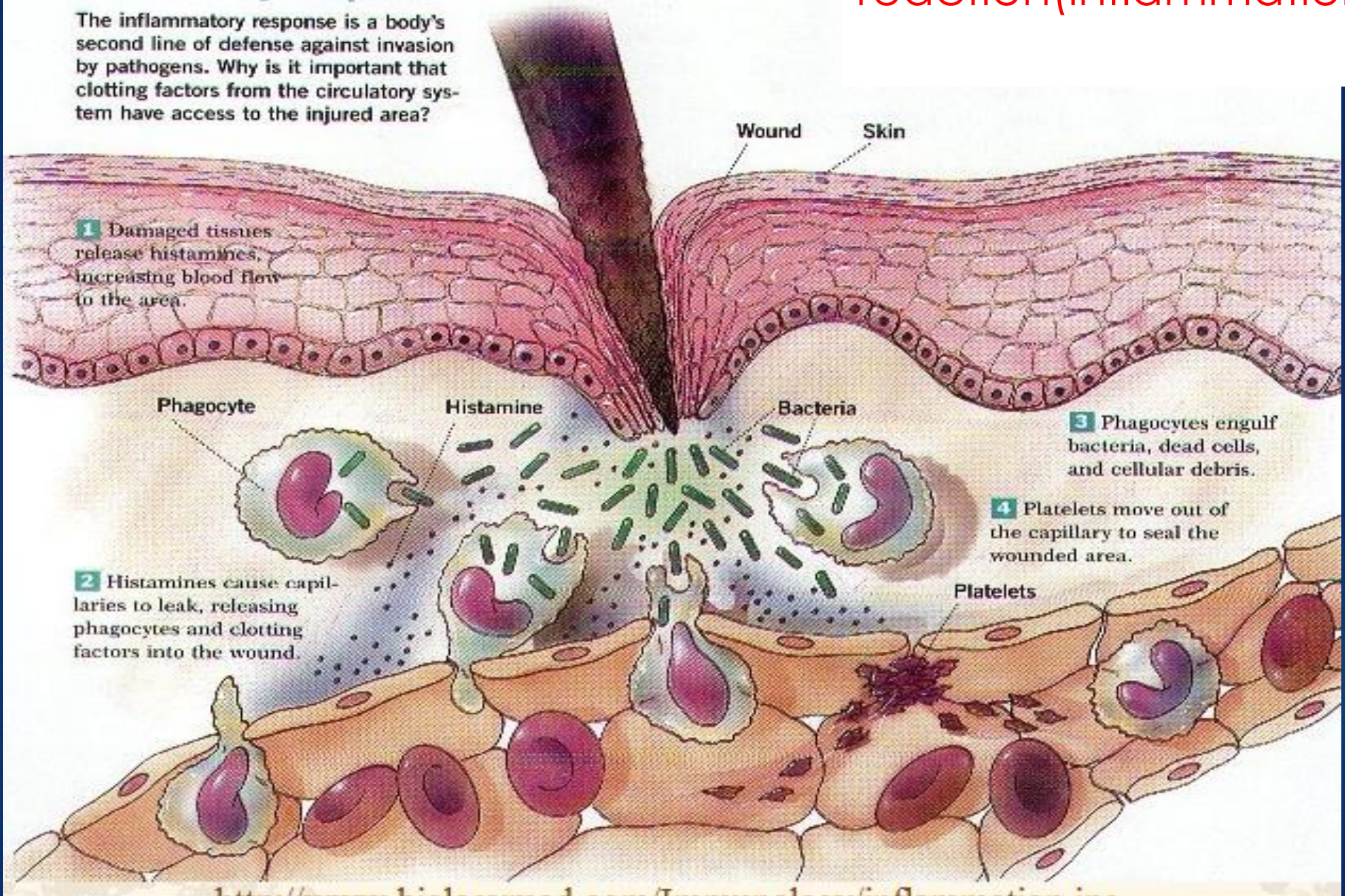
- ▶ the immediate defense mechanism, it provides host defense by two main reactions:
- ▶ 1- Inflammation to destroy microbes and ingest and removing damaged and dead tissue .
- ▶ 2- Antiviral defense: release of anti-viral substances(interferons)
- ▶ However, in many situations this response fails to neutralize the infection and a more powerful response is needed



non specific immune reaction (inflammation)

Steps of the Inflammatory Response

The inflammatory response is a body's second line of defense against invasion by pathogens. Why is it important that clotting factors from the circulatory system have access to the injured area?



2. second line defense

Adaptive immunity (also called Acquired, or specific immunity)

- ▶ It consists of mechanisms that are normally silent but upon stimulation, will respond (or **adapt**) to offending pathogen by generating more potent mechanisms

Adaptive immunity develops later, **after exposure to microbes**, and is even **more powerful** than innate immunity in combating infections.

*-It consists of B and T lymphocytes and their **products**, including antibodies and cytokines.*

- Differences between innate and adaptive immunity

	Innate immunity	Adaptive immunity
development	Present since birth	Develop after birth
Specificity	Not antigen-specific	Antigen-specific
Response time	There is immediate (rapid) response	There is a lag time between exposure and maximal response(slow)
potency	Less potent	More potent
inheritance	inherited	No inheritance
component	Epithelial, cells(macrophage,dendritic cells and NK cells) and complement	B and T cells and their products
Memory cells	Exposure results in NO immunologic memory	Exposure results in immunologic memory (The antigen-specific cells that survive are responsible for memory. •Vaccines depend on the memory cells)

There are **two types of adaptive immunity**:

1-Humoral immunity,

- ▶ which protects against **extracellular microbes and their toxins**
- ▶ mediated by B (bone marrow-derived) lymphocytes and their secreted products, antibodies (also called immunoglobulins, Ig),

2-Cell-mediated (or cellular) immunity

- ▶ which is responsible for defense against **intracellular microbes.g. mycobacterium, viruses, tumor cells and parasites.**
- ▶ mediated by T (thymus-derived) lymphocytes.

Organs and tissues of the Immune System:

1. primary or (central) lymphoid organs:

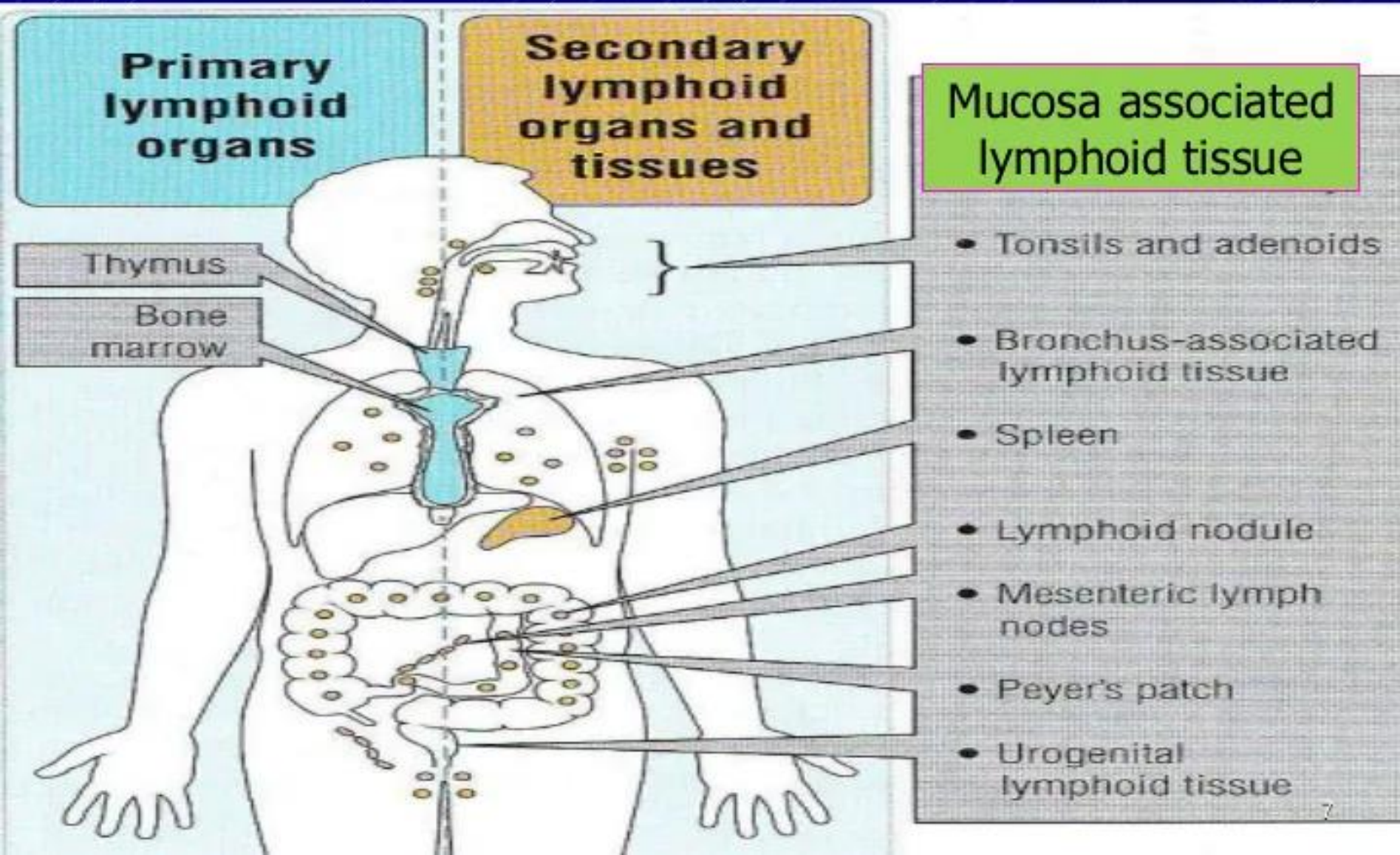
in which T and B lymphocytes mature and become competent to respond to antigens.

- ▶ It consists of bone marrow and thymus

2. secondary or(peripheral) lymphoid organs: in which adaptive immune responses to microbes are initiated.

- ▶ It consist of the lymph nodes,
- ▶ spleen,
- ▶ mucosa associated lymphoid tissues.

Lymphopoiesis in central & Peripheral lymphoid organs and mix together constantly to maintain **Lymphocyte traffic**.



Cells of the Immune System



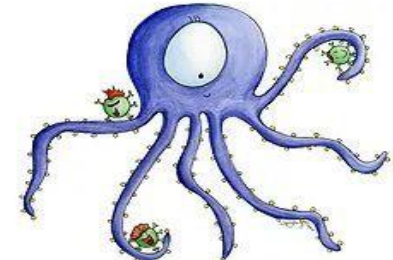
NK Cell



Cytotoxic T Cell



Helper T Cell



Follicular Dendritic Cell



Macrophage



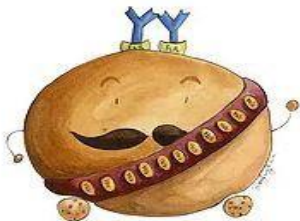
Treg



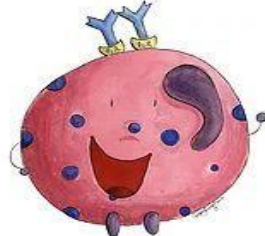
B Cell



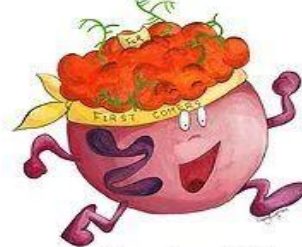
Plasma Cell



Mast Cell



Basophil



Neutrophil



Eosinophil

1.T Lymphocytes :

- ▶ Thymus-derived.
- ▶ T cells constitute 60% to 70% of the lymphocytes in peripheral blood.
- ▶ They are the major lymphocyte population in splenic periarteriolar sheaths and lymph node paracritical zones
- ▶ Each T cell recognizes a specific cell-bound antigen by means of an antigen-specific T-cell receptor (TCR).
- ▶ They can not recognize free antigens but only those who presented by other (antigen-presenting cells) bound to specific molecules called major histocompatibility complex
- ▶ T-cells also express co-receptors including the **CD4** (in 60% of T-cells) and CD8 in 40%
- ▶ CD4 expressing cells (cytokine-secreting Helper cells) that help macrophages and B lymphocytes to combat infections and producing Abs from B- lymphocytes
- ▶ CD8 expressing cells directly kill virus-infected cells or tumor cells(cytotoxic or killer cells)
- ▶ T cells that function to suppress immune responses are called regulatory T lymphocytes

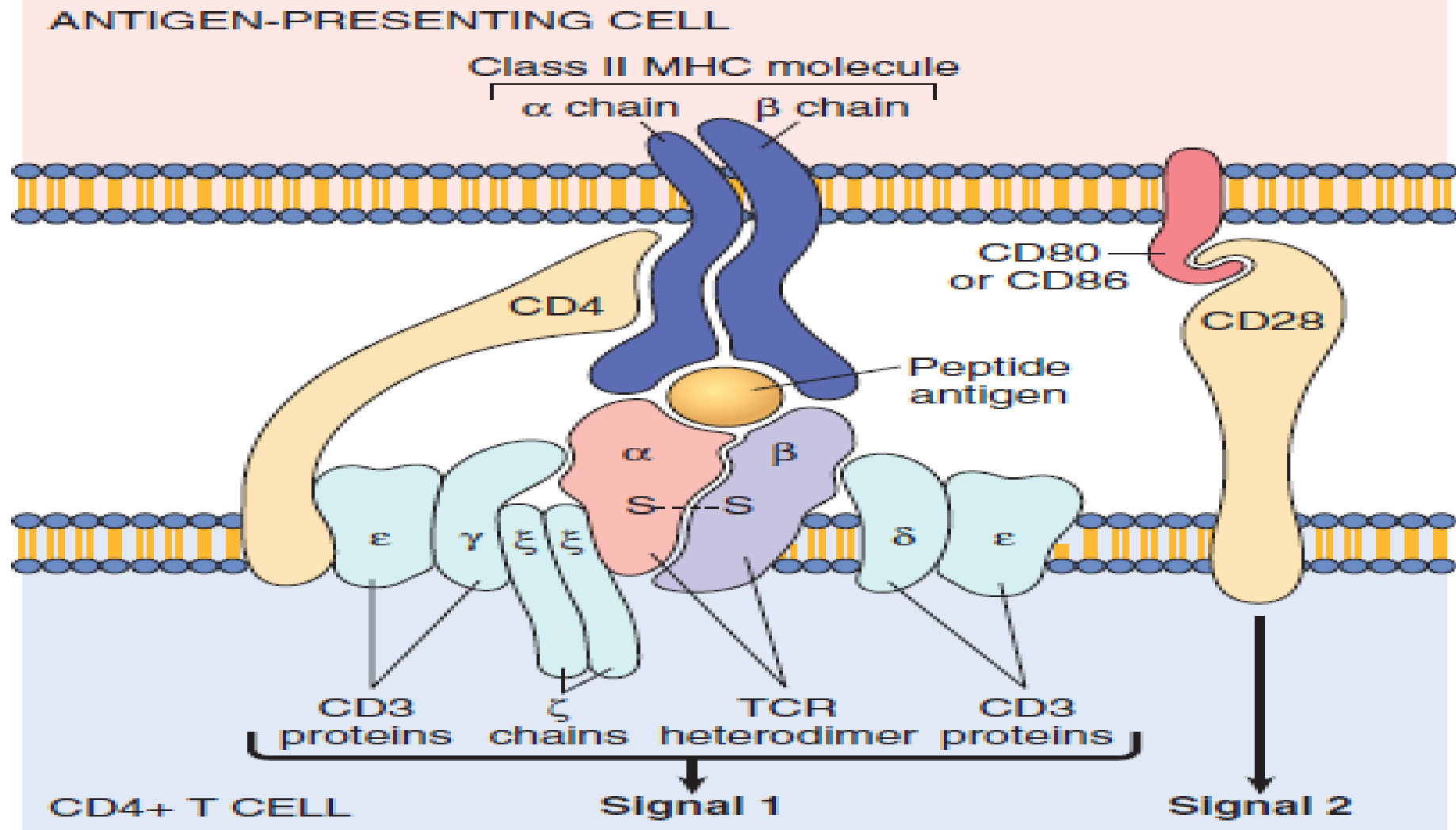
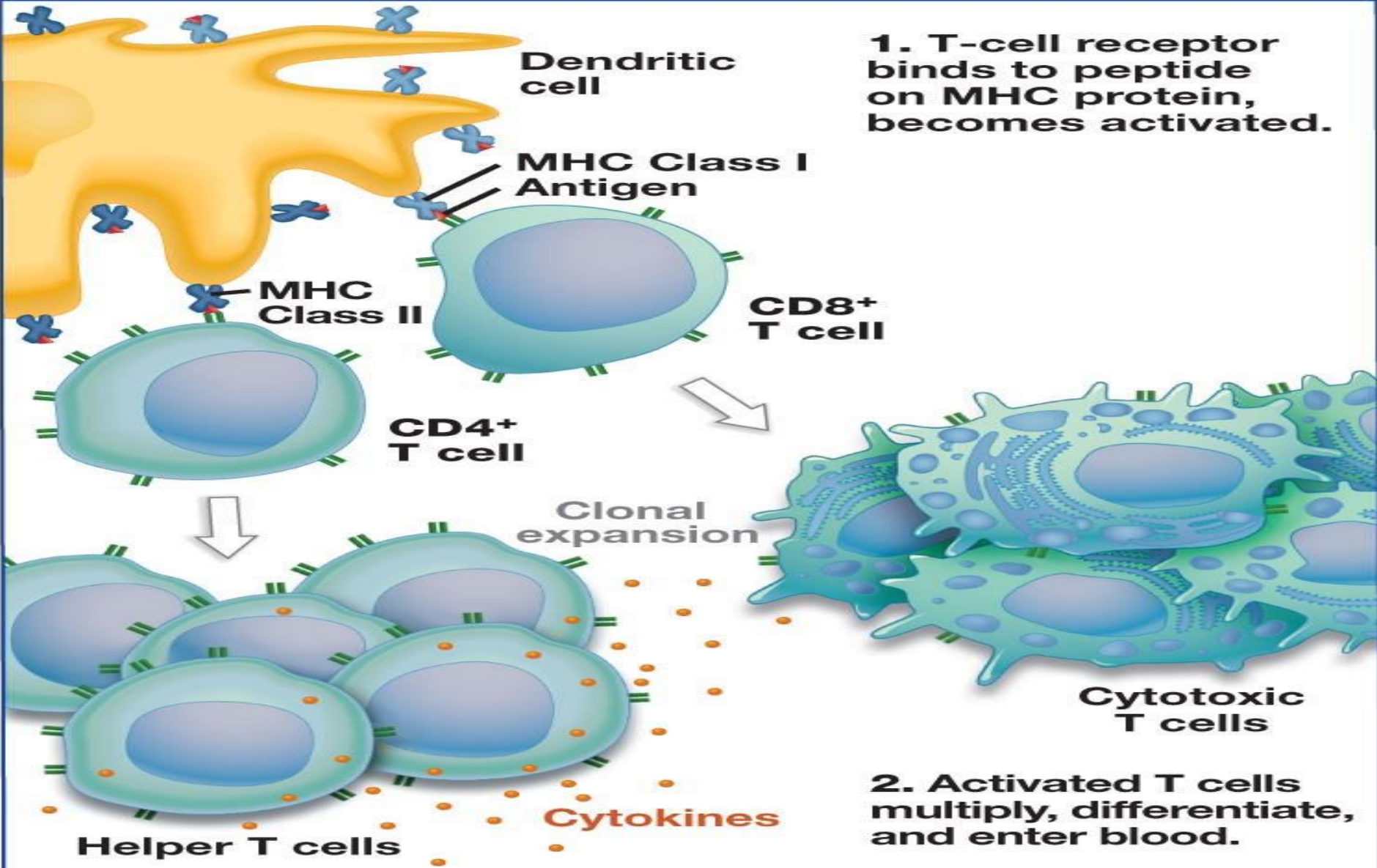
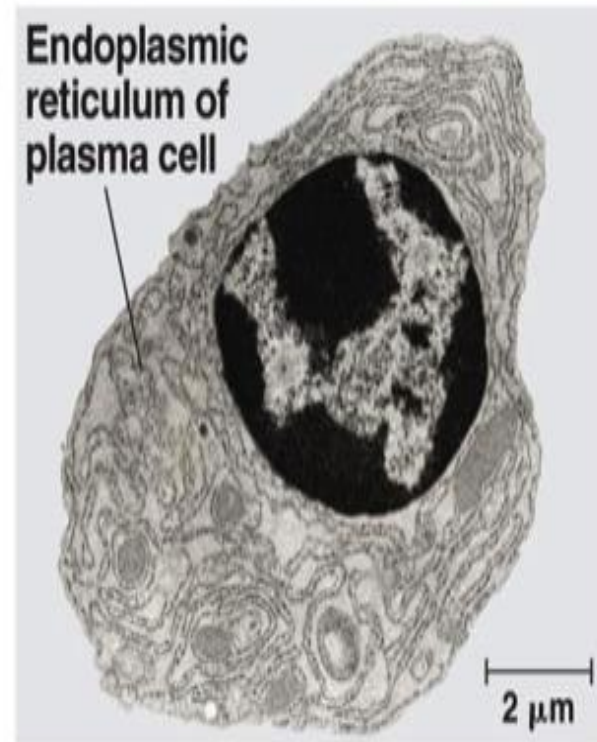
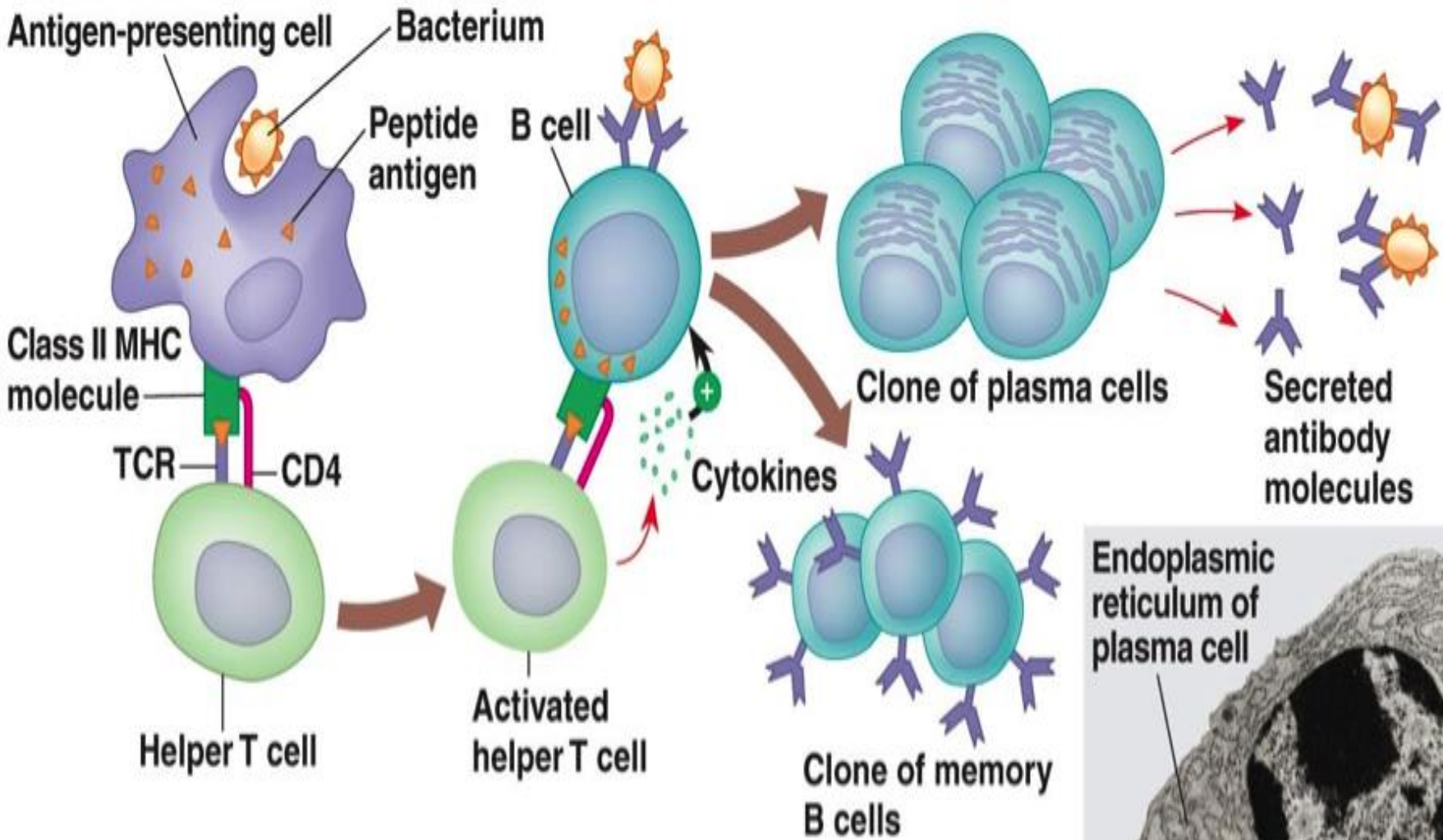


Fig. 5.5 The T-cell receptor (TCR) complex and other molecules involved in T-cell activation. The TCR heterodimer, consisting of an α chain and a β chain, recognizes antigen (in the form of peptide-MHC complexes expressed on antigen-presenting cells), and the linked CD3 complex and ζ chains initiate activating signals. CD4 and CD28 are also involved in T-cell activation. (Note that some T cells express CD8 and not CD4; these molecules serve analogous roles.) The sizes of the molecules are not drawn to scale. *MHC*, Major histocompatibility complex.

- ▶ When an antigen binds to TCR on surface of T cell and CD4 and CD8 molecules bind to specific MHC molecules, T cells become **activated** and release locally acting proteins called **cytokines**.
- ▶ These cytokines activate more T cells resulting in elimination of antigen.
- ▶ At the same time, some of activated T cells differentiate into **memory cells** which provide immunity and respond rapidly after subsequent exposure to the same antigen.
- ▶ Cytokines secreted by CD4+ T cells also stimulate other cells of the immune system e.g. **B cells**, **macrophages** and **NK cells**.

T cell activation



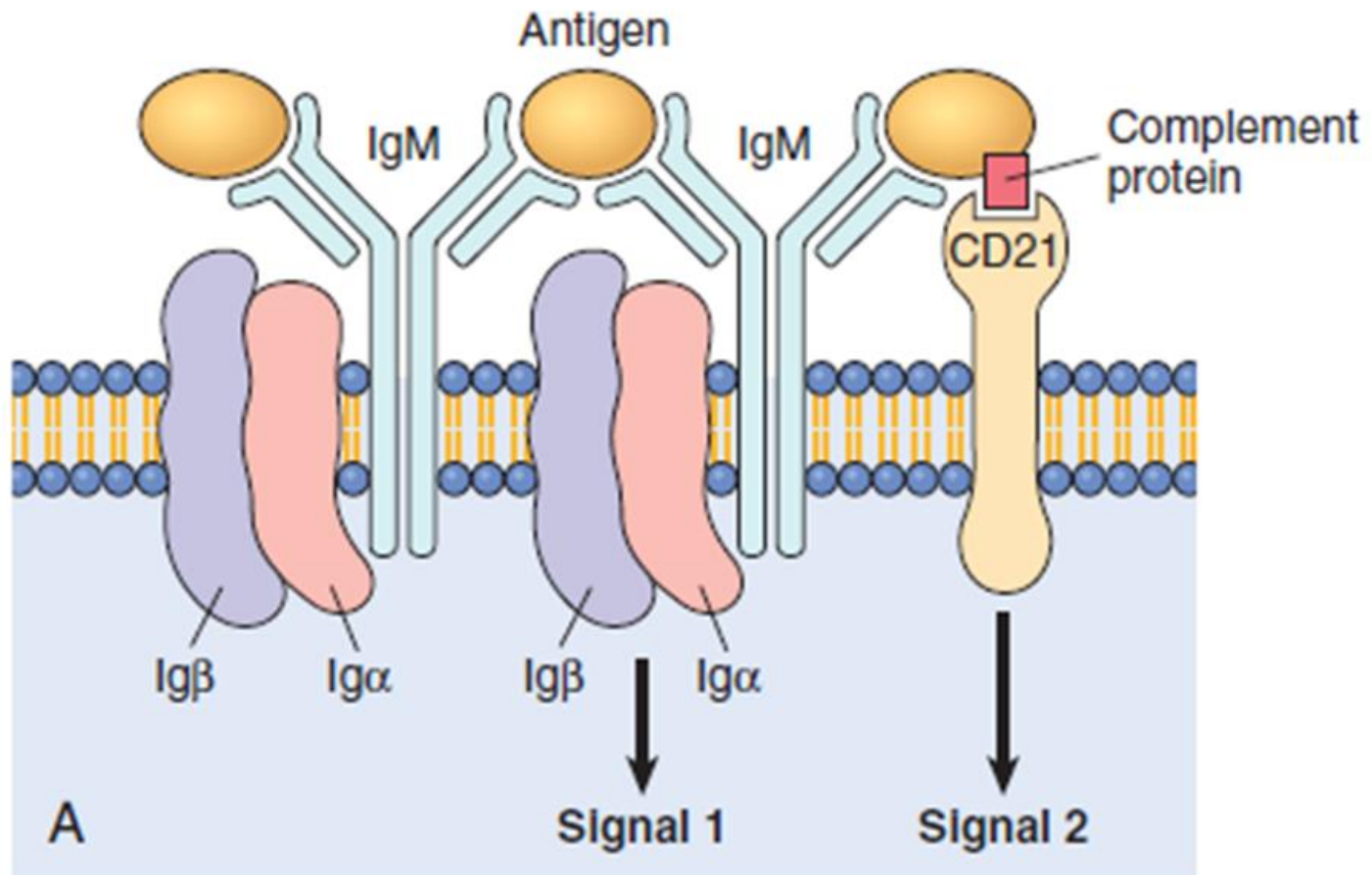


- ▶ CD4+ helper T cells can recognize and respond to antigen displayed only by class II MHC molecules ,
- ▶ whereas CD8+ cytotoxic T cells recognize cell-bound antigens only in association with class I MHC molecule
- ▶ Just to remind you by simple equation:
- ▶ Always the result is 8 (CD 4X MHC 2=8)
- ▶ (CD8 XMHC 1=8)

2. B Lymphocytes :

- ▶ Derived and mature in bone marrow
- ▶ represent 10-20% of circulating peripheral lymphocytes population
- ▶ cells that produce antibodies and are thus the effector cells of humoral immunity.
- ▶ **They also are present in bone marrow and in the follicles of peripheral lymphoid tissues (lymph nodes, spleen, tonsils, and other mucosal tissues).**
- ▶ -B cells recognize antigen by means of membrane-bound antibody of the (IgM) class, expressed on the surface which together with other molecules form the B-cell receptor complex (in comparison with T-cell receptor complex)
- ▶ Unlike T-lymphocytes, B-cell receptors do not need MHC molecules to recognize antigens .
- ▶ Upon activation of B-cells(through engagement with certain antigen) they transform to plasma cells and produce specific antibodies
- ▶ There are five classes, or isotypes, of immunoglobulins: IgG, IgM, and IgA constitute more than 95% of circulating antibodies

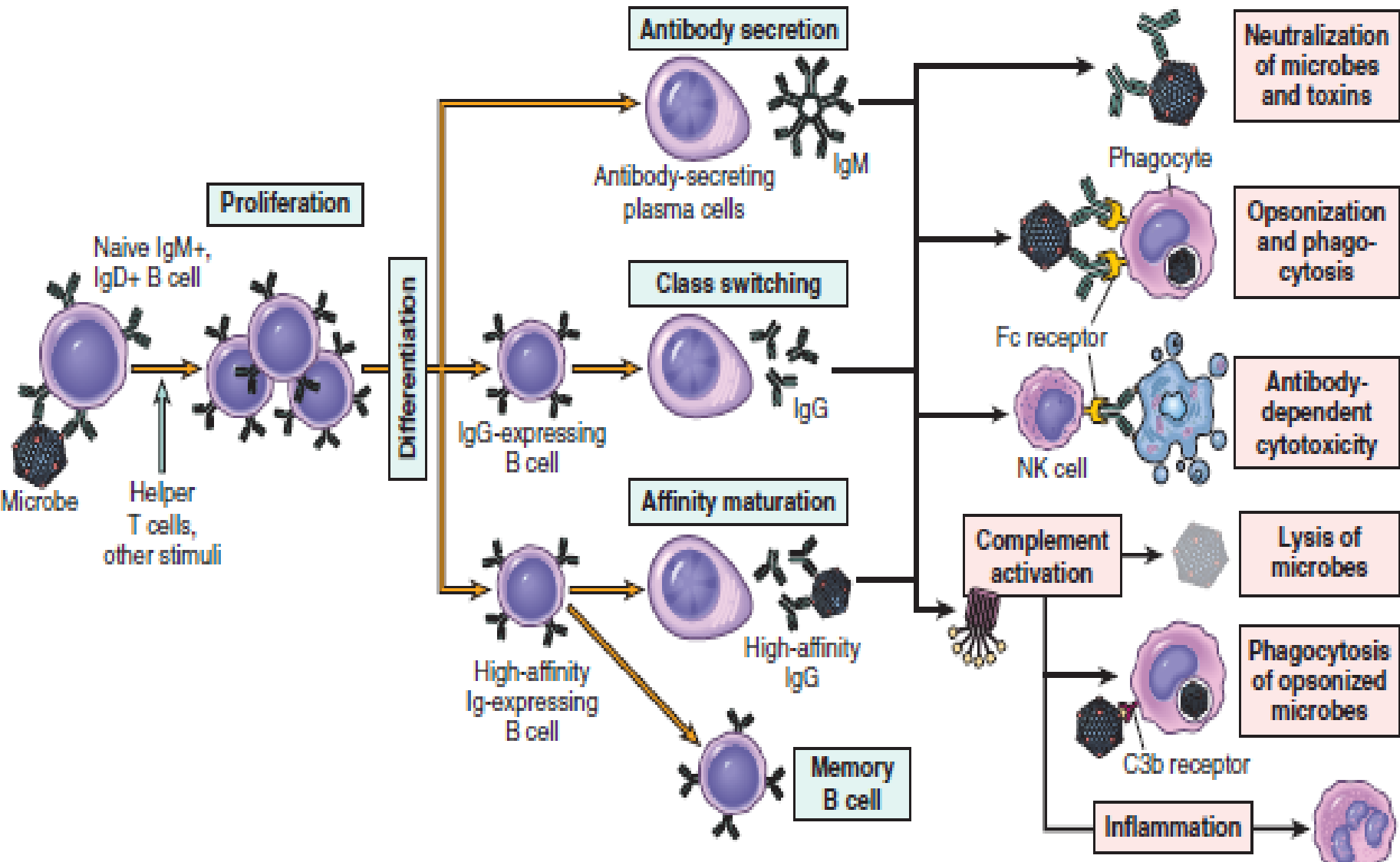
B-cell receptor complex(BCR)



Humoral Immunity

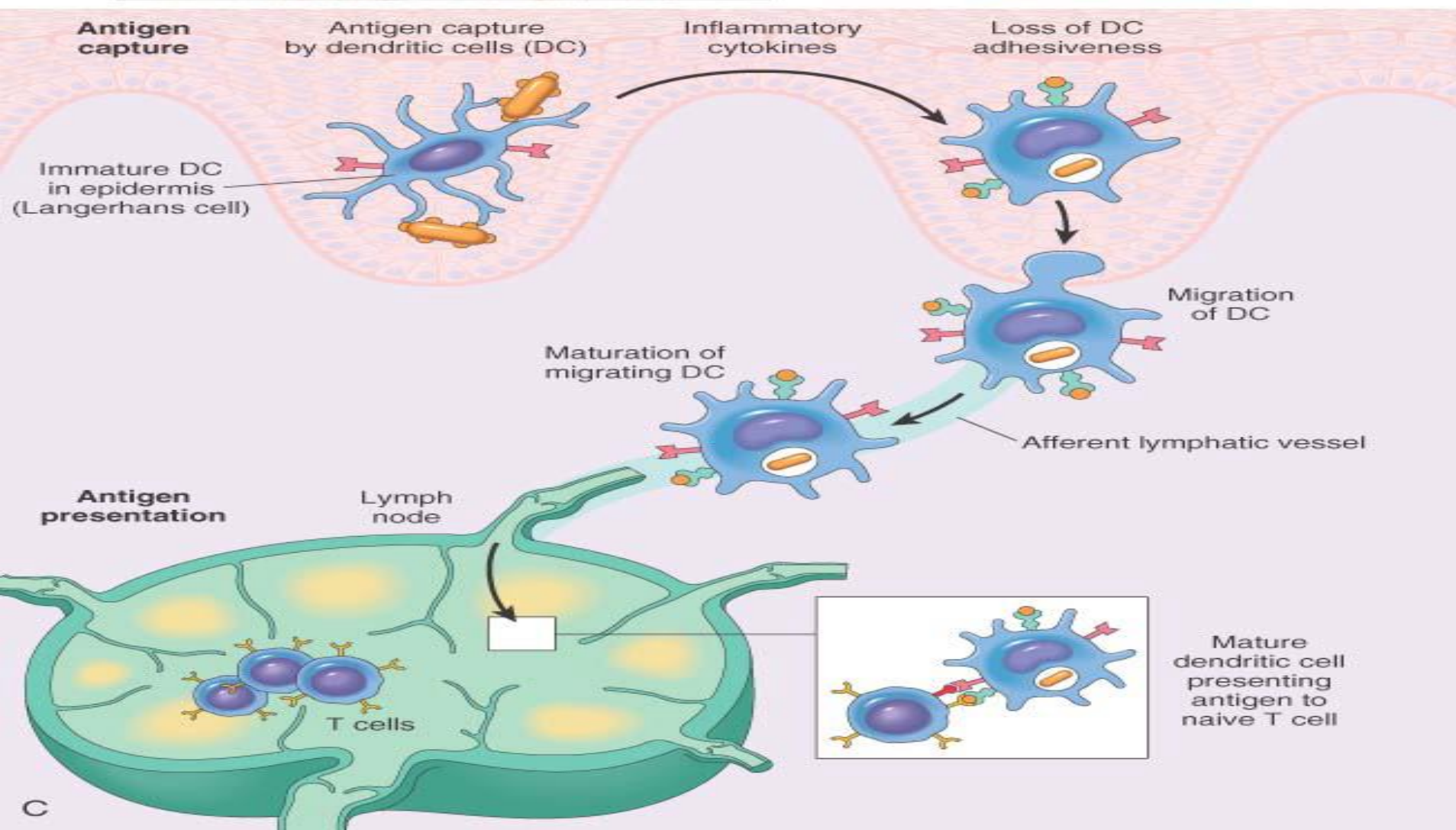
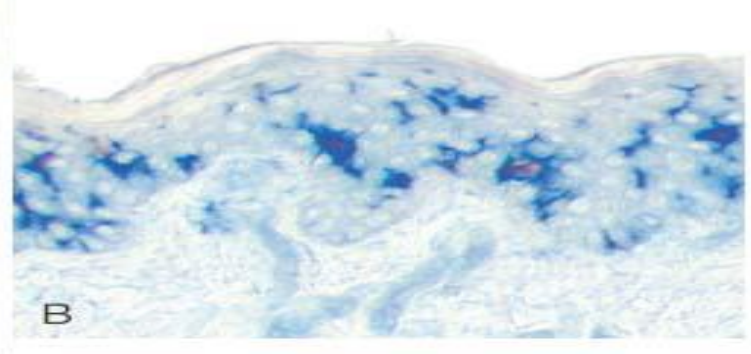
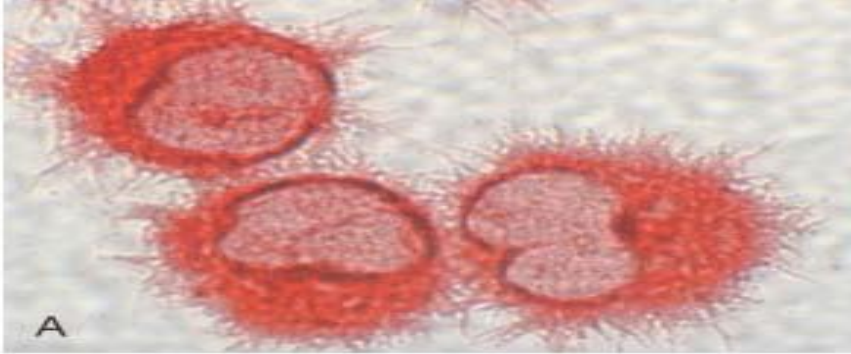
ANTIBODY PRODUCTION

ANTIBODY EFFECTOR FUNCTIONS



4. Antigen-Presenting Cells (APCs)

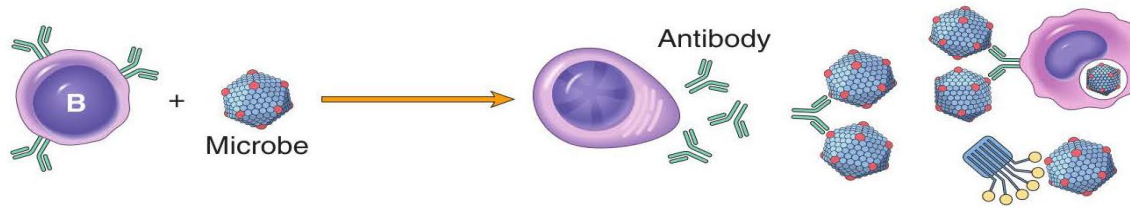
- ▶ APCs capture microbes and other antigens, transport them to lymphoid organs, and display them for recognition by lymphocytes.
- ▶ The most efficient APCs are Dendritic Cells DCs, which are located in epithelia and most tissues.
 - Macrophages are other Antigen-Presenting Cells (APC).



ANTIGEN RECOGNITION

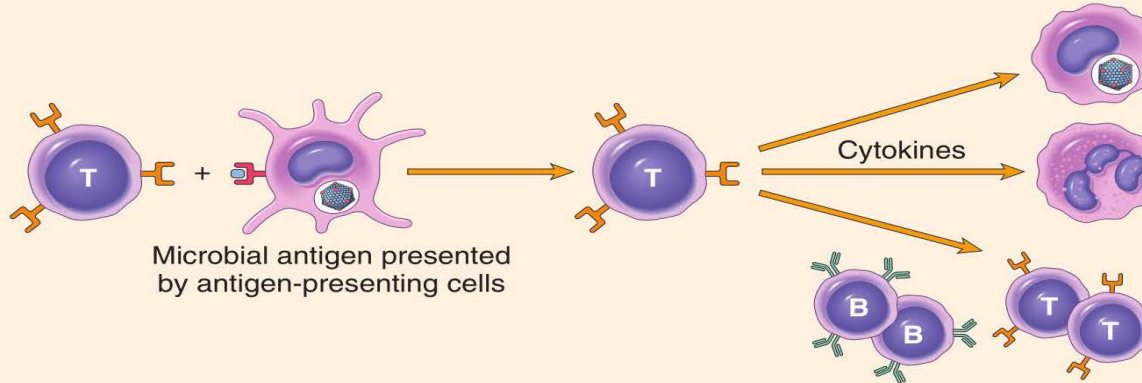
FUNCTION

B lymphocyte



Neutralization of microbe,
phagocytosis,
complement activation

Helper
T lymphocyte

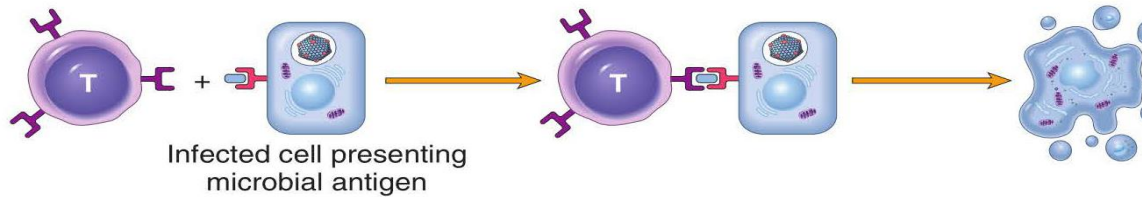


Activation of macrophages

Inflammation

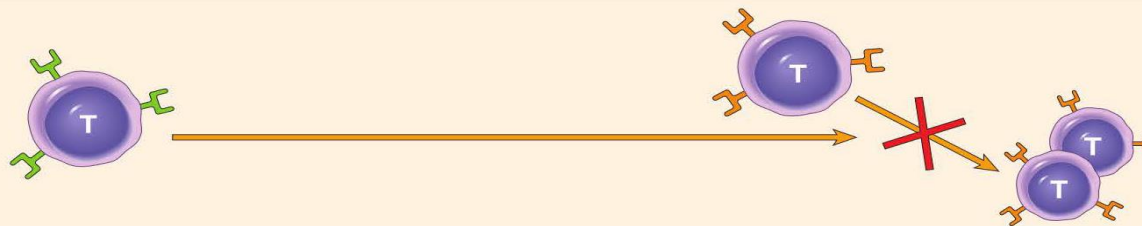
Activation (proliferation
and differentiation) of
T and B lymphocytes

Cytotoxic
T lymphocyte
(CTL)



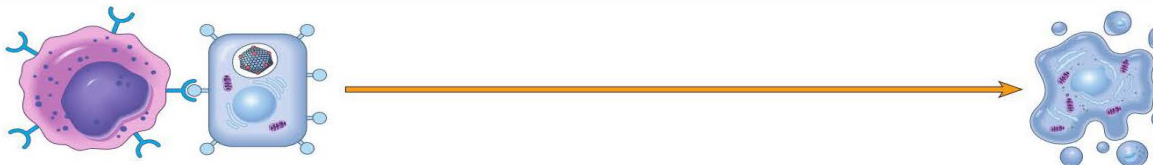
Killing of infected cell

Regulatory
T lymphocyte



Suppression of
immune response

Natural
killer (NK)
cell



Killing of infected cell

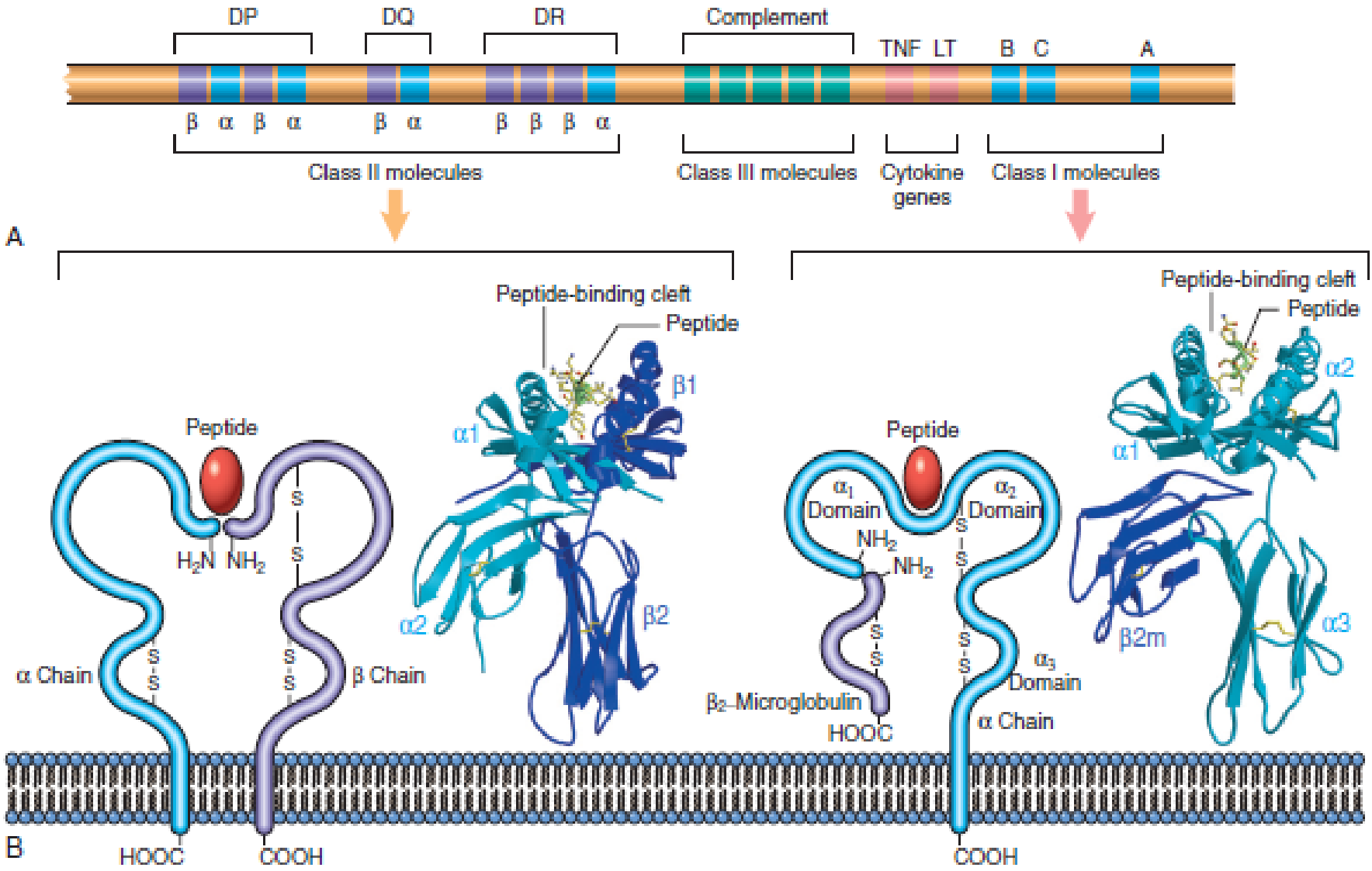
Figure 6-4 The principal classes of lymphocytes and their functions. B and T lymphocytes are cells of adaptive immunity and natural killer (NK) cells are cells of innate immunity. Several more classes of lymphocytes have been identified, including NK-T cells and so-called innate lymphoid cells (ILCs); the functions of these cells are not established.



**Major Histocompatibility
Complex Molecules(MHC)**

- ▶ In order that T-lymphocytes of both helper and cytotoxic types recognize a particular antigen and mount an immune response, the antigen should be presented to them by specific molecules called the major histocompatibility molecules
- ▶ MHC molecules are encoded by specific genes on chromosome 6 and called Human leukocytes antigen system genes (**HLA genes**)
- ▶ There are two types of MHC molecules on human cells, MHC class I and MHC class II

MHC



On the basis of their chemical structure, tissue distribution, and function, MHC gene products fall into two main categories:

1. Class I MHC molecules are encoded by three closely linked loci, designated HLA-A, HLA-B, and HLA-C.

- ▶ these present on every nucleated cell,
- ▶ present only antigens from inside the cytoplasm and engaged CD8 positive T-cells .
- ▶ Thus T-cells in each human recognize MHC I from the same human and if a new transplant introduced into the body with different MHC I molecules, an immune response is triggered
- ▶ If a normal cell transformed into neoplastic cell new antigens produced and presented on MHC I to T-cells, same applied to virus infected cell

CD8+ T cells can respond to peptides displayed by class I molecules.

-In general, class I MHC molecules bind and display peptides derived from proteins synthesized in the cytoplasm of the cell (e.g., viral antigens).

2. Class II MHC molecules :

- ▶ encoded by genes in the HLA-D region, which contains at least three subregions: DP, DQ, and DR.
- ▶ CD4+ T cells can respond to peptides displayed by class II molecules.

-Class II MHC expression is restricted to a few types of cells, mainly APCs (dendritic cells [DCs]), macrophages, and B cells).

- ▶ they bound antigens(peptides) from outside the cell like those of microbes and present them to CD-4 positive T-cells
- ▶ In general, class II MHC molecules bind to peptides derived from proteins synthesized outside the cell (e.g., those derived from **extracellular** bacteria) and ingested into the cell.

▶ 3. MHC class III molecules:

- ▶ These include complement components and the cytokines (**TNF:tumor necrosis factor** and **lymphotoxin**)

Comparison between class I MHC and Class II MHC

	MHC Class I	MHC Class II
Nomenclature	HLA-A,HLA-B,HLA-C	HLA-DP,HLA-DQ,HLA-DR
Found in	All nucleated cell	Macrophage, B- cells, dendritic cells.
Recognized by	CD8+ T cytotoxic Cells	CD4+ T helper Cells
Function	Presentation of Ag to TC cells leading to elimination of tumor or infected cells	Presentation of Ag to TH cells which secrete cytokines

HLA polymorphism:

- ▶ **Each individual expresses maternal and paternal alleles of the class I MHC and class II MHC loci.**
- ▶ **The HLA system is highly polymorphic (highly different among different people) this is due to very variable (polymorphic) HLA genes, with thousands of alleles of gene at each locus in the population, so the possibility for any two different persons to have same HLA allele is very low (except for identical twins) and Siblings (brothers and sisters) have 25% possibility to have same major HLA alleles)**
- ▶ **Each person expresses a unique MHC antigenic profile on his or her cells.**

- ▶ **The implications of HLA polymorphism :**
- ▶ are obvious in the context of **transplantation**—because each person has HLA alleles that differ to some extent from every other person's, grafts from virtually any donor will evoke immune responses in the recipient and be rejected (except for identical twins because they have same alleles with no possibility for transplant rejection)
- ▶ Many **autoimmune diseases** or certain **types of allergy** are associated with particular HLA alleles.



▶ Immuno pathology

Disorders of immune system :

These may result from:

1. Excessive immune responses
(hypersensitivity reactions)
2. Unwanted or inappropriate immune response (Autoimmune diseases)
3. Inadequate immune responses
(immunodeficiency disease)

Hypersensitivity reaction:

- ▶ Individuals who have been previously exposed to an antigen are said to be **sensitized**.
- ▶ Sometimes, **repeat exposures** to the same antigen trigger an **excessive response to antigen**, a pathologic reaction; described as **hypersensitivity**.
- ▶ The immune activation (like a two edge sword) leads to production of antibody and T-cell response that are generally protective against infection. such responses may also potentially damage host tissue.
- ▶ Normally this damage is only trivial and innocent injury because this immune reaction is **balanced and controlled**.
- ▶ **Hypersensitivity** usually results from an imbalance between the effector mechanisms of immune responses and the control mechanisms that serve to normally limit such responses.
- ▶ in many hypersensitivity diseases, the underlying cause is a **failure of normal regulation**.

Causes of hypersensitivity reactions

- ▶ 1-Autoimmunity: inappropriate reactions against (endogenous) self antigens which are normally in (self-tolerance) by the body
- ▶ 2-reactinos against environmental (exogenous) antigens:
- ▶ about 20% of population are allergic to normally non-infectious and harmless exogenous antigens like pollen, animal dander, dust, drugs, food and various chemicals.
- ▶ this allergy is thought to be genetically predisposed
- ▶ The immune responses against such exogenous antigens may take a variety of form, ranging from annoying but trivial discomforts, such as sneezing, lacrimation or Itching of the skin, to potentially fatal diseases, such as bronchial asthma and anaphylaxis.



▶ 3- Reactions against microbes:

- ▶ **some viral infection** may require destroying host tissue to eradicate the disease e,g **viral hepatitis**
- ▶ Some microorganisms can stimulate macrophages and T-lymphocytes resulting in systemic pathology from excessive cytokines elaboration (**cytokine storm**)
- ▶ **In TB**, excessive T-cell responses that walls off the offending agent with activated macrophages(epitheloid histiocytes) forming a granuloma and end with scar causes tissue destruction .
- ▶ or antibodies against a microbe occasionally **cross-react** with **self-antigens** like in **Rheumatic fever**
- ▶ if the reaction to microbe is severe or the microbe is persistent, excessive antibody formation binding to microbe forming **immune complexes** may deposit in tissue causing destruction, e.g poststreptococcal glomerulonephritis

Classification of hypersensitivity reactions

- ▶ These are classified according to mechanism of immune injury into 4 types
- ▶ Three of the hypersensitivity reactions are based on antibody mediated injury and the fourth is T-cell mediated injury

▶ Type I (immediate) hypersensitivity reaction

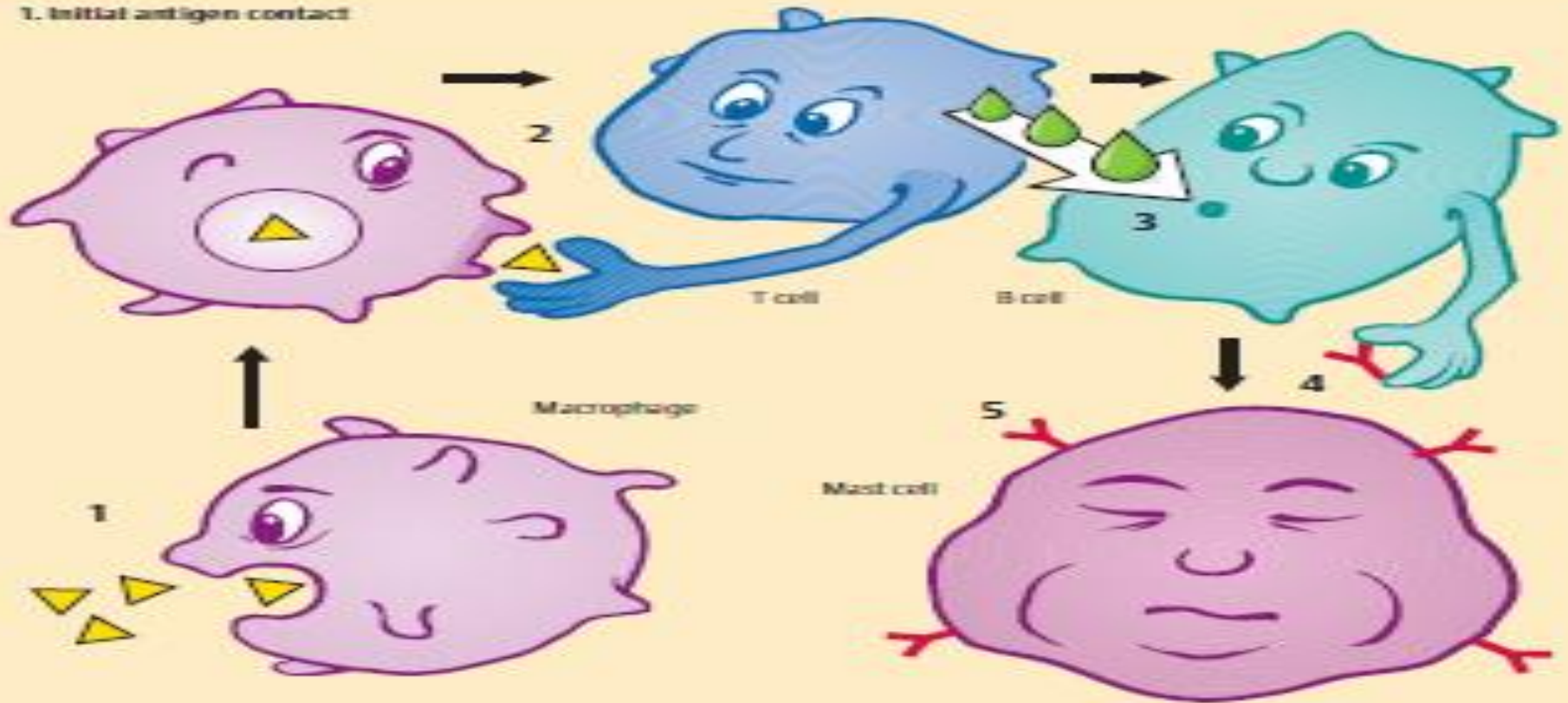
- ▶ Also called the immediate hypersensitivity reaction because of rapid action (within minutes)
- ▶ It happens when an environmental antigen enter the body (usually called allergen) and interact with IgE on mast cells leading to their activation in previously sensitized person to the Ag .
- ▶ The reaction could be local or systemic
- ▶ It might be merely annoying like seasonal rhinitis to severe asthma to fatal anaphylaxis
- ▶ Example of diseases
- ▶ Local reaction
- ▶ Atopic dermatitis (acute eczema)
- ▶ Allergic rhinitis (Hay fever) often associated with: Atopic conjunctivitis
- ▶ Extrinsic allergic asthma
- ▶ Food allergy
- ▶ Systemic reaction
- ▶ Systemic anaphylaxis e,g, Penicillin, bee venom

Sequence of events in Type I reaction

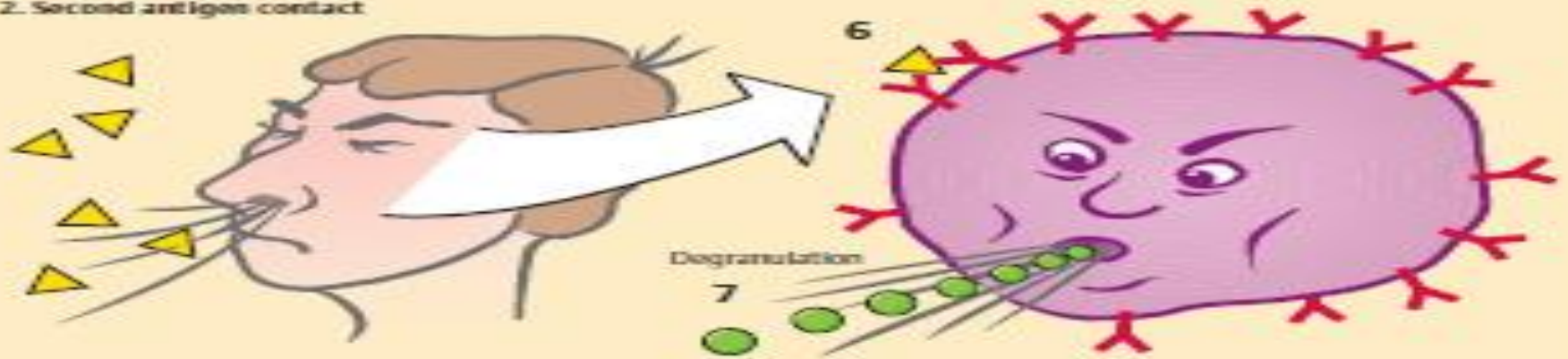
- ▶ Activation of T-helper cells: upon entry of the specific antigen, naive T-cells stimulated into TH2-cells that stimulate B-cell to produce IgE in large amounts
- ▶ Sensitization of mast cell by IgE antibody: mast cells are widely distributed in all tissues they have high affinity receptor for IgE and they bind even small amount of IgE in the blood
- ▶ Activation of mast cells and release of mediators: upon entry of the specific antigen to which the person is already sensitized before, binding with the specific IgE on nearby mast cells lead to their activation and release of mediators, histamine and lipid mediators(prostaglandins and leukotriens) cause:
 - ▶ vasodilation, increased vascular permeability, smooth muscle contraction(bronchospasm) and increased mucous secretions

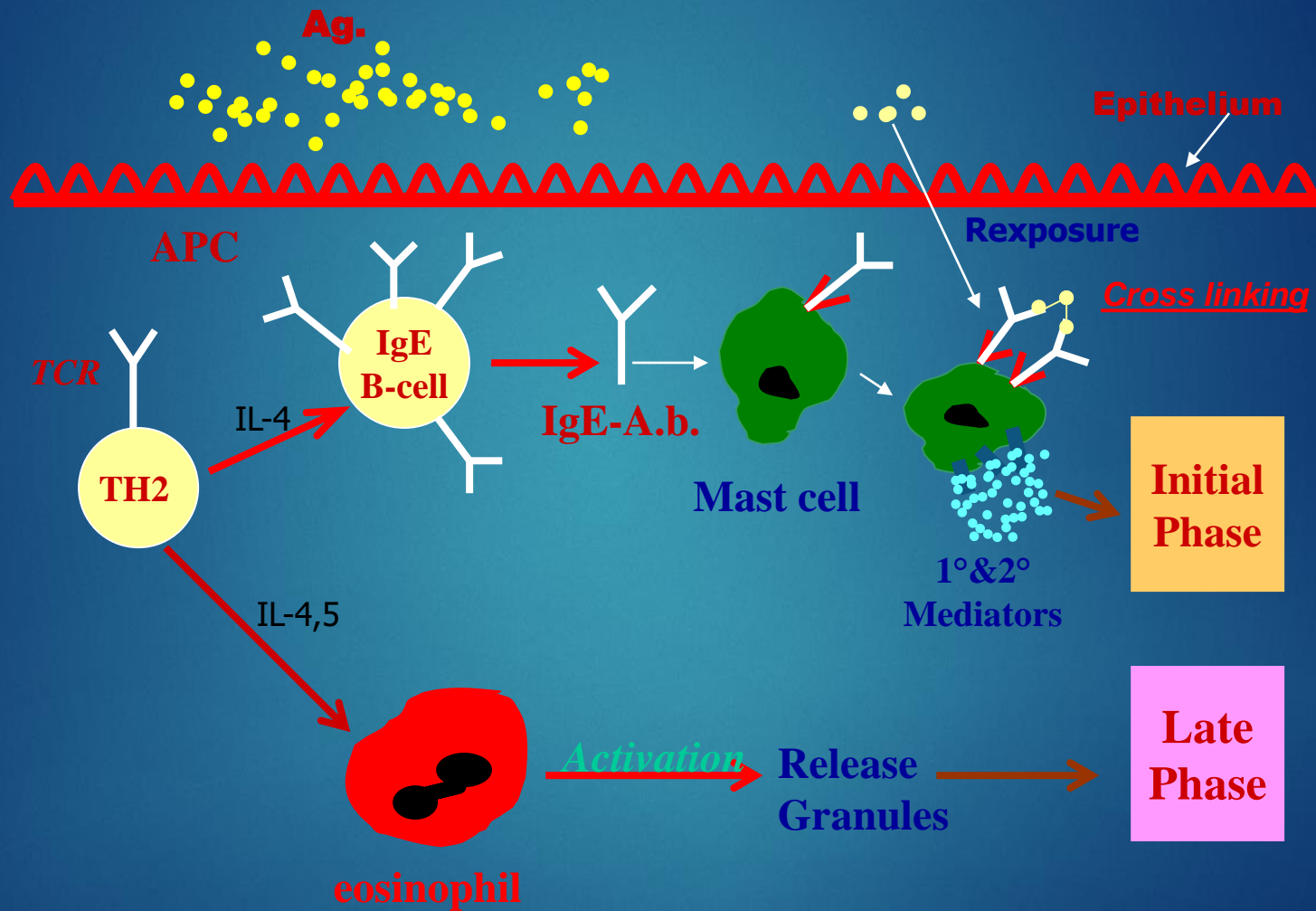
A Type I hypersensitivity reaction

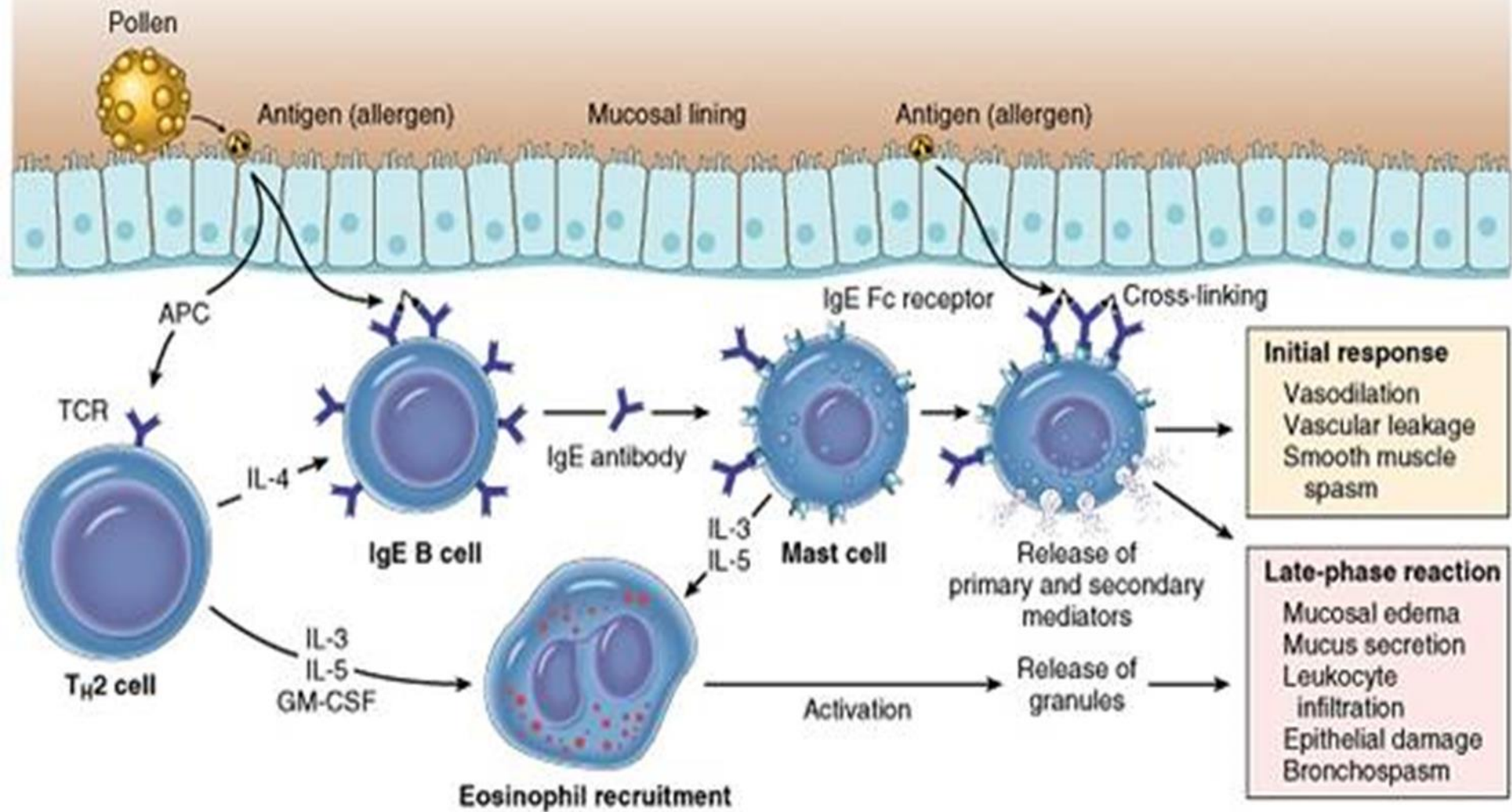
1. Initial antigen contact



2. Second antigen contact







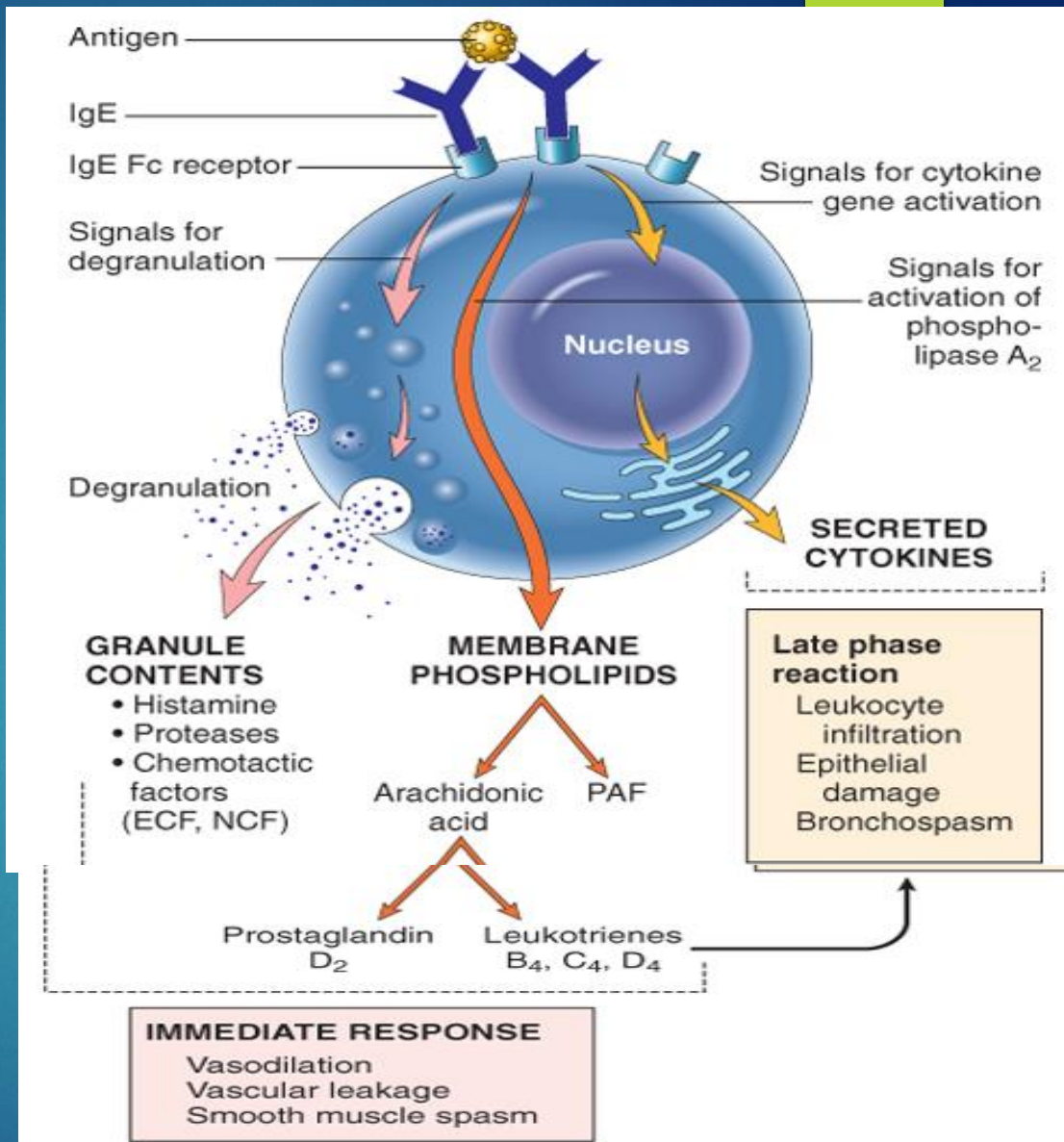
Initial response
 Vasodilation
 Vascular leakage
 Smooth muscle spasm

Late-phase reaction
 Mucosal edema
 Mucus secretion
 Leukocyte infiltration
 Epithelial damage
 Bronchospasm

1- Vasoactive amine released from granule stores :e.g, *Histamine*,

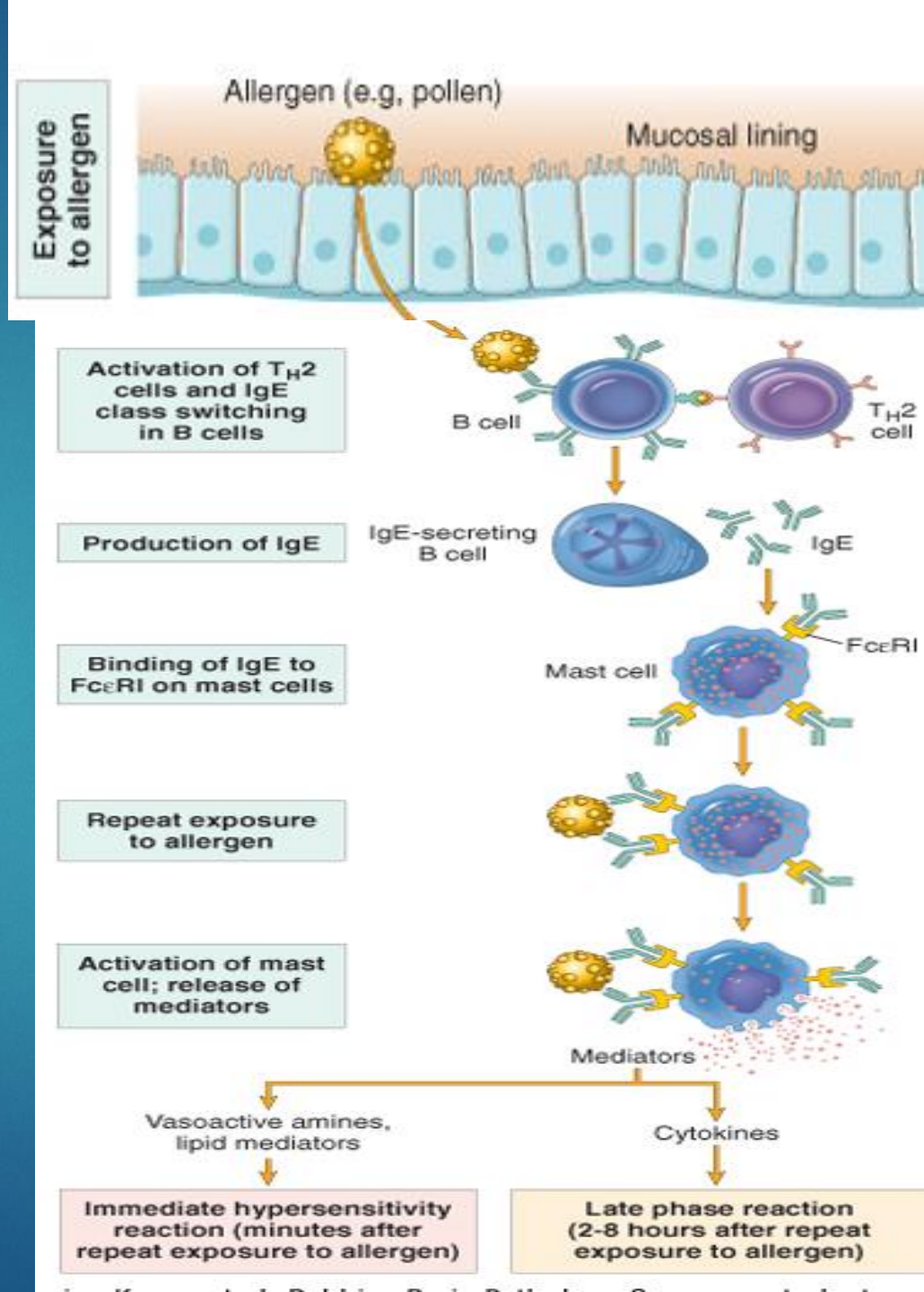
2-Newly synthesized lipid mediators e.g, *Prostaglandins & Leukotrienes*

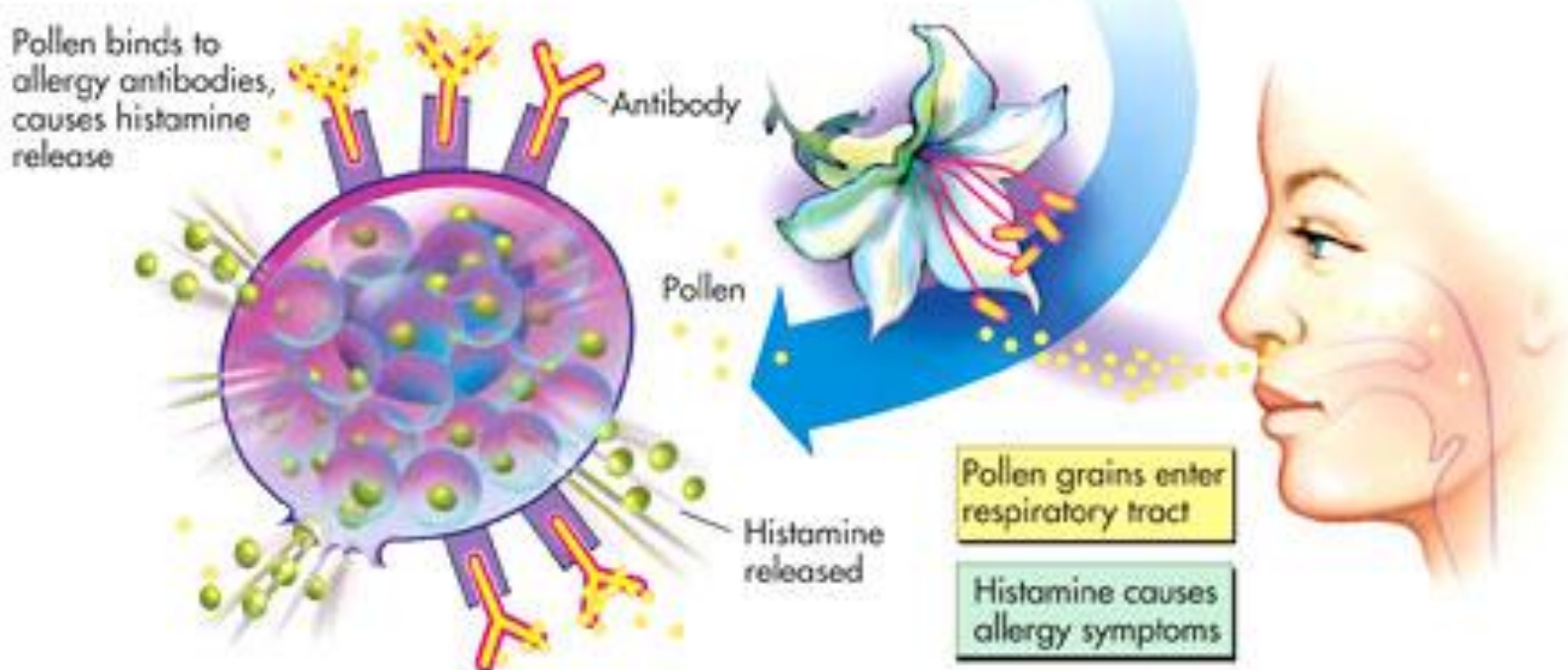
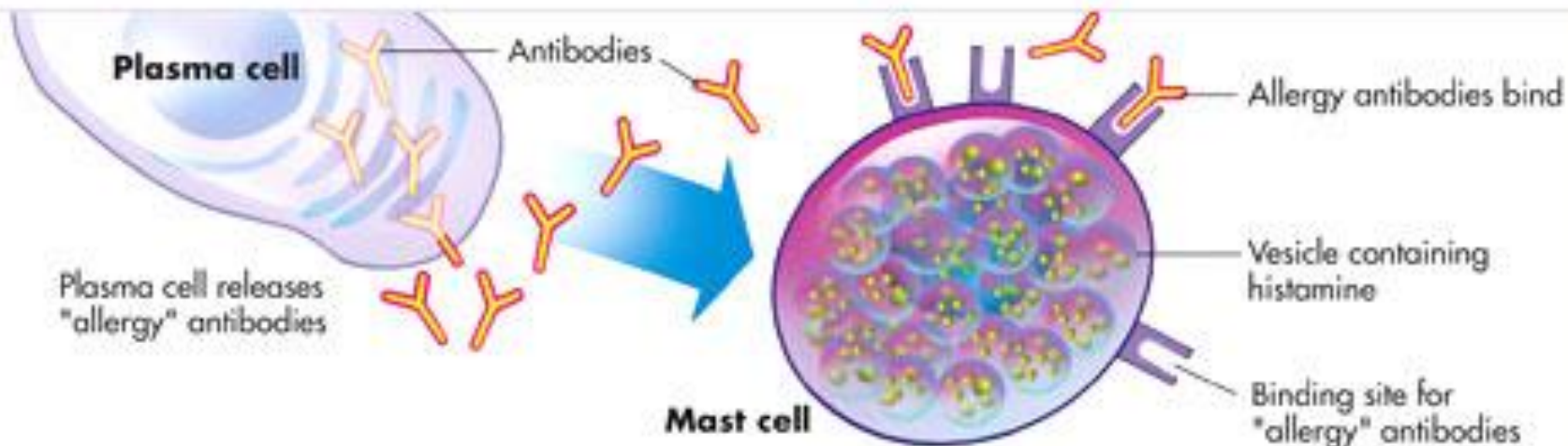
3- Cytokines these are important for the late phase e.g. *TNF & Chemokines for leukocytes ,IL-4 & IL-5*



Sequence of events in immediate (type 1) hypersensitivity

- initiated by the introduction of an allergen,
- which stimulates T_H2 responses & IgE production.
- IgE binds to Fc receptors on mast cells,
- & exposure to the allergen --activates the mast cells to secrete the mediators that are responsible for the pathologic manifestations of immediate hypersensitivity





▶ Development and pathogenesis of allergies

- ▶ It is believed that both genetic and environmental factors play part
- ▶ **Atopy:** An increased genetic propensity or familial predisposition to develop immediate hypersensitivity reactions, this may be due to polymorphism in HLA genes, cytokines genes..etc .
- ▶ atopic people have high IgE serum levels and more TH2 cells
- ▶ but how the disease associated polymorphisms influence the development of allergies is not known.

- ▶ Environmental factors plays another significant part, an increasing incidence of allergies in developed countries may be due to:
- ▶ many antigens in industrial societies.
- ▶ It is now being hypothesized to: lower exposure to infections early in life (hygiene hypothesis)=(less microbial antigens early in life=more allergies later)
- ▶ early childhood and even prenatal exposure to microbial antigens educates the immune system in such a way that subsequent pathologic responses against common environmental allergens are prevented.
- ▶ Thus, too much hygiene in childhood may increase allergies later in life. This hypothesis, however, is difficult to prove, and the underlying mechanisms are not defined.

Clinical and pathologic manifestations

- ▶ Type I reaction has two phases:
- ▶ immediate phase in 5-30 minutes after antigen exposure due to histamine and other pre-stored mediators in mast cells leading to bronchospasm and vascular dilation and then subsides in 60 minutes
- ▶ The late phase: starts few hours(2-8 hrs) later and last for even days with inflammation, tissue destruction, recruitment of neutrophils and eosinophils and mucosal damage

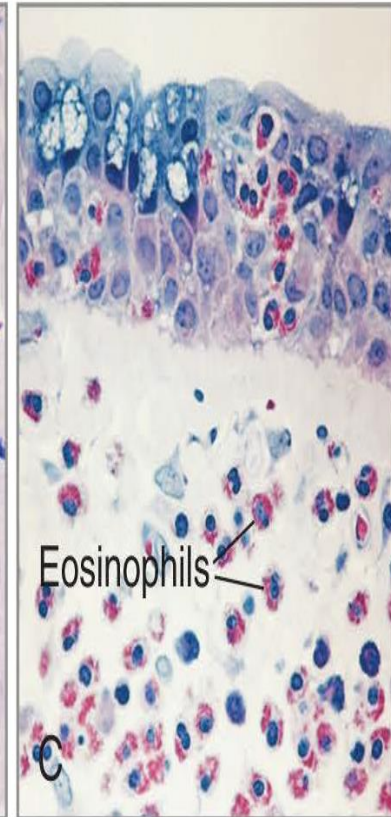
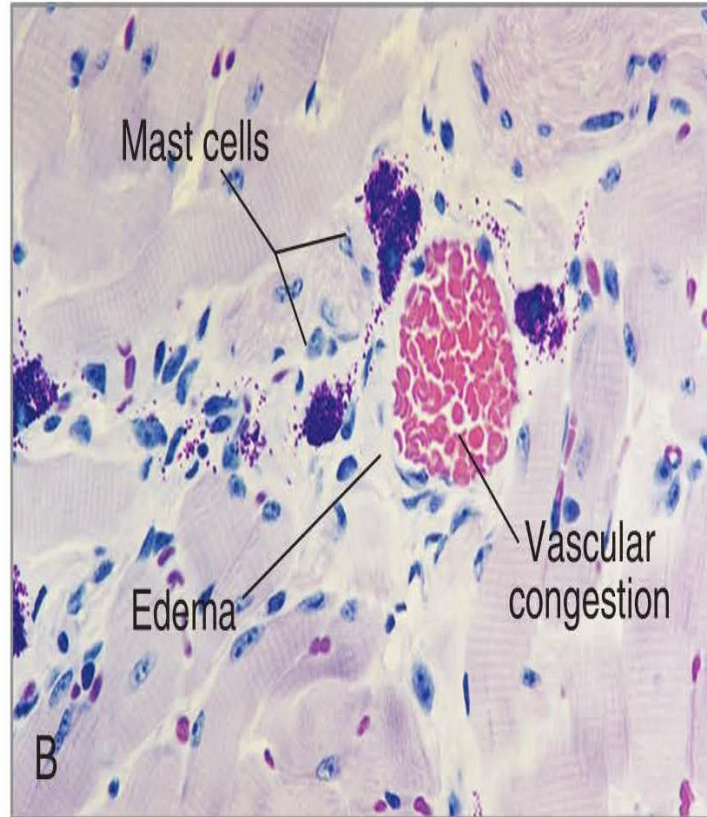
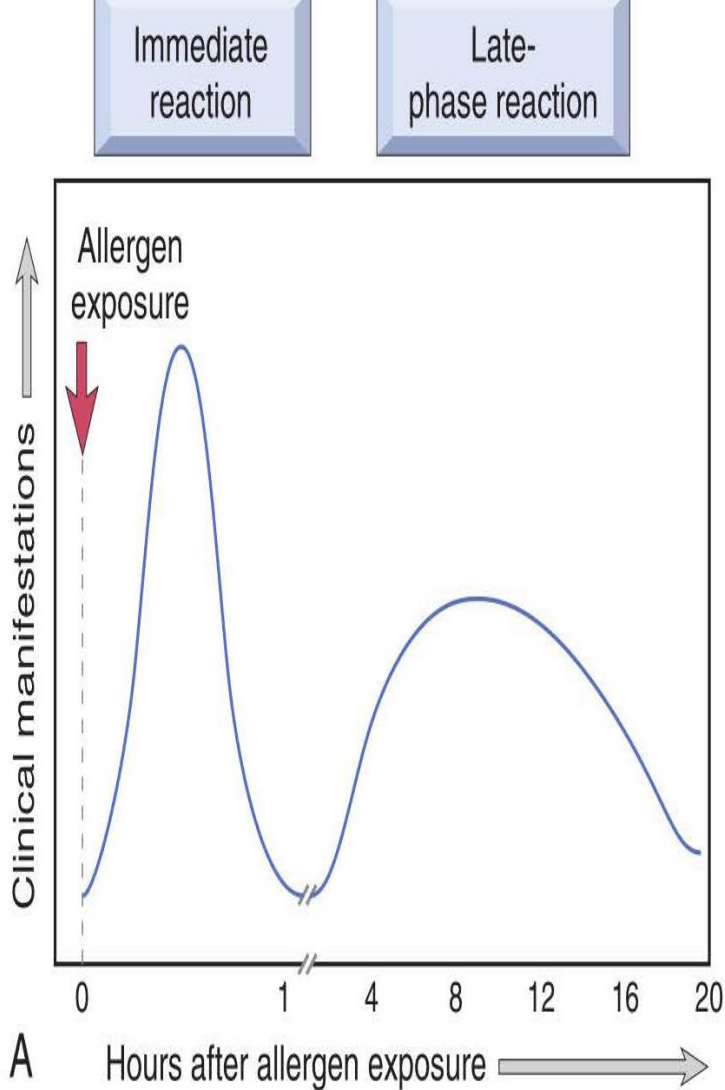


Figure 6-13 Phases of immediate hypersensitivity reactions. **A**, Kinetics of the immediate and late-phase reactions. The immediate vascular and smooth muscle reaction to allergen develops within minutes after challenge (allergen exposure in a previously sensitized individual), and the late-phase reaction develops 2 to 24 hours later. The immediate reaction (**B**) is characterized by vasodilation, congestion, and edema, and the late-phase reaction (**C**) is characterized by an inflammatory infiltrate rich in eosinophils, neutrophils, and T cells. (Courtesy Dr. Daniel Friend, Department of Pathology, Brigham and Women's Hospital, Boston, Mass.)

Systemic exposure to protein antigens (e.g., in bee venom) or drugs (e.g., penicillin) or food allergens (e.g., peanuts, walnut, shellfish, strawberry, egg, food additives ...etc) may result in systemic anaphylaxis.

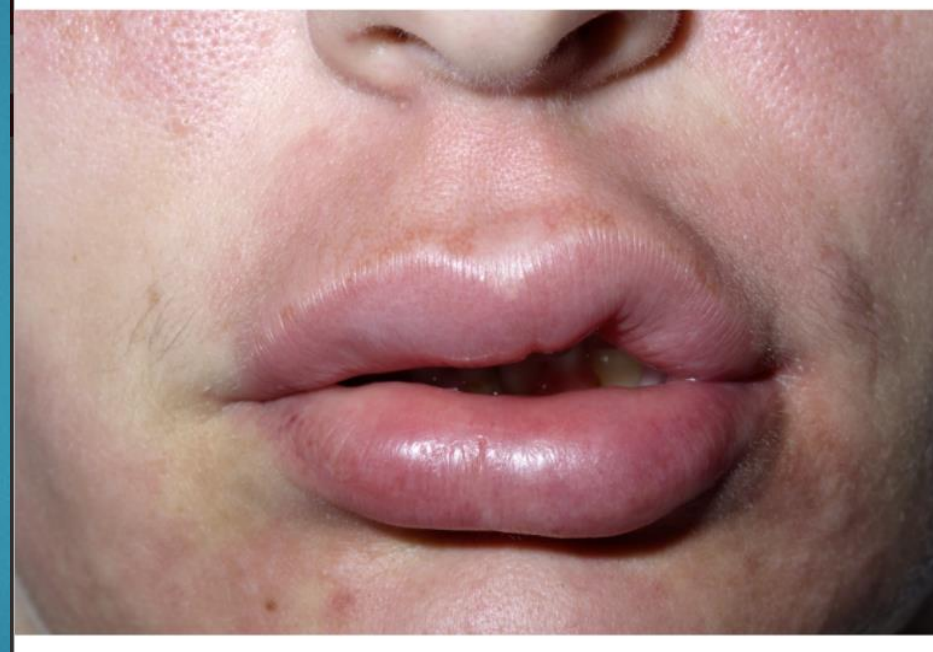
- ▶ Within minutes of the exposure in a sensitized host, itching, urticaria (hives), and skin erythema appear, followed in short order by pulmonary bronchoconstriction and hypersecretion of mucus.
- ▶ **Laryngeal edema** causing upper airway obstruction.
- ▶ Without immediate intervention, there may be **anaphylactic shock** and **death**.

Type 1 hypersensitivity reaction

Urticaria (hives)



Angioedema



Urticaria and angioedema are two manifestations seen in some allergies and are due to effect of histamine and other mediators released from mast cells during type I hypersensitivity with vasodilation and edema

Local reactions

generally occur when the antigen is confined to a particular site, such as:

- ▶ skin (contact, causing urticaria).
- ▶ GIT (ingestion, causing diarrhea),
- ▶ lung (inhalation, causing bronchoconstriction), hay fever

THANK YOU