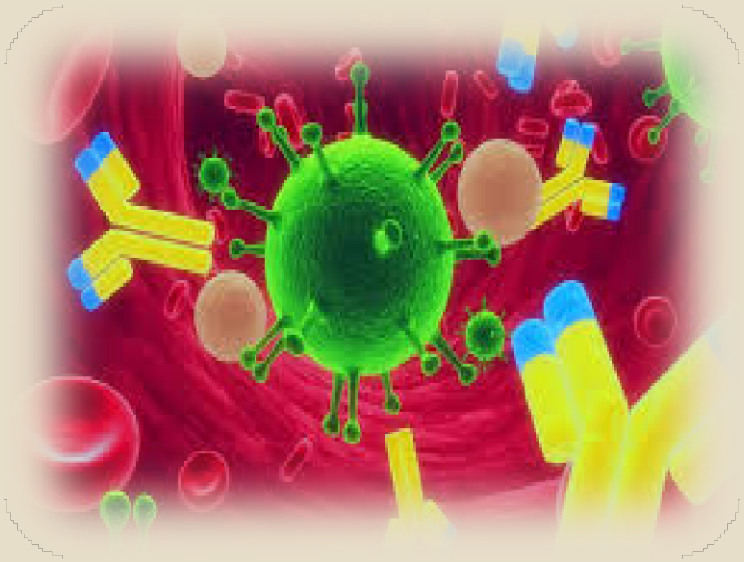
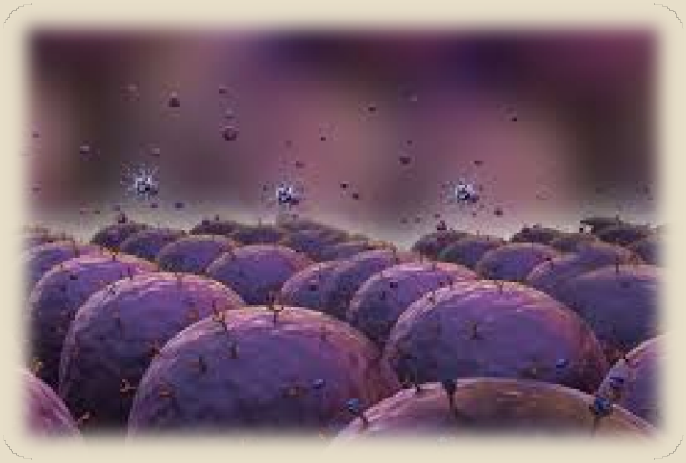


IMMUNOLOGY



Princy

Immunology and immune system

- The Latin term *immunis,* meaning “exempt from” is the source of the English word immunity, meaning the state of protection from infectious disease.

- Immune system – The immune system is a system of **cells**, **tissues** and their **soluble products** and **organs** that recognizes, attacks and destroys entities that could endanger the health of an individual.
- The normal functioning of the immune system gives rise to immunity.

- **Immunity**—the state of protection from infectious diseases.

- Immunology is the science that studies the nature and functioning of the immune system.

- The immune system is a remarkably versatile defence system that has evolved to protect animals from invading pathogenic microorganisms and cancer.

- It is able to generate an enormous variety of cells and molecules capable of specifically recognizing and eliminating an apparently limitless variety of foreign invaders.

- The primary functions of a healthy functioning immune system can be summarized as

1. Recognition of self and foreign material such as pathogens.

2. Attack and destruction of foreign invaders.

3. Surveillance of the body.

RAS

Immune response – the specific response of immune system to ‘non- self’.

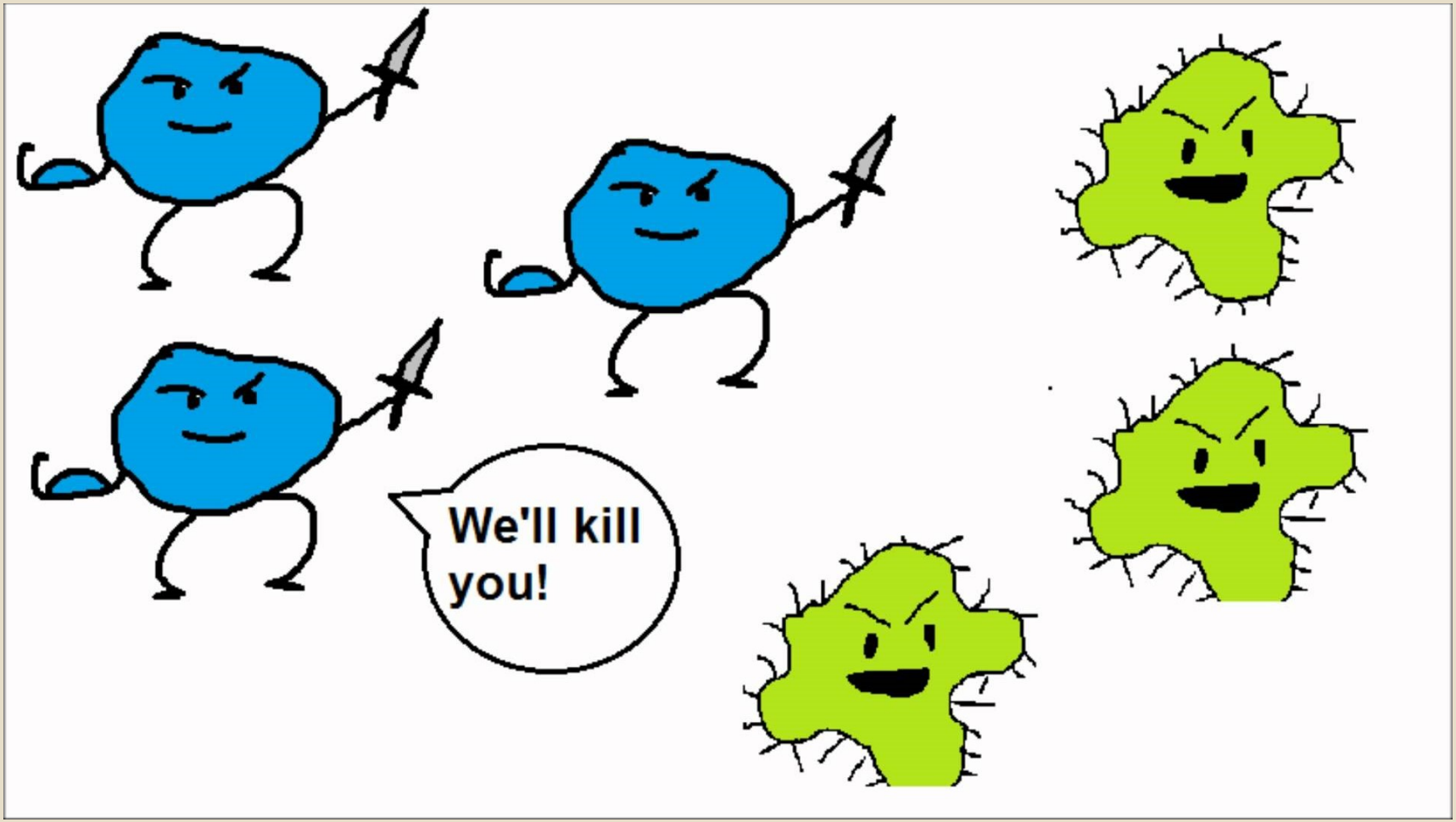
- Functionally, an immune response can be divided into two related activities— recognition and response.
- Immune recognition is remarkable for its specificity.
- The immune system is **able to recognize subtle chemical differences that distinguish one foreign pathogen from another**.
- Furthermore, the system is able to discriminate between foreign molecules and the body's own cells and proteins.
- Foreign matter is often called **non-self.**

- Normal cells of the body, called **self**, are monitored and recognized and are usually not attacked by the immune system.

- The ability to evaluate non-self and thus spare self from attack is central to the effectiveness of the immune system.

Cell Mediated Immunity (CMI) and Humoral immunity

- At the turn of the 20th century, there were two schools of thought on what mechanisms underlay immune responses.
- One group of scientists believed that immunity depended primarily on the *actions of cells* that destroyed or removed unwanted material from the body.
- This clearance process was referred to as cell-mediated immunity.


We'll kill you!

- However, another group of researchers was convinced that soluble molecules in the serum of the blood could directly eliminate foreign entities without the need for cellular involvement.

- In this case, the clearance process was referred to as humoral immunity.

- The term derived from the historical description of **body fluids** in latin as "**humors**."

- Today, we know that both cell-mediated and humoral responses occur simultaneously during an immune response and that both are often required for complete clearance of a threat.

- Immunity has both a less specific and more specific component.
- The less specific component - **innate immunity,** provides the first line of defence against infection.
- The specific component- **adaptive immunity,** does not come into play until there is an antigenic challenge to the organism.

Innate immunity & Adaptive immunity

- Innate/natural immunity is the non specific immunity, inborn and unchanging, resulting from the genetic nature of the host.
- E.g. humans are naturally immune to many of the infectious diseases that affect animals. When antigen is encountered, these mechanisms always respond in the same manner, regardless of the nature of the antigen.

- Adaptive immunity – is the specific immunity results from the development of immune response when an individual is stimulated by an antigen such as those associated with invading microbes. This response is specific to a particular antigen.

- If presented with a new antigen, the response will not be the same as a response to another antigen.

Innate immunity

- Most components of innate immunity are present before the onset of infection and constitute a set of *disease-resistance mechanisms that are not specific to a particular pathogen* but that include cellular and molecular components that recognize classes of molecules peculiar to frequently encountered pathogens.

- The innate response is not enhanced by previous exposure to the foreign organism and the response time is very rapid usually occurring in minutes or hours.

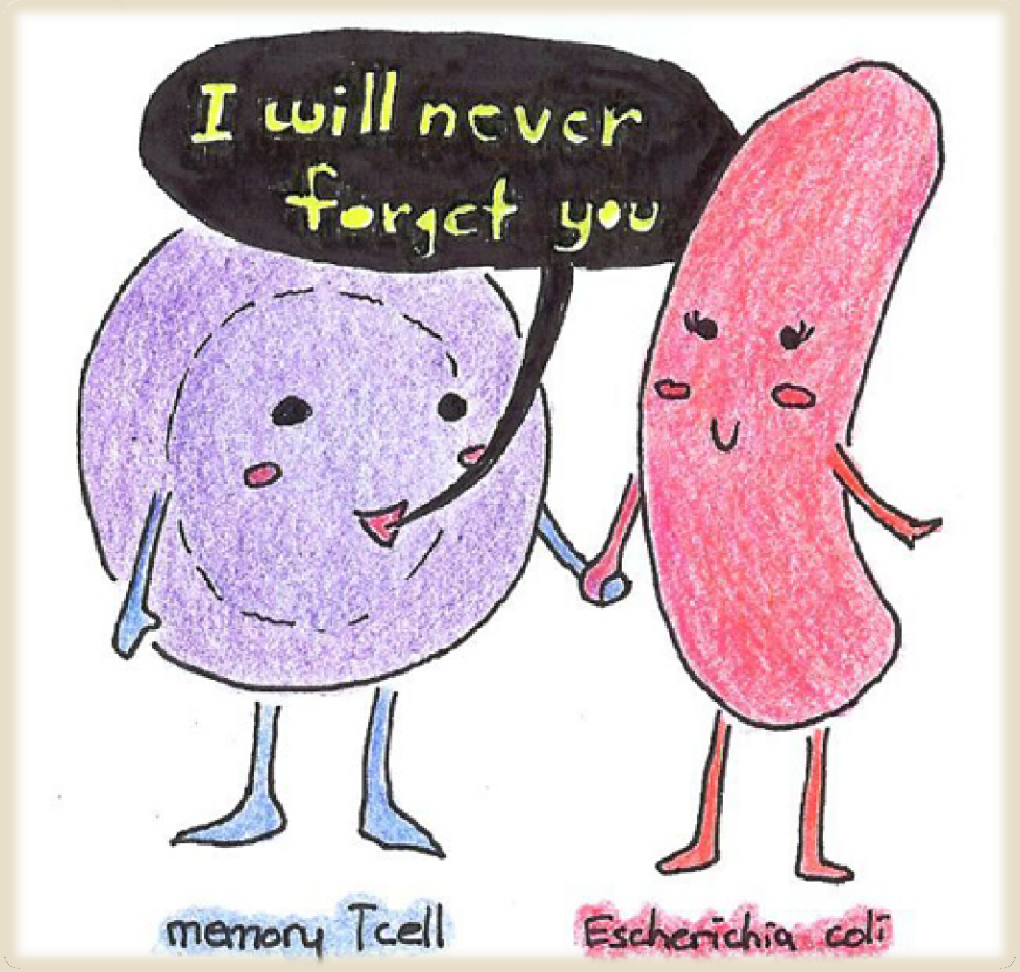
- Phagocytic cells, such as macrophages and neutrophils, barriers such as skin, and a variety of antimicrobial compounds synthesized by the host all play important roles in innate immunity.

- Innate immune system is **uniform in all members of a species.**

Adaptive immunity

- Adaptive immunity responds to the challenge with a high degree of specificity as well as the remarkable property of "memory."
- Typically, there is an adaptive immune response against an antigen within five or six days after the initial exposure to that antigen.
- The major agents of adaptive immunity are lymphocytes and the antibodies and other molecules they produce.

- Exposure to the same antigen some time in the future results in **a memory response**: the immune response to the second challenge occurs more quickly than the first, is stronger, and is often more effective in neutralizing and clearing the pathogen.



- Because adaptive immune responses require some time to marshal, innate immunity provides the first line of defence during the critical period just after the host's exposure to a pathogen.

- In general, most of the microorganisms encountered by a healthy individual are readily cleared within a few days by defence mechanisms of the innate immune system before they activate the adaptive immune system.

Sl. No.	Innate immunity	Adaptive immunity
1.	Less specific component of immune system.	More specific component of immune system.
2.	First line of defense against infection.	Does not come into play until there is an antigenic challenge to the organism.
3.	Inborn	Acquired
4.	Unchanging and uniform in all members of a species.	Changing and variable in members of a species.
5.	Resulting from the genetic nature of the host.	Results from the development of immune response when an individual is stimulated by an antigen such as those associated with invading microbes.

Sl. No.	Innate immunity	Adaptive immunity
6.	Always respond in the same manner	Variable depends on the antigen. If presented with a new antigen, the response will not be the same as a response to another antigen.
7.	Components of innate immunity are present before the onset of infection.	Components present after the onset of infection.
8.	Innate response is not enhanced by previous exposure to the foreign organism.	Remarkable property of **memory response** and immune response to the second challenge occurs more quickly and enhanced/stronger than the first. It is often more effective in neutralizing and cleaning pathogen.
9.	Response time is very rapid (usually occurring in minutes or hours).	Response against an antigen within five or six days after the initial exposure to that antigen.

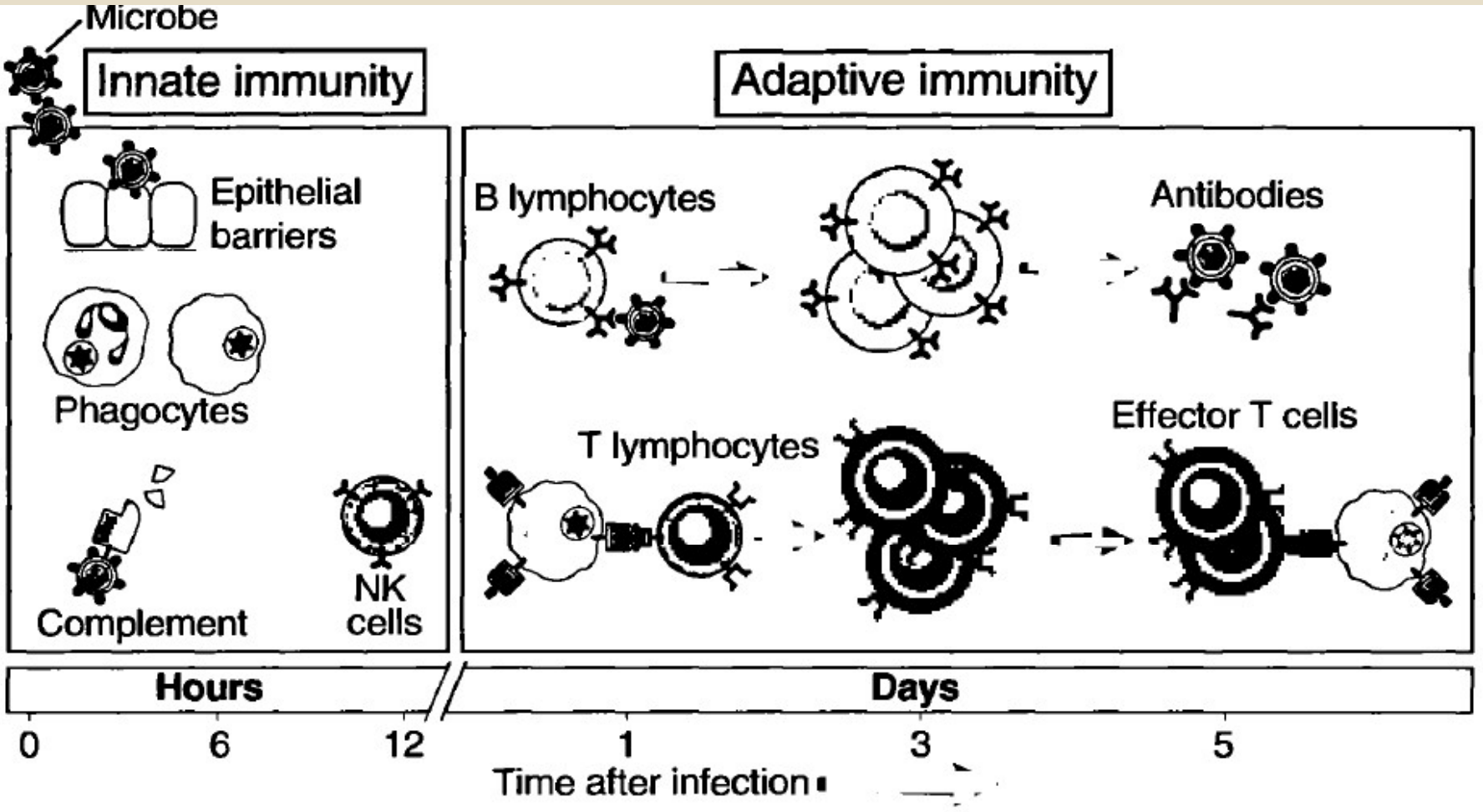
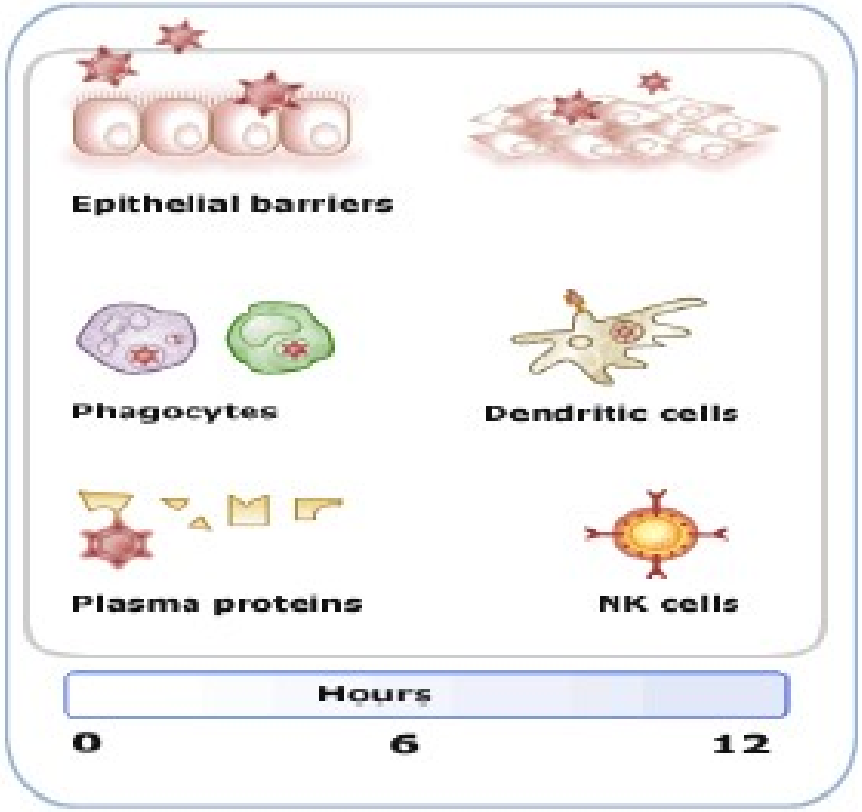
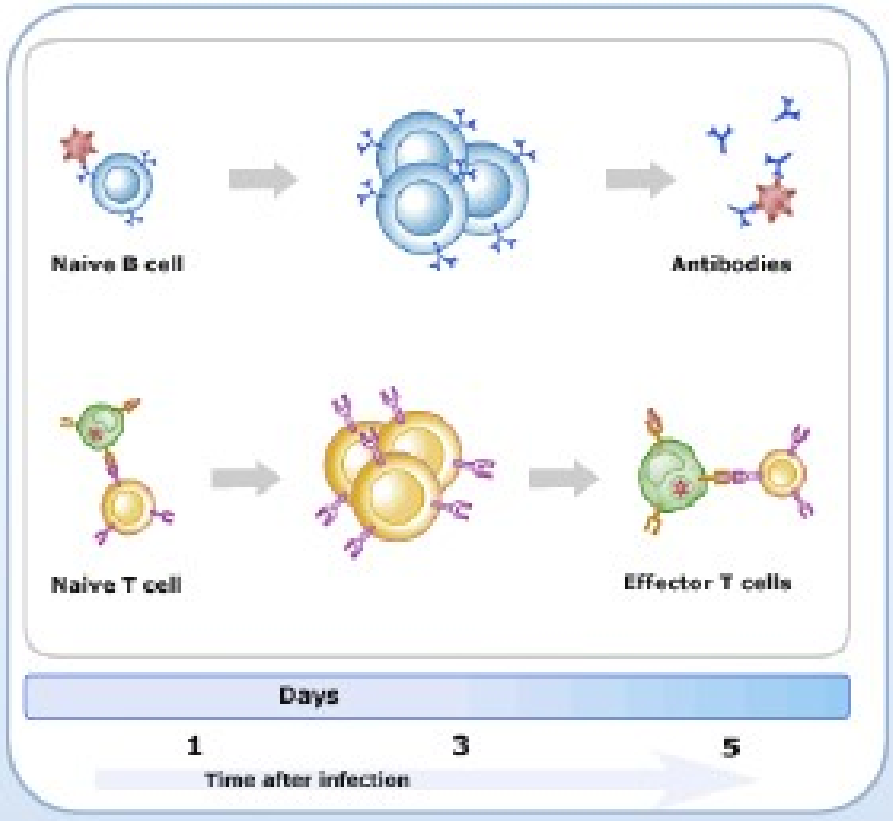


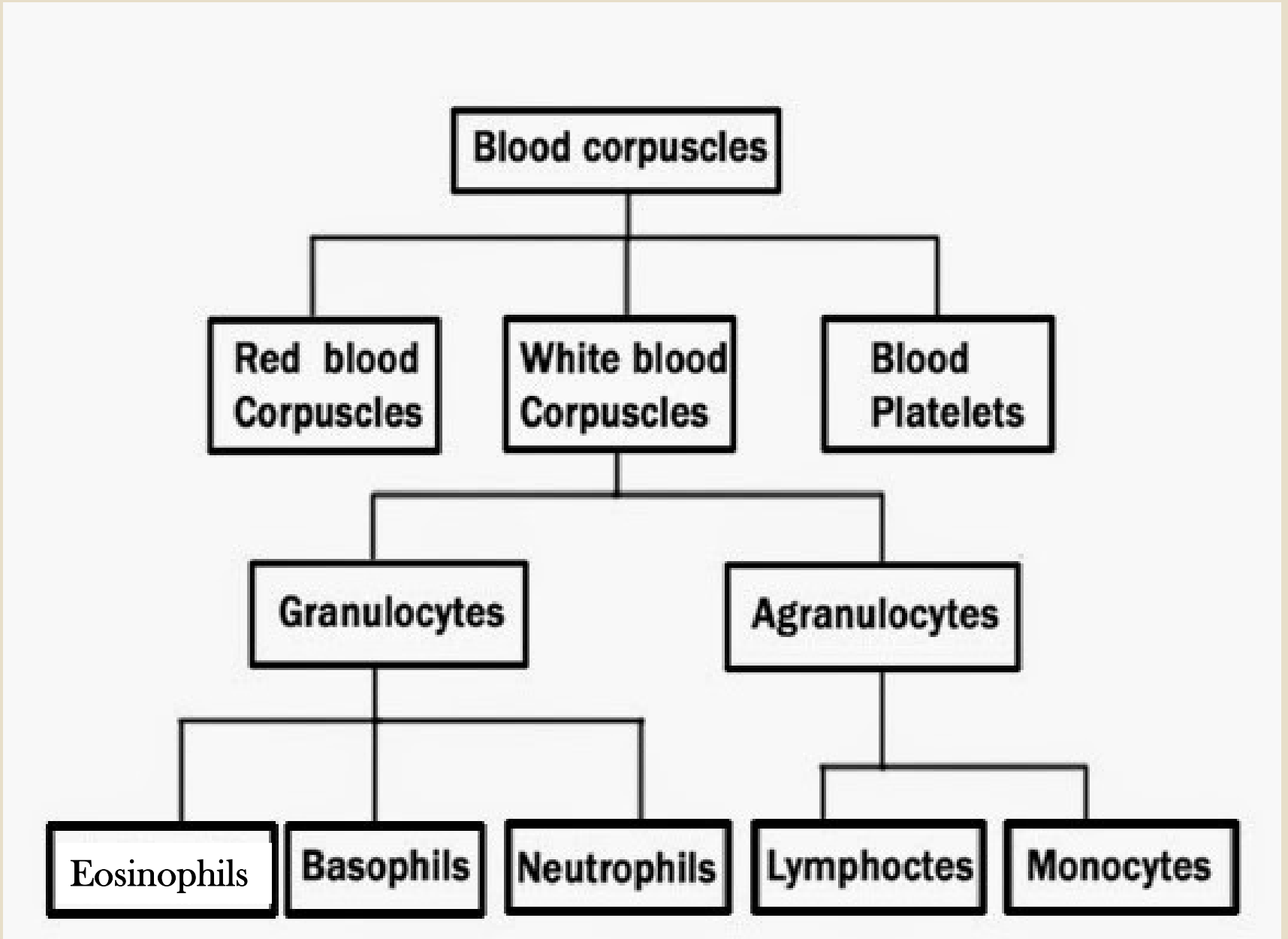
Figure 1–3 The principal mechanisms of innate and adaptive immunity. The mechanisms of innate immunity p the initial defense against infections. Some of the mechanisms prevent infections (e.g., epithelial barriers) and others nate microbes (e.g., phagocytes, NK cells, and the complement system). Adaptive immune responses develop later a mediated by lymphocytes and their products. Antibodies block infections and eliminate microbes, and T lymphocytes cate intracellular microbes. The kinetics of the innate and adaptive immune responses are approximations and may different infections.

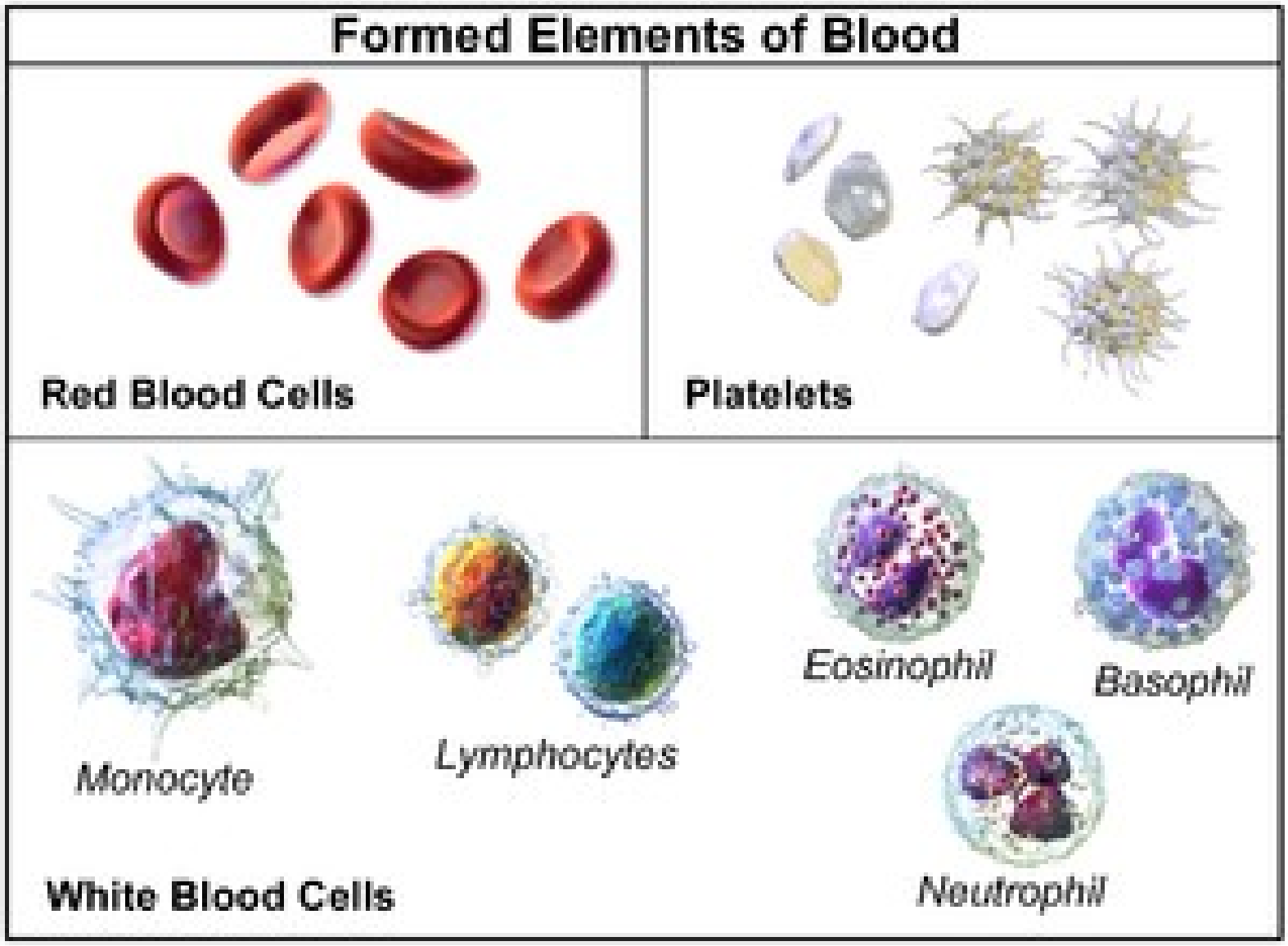
Innate Immunity



Adaptive Immunity




Blood corpuscles
Red blood Corpuscles
White blood Corpuscles
Blood Platelets
Granulocytes
Agranulocytes
Eosinophils
Basophils
Neutrophils
Lymphoctes
Monocytes


Formed Elements of Blood
Red Blood Cells
Platelets
Monocyte
Lymphocytes
Eosinophil
Basophil
Neutrophil
White Blood Cells

- The cells that participate in the immune response are white blood cells, or leukocytes.

.

Hematopoiesis

- All blood cells arise from a type of cell called the **hematopoietic stem cell (HSC).**

- **Stem cells are cells that can differentiate** into other cell types; they are self-renewing—they maintain their population level by cell division.

- In humans, **hematopoiesis, the** formation and development of red and white blood cells, begins in the embryonic yolk sac during the first weeks of development.

- A hematopoietic stem cell is *multipotent* - able to differentiate in various ways.

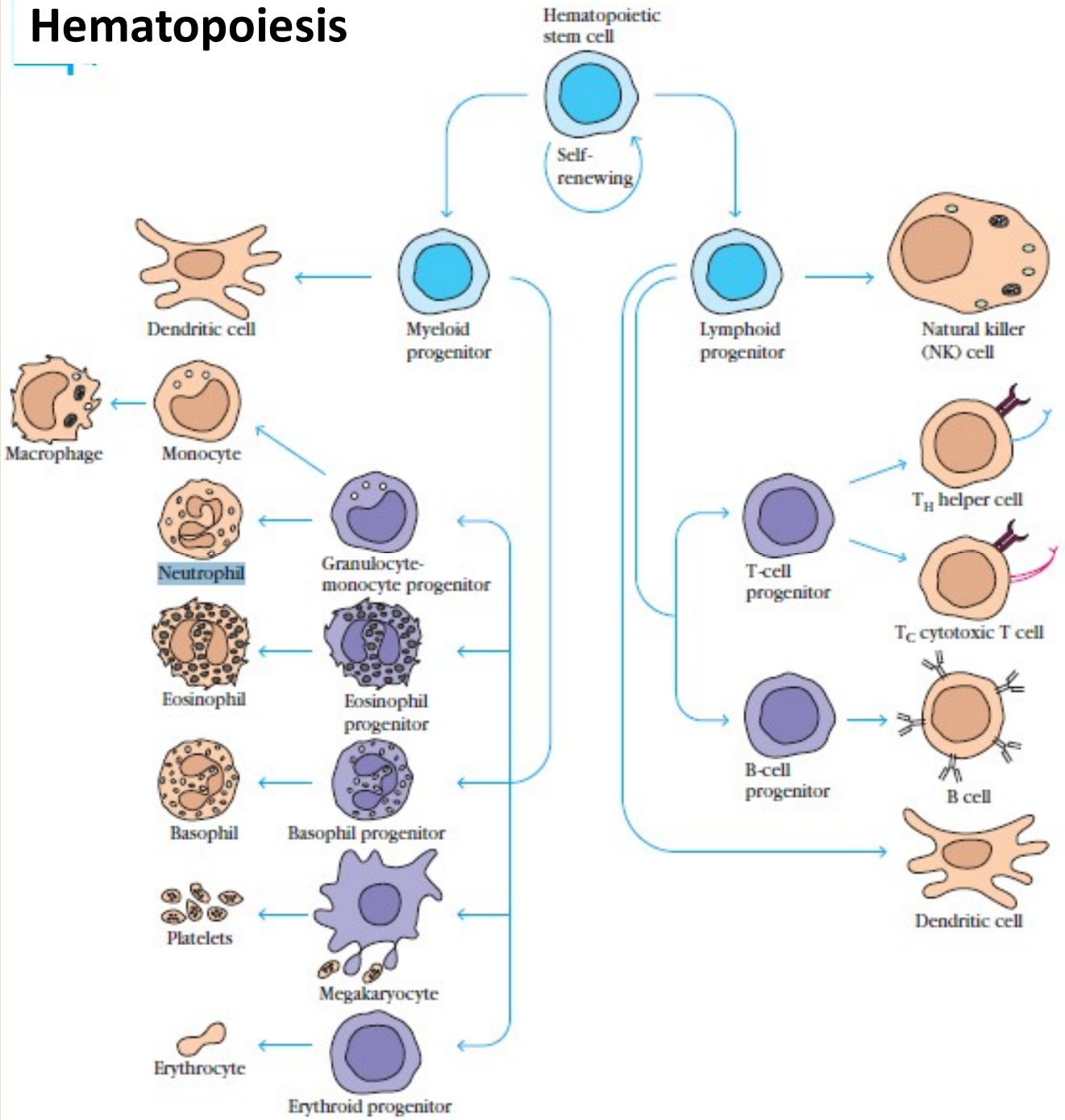
- Early in hematopoiesis, a **multipotent stem cell** differentiates along one of two pathways, giving rise to either

- a common **lymphoid progenitor cell** or
- a common **myeloid progenitor cell.**

- **The types and amounts of growth factors** in the microenvironment of a particular stem cell or progenitor cell control its differentiation.

- During the development of the lymphoid and myeloid lineages, stem cells differentiate into **progenitor cells, which have lost the** capacity for self-renewal and are committed to a particular cell lineage.

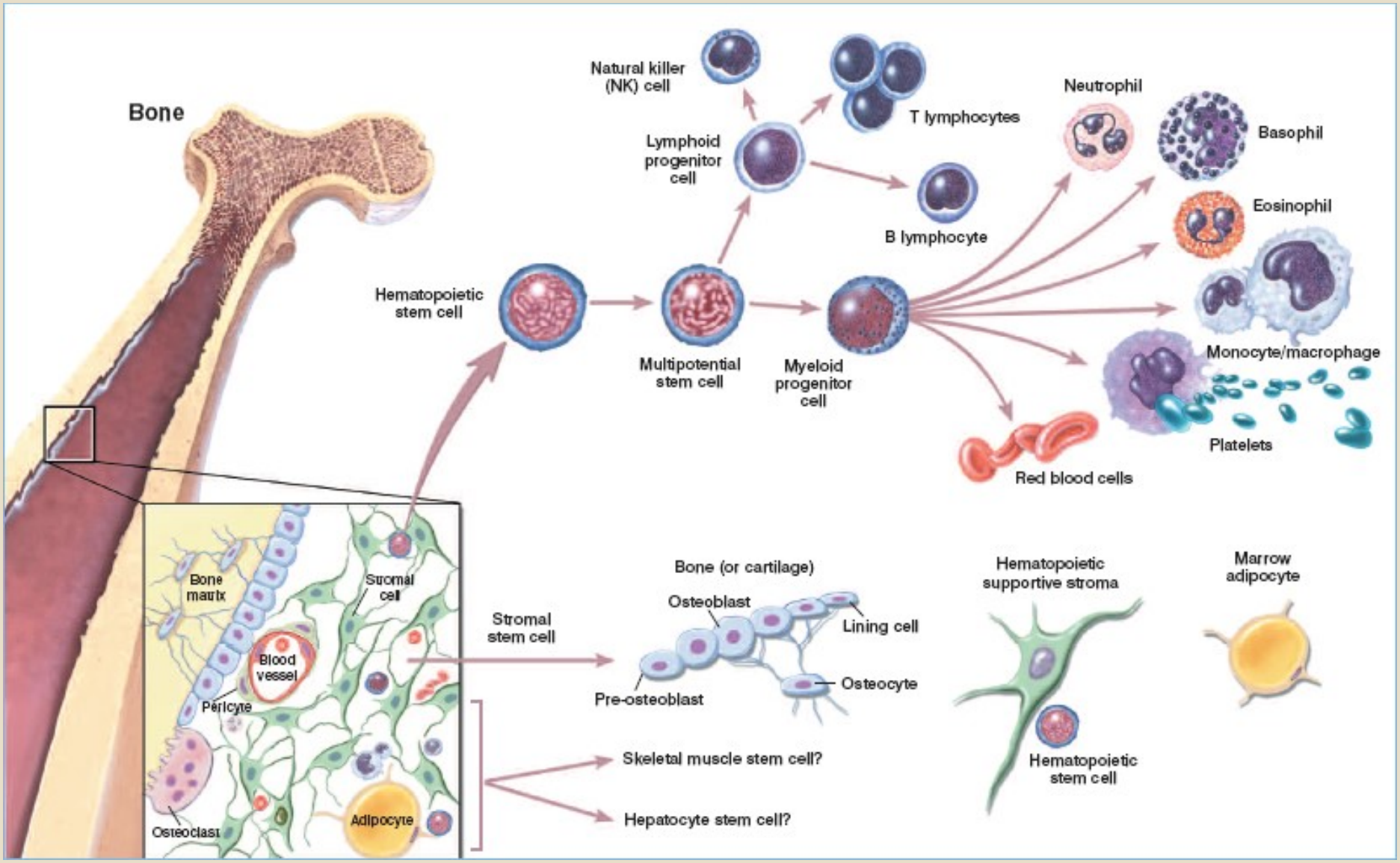
Hematopoiesis

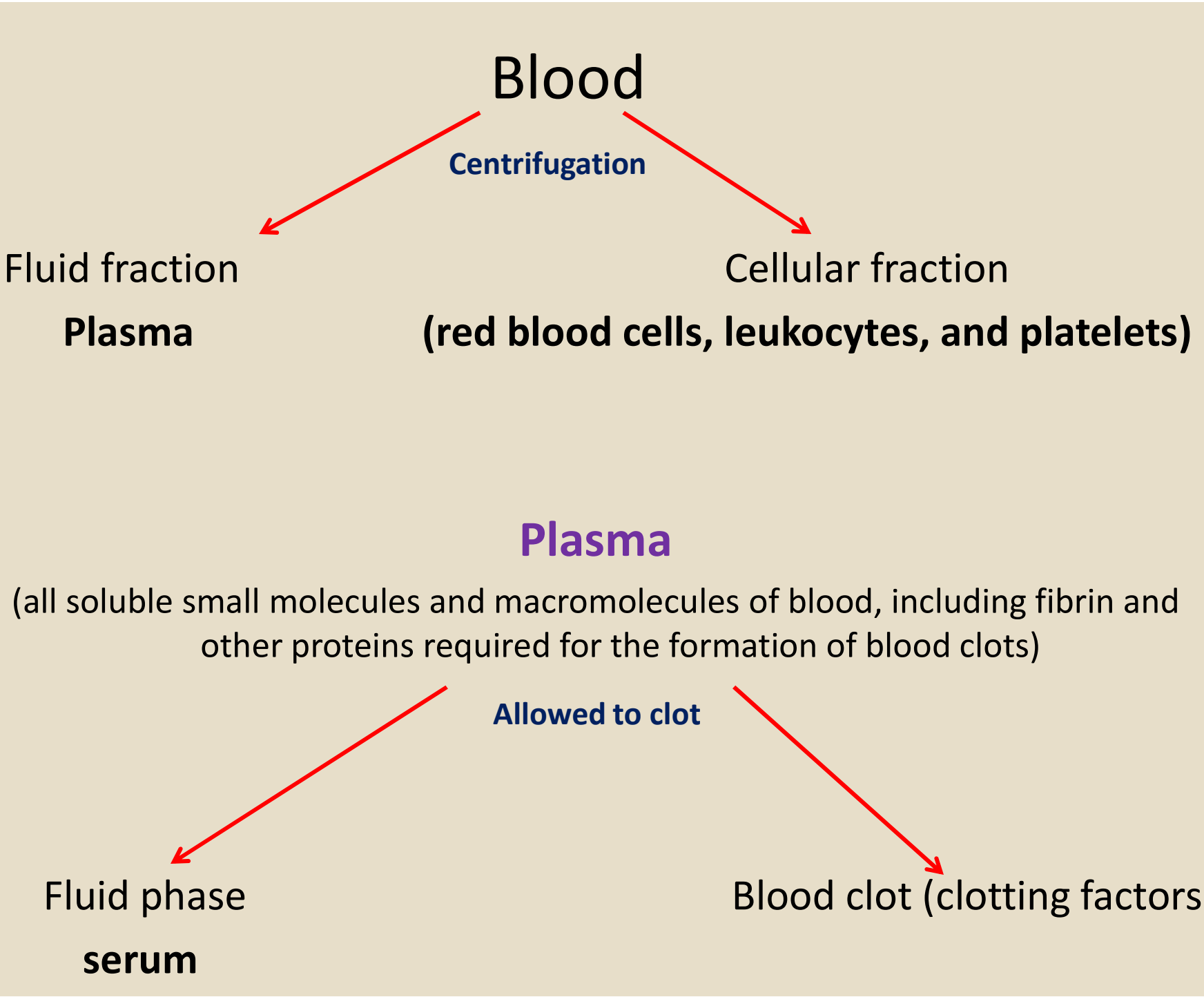


Self-renewing hematopoietic stem cells give rise to lymphoid and myeloid progenitors.

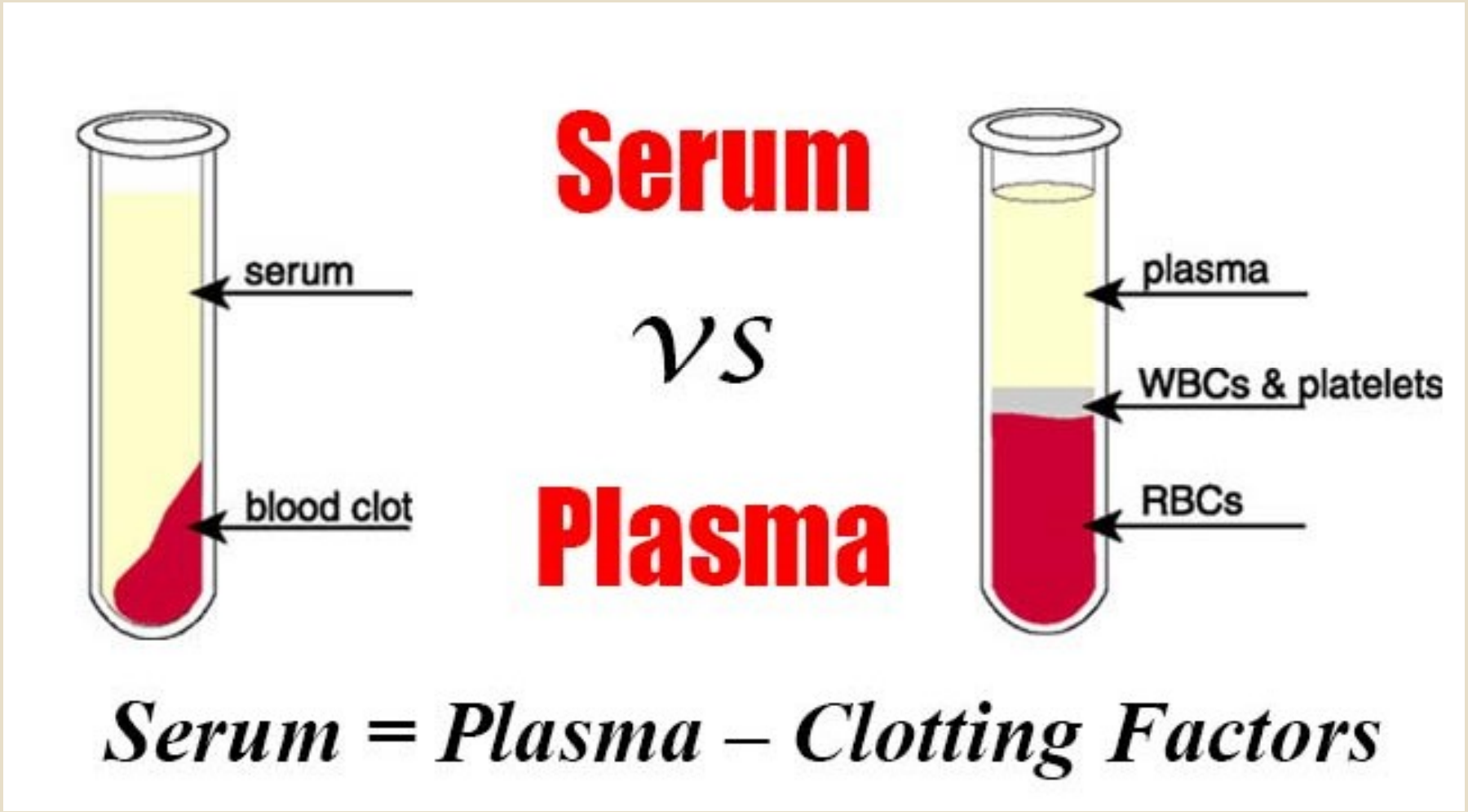
All lymphoid cells descend from lymphoid progenitor cells and all cells of the myeloid lineage arise from myeloid progenitors.

Some dendritic cells come from lymphoid progenitors, others from myeloid precursors.


Bone
Natural killer (NK) cell
T lymphocytes
Neutrophil
Basophil
Lymphoid progenitor cell
B lymphocyte
Eosinophil
Hematopoietic stem cell
Multipotential stem cell
Myeloid progenitor cell
Monocyte/macrophage
Platelets
Red blood cells
Bone matrix
Stromal cell
Blood vessel
Pericyte
Osteoclast
Adipocyte
Stromal stem cell
Bone (or cartilage)
Osteoblast
Lining cell
Osteocyte
Pre-osteoblast
Skeletal muscle stem cell?
Hepatocyte stem cell?
Hematopoietic supportive stroma
Hematopoietic stem cell
Marrow adipocyte

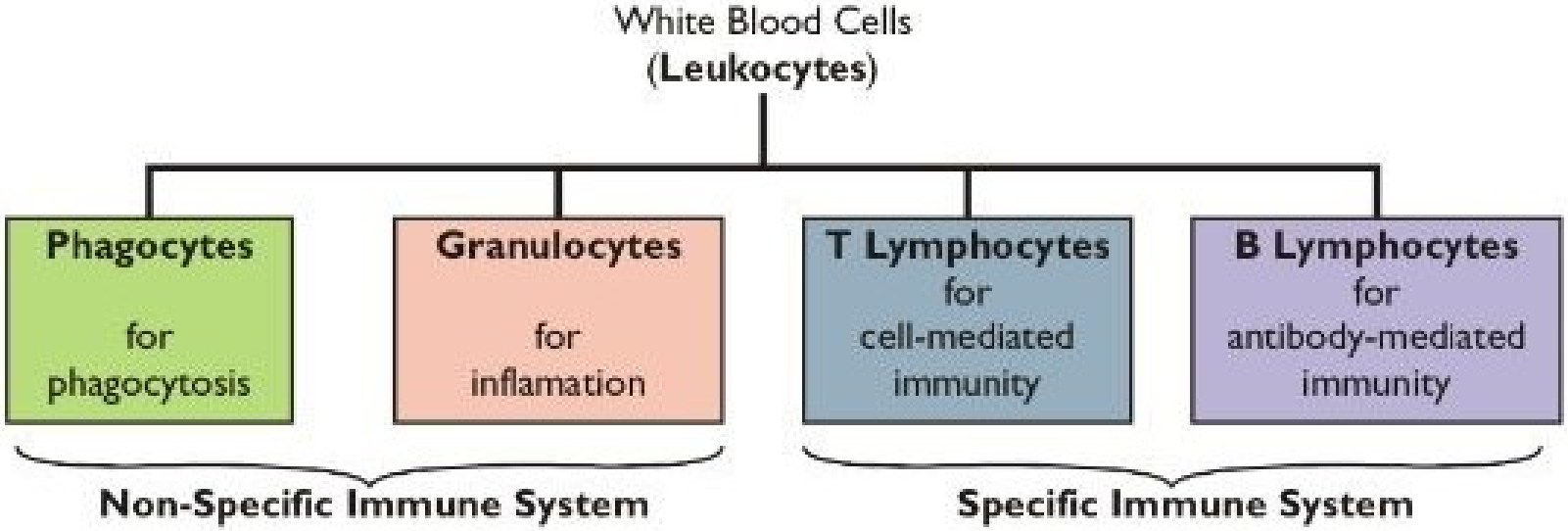

Blood
Centrifugation
Fluid fraction
Plasma
Cellular fraction
(red blood cells, leukocytes, and platelets)
Plasma
(all soluble small molecules and macromolecules of blood, including fibrin and other proteins required for the formation of blood clots)
Allowed to clot
Fluid phase
serum
Blood clot (clotting factors)

Antibodies reside in the serum.



The Immune System

The Immune System is the body's defence system against disease. It is made up of white blood cells (or leukocytes), which are found in the blood, lymph, tissue fluid and body cavities (such as alveoli). There are dozens of different kinds of leukocytes, which fall into four categories:



Innate immunity

- Innate immunity can be seen to comprise four types of defensive barriers:

- Anatomical/ structural barriers
- Physiological barriers
- Phagocytic barriers and
- Inflammatory barriers

TABLE 1-2 Summary of nonspecific host defenses

Type	Mechanism
Anatomic barriers	
Skin	Mechanical barrier retards entry of microbes. Acidic environment (pH 3–5) retards growth of microbes.
Mucous membranes	Normal flora compete with microbes for attachment sites and nutrients. Mucus entraps foreign microorganisms. Cilia propel microorganisms out of body.
Physiologic barriers	
Temperature	Normal body temperature inhibits growth of some pathogens. Fever response inhibits growth of some pathogens.
Low pH	Acidity of stomach contents kills most ingested microorganisms.
Chemical mediators	Lysozyme cleaves bacterial cell wall. Interferon induces antiviral state in uninfected cells. Complement lyses microorganisms or facilitates phagocytosis. Toll-like receptors recognize microbial molecules, signal cell to secrete immunostimulatory cytokines. Collectins disrupt cell wall of pathogen.
Phagocytic/endocytic barriers	Various cells internalize (endocytose) and break down foreign macromolecules. Specialized cells (blood monocytes, neutrophils, tissue macrophages) internalize (phagocytose), kill, and digest whole microorganisms.
Inflammatory barriers	Tissue damage and infection induce leakage of vascular fluid, containing serum proteins with antibacterial activity, and influx of phagocytic cells into the affected area.

The Skin and the Mucosal Surfaces Provide Protective Barriers Against Infection

- Physical and anatomical barriers that tend to prevent the entry of pathogens are an organism's first line of defense against infection.

- The skin and the surface of mucous membranes are included in this category because they are effective barriers to the entry of most microorganisms.

- The skin consists of two distinct layers:

  A thinner outer layer—the **epidermis**

  A thicker layer—the **dermis.**

- The epidermis contains several layers of tightly packed epithelial cells.

- **The outer epidermal layer consists of dead cells** and is filled with a waterproofing protein called keratin.

- The dermis, which is composed of **connective tissue**, contains **blood vessels**, **hair follicles**, **sebaceous glands**, and **sweat glands**. The sebaceous glands are associated with the hair follicles and produce an oily secretion called **sebum.**

- Sebum consists of **lactic acid** and **fatty acids**, which maintain the pH of the skin between 3 and 5; this pH inhibits the growth of most microorganisms.

- Breaks in the skin resulting from scratches, wounds, or abrasion are obvious routes of infection.

- The skin may also be penetrated by biting insects (e.g., mosquitoes, mites, ticks, fleas, and sand flies); if these harbour pathogenic organisms, they can introduce the pathogen into the body as they feed.

- The protozoan that causes malaria, for example, is deposited in humans by mosquitoes when they take a blood meal.

- The conjunctivae and the alimentary, respiratory, and urogenital tracts are lined by mucous membranes, not by the dry, protective skin that covers the exterior of the body.

- These membranes consist of an **outer epithelial layer** and an underlying layer of connective tissue. Although many pathogens enter the body by binding to and penetrating mucous membranes, a number of nonspecific defence mechanisms tend to prevent this entry.

- The viscous fluid called mucus, which is secreted by epithelial cells of mucous membranes, entraps foreign microorganisms.

- For example, saliva, tears, and mucous secretions act to wash away potential invaders and also contain antibacterial or antiviral substances.

- In the lower respiratory tract, the mucous membrane is covered by **cilia,** hair like protrusions of the epithelial-cell membranes.
- The synchronous movement of cilia propels mucus-entrapped microorganisms from these tracts.
- In addition, non pathogenic organisms tend to colonize the epithelial cells of mucosal surfaces.
- These *normal flora* generally outcompete pathogens for attachment sites on the epithelial cell surface and for necessary nutrients.
- E.g. *Micrococcus, Streptococcus*

Physiological barriers

- The physiologic barriers that contribute to innate immunity include temperature, pH, and various soluble and cell associated molecules.

- Many species are not susceptible to certain diseases simply because their normal body temperature inhibits growth of the pathogens.

- Chickens, for example, have innate immunity to anthrax because their high body temperature inhibits the growth of the bacteria.

- Gastric acidity is an innate physiologic barrier to infection because very few ingested microorganisms can survive the low pH of the stomach contents.

- One reason newborns are susceptible to some diseases that do not afflict adults is that their stomach contents are less acid than those of adults.

- A variety of soluble factors contribute to innate immunity, among them the soluble proteins lysozyme, interferon, and complement.

- **Lysozyme,** a hydrolytic enzyme found in mucous secretions and in tears, is able to cleave the peptidoglycan layer of the bacterial cell wall.

- **Interferon** comprises a group of proteins produced by virus-infected cells. Among the many functions of the interferons is the ability to bind to nearby cells and induce a generalized antiviral state.

- **Complement,** is a group of serum proteins that circulate in an inactive state. A variety of specific and nonspecific immunologic mechanisms can convert the inactive forms of complement proteins into an active state with the ability to damage the membranes of pathogenic organisms, either destroying the pathogens or facilitating their clearance.

- Complement may function as an effector system that is triggered by **binding of antibodies to certain cell surfaces**, or **it may be activated by reactions between complement molecules and certain components of microbial cell walls.**

- Reactions between complement molecules or fragments of complement molecules and cellular receptors trigger activation of cells of the innate or adaptive immune systems.

- Recent studies on **collectins** indicate that these surfactant proteins may kill certain bacteria directly by disrupting their lipid membranes or, alternatively, by aggregating the bacteria to enhance their susceptibility to phagocytosis.

- Many of the molecules involved in innate immunity have the property of **pattern recognition,** the ability to recognize a given class of molecules.

- Because there are certain types of molecules that are unique to microbes and never found in multicellular organisms, the ability to immediately recognize and combat invaders displaying such molecules is a **strong feature of innate immunity.**

- Molecules with pattern recognition ability **may be soluble**, like lysozyme and the complement components, or they **may be cell-associated receptors.**

- Among the class of receptors designated the **toll-like receptors (TLRs),** TLR2 recognizes the lipopolysaccharide (LPS) found on Gram-negative bacteria.

- It has long been recognized that systemic exposure of mammals to relatively small quantities of purified LPS leads to an acute inflammatory response.

- The mechanism for this response is via a TLR on macrophages that recognizes LPS and elicits a variety of molecules in the inflammatory response upon exposure.

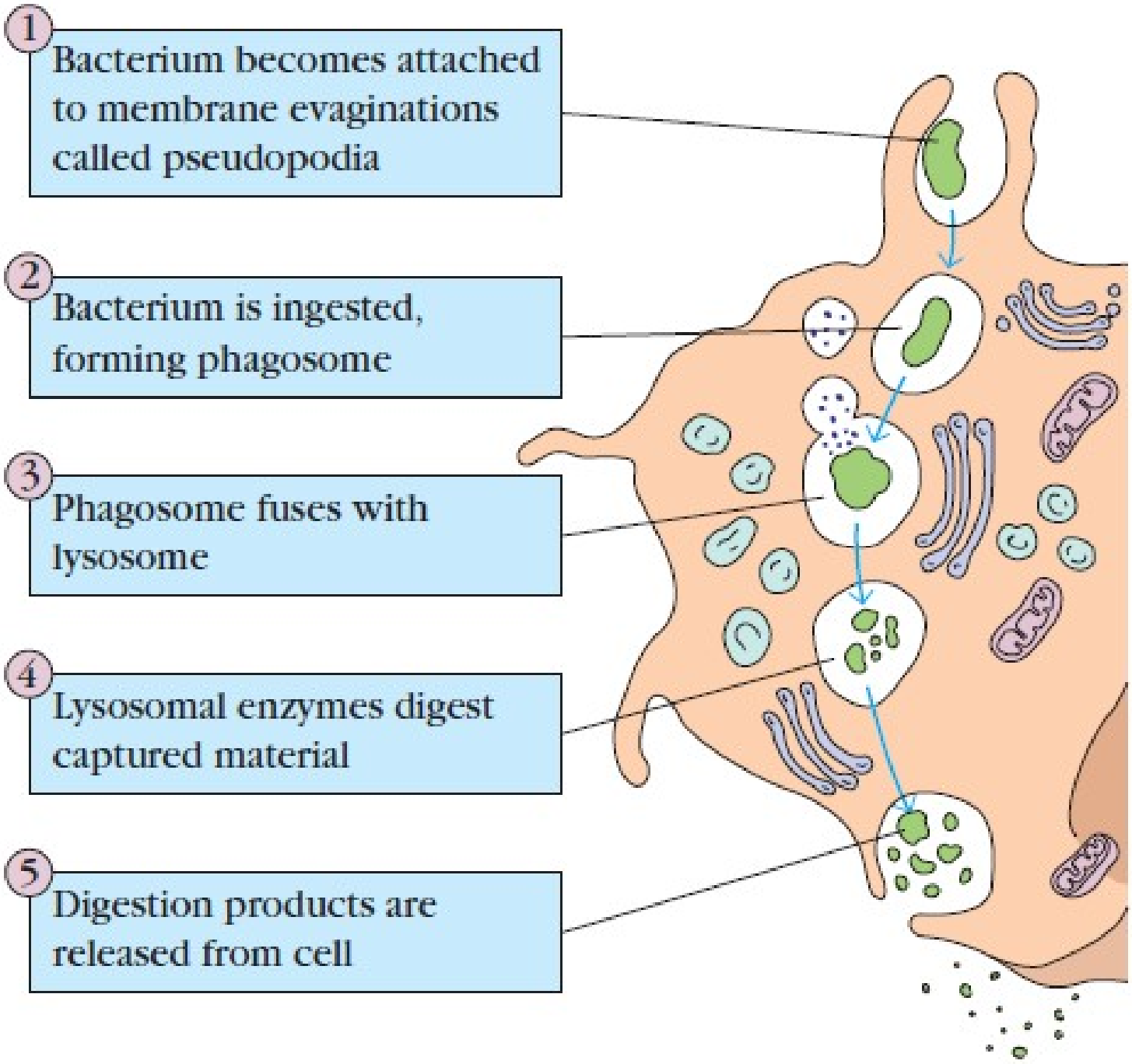
- When the TLR is exposed to the LPS upon local invasion by a Gram-negative bacterium, the contained response results in elimination of the bacterial challenge.

Cells That Ingest and Destroy Pathogens Make Up a **Phagocytic Barrier** to Infection

- Another important innate defense mechanism is the ingestion of extracellular particulate material by **phagocytosis.**

- Phagocytosis is one type of **endocytosis,** the general term for the uptake by a cell of material from its environment.

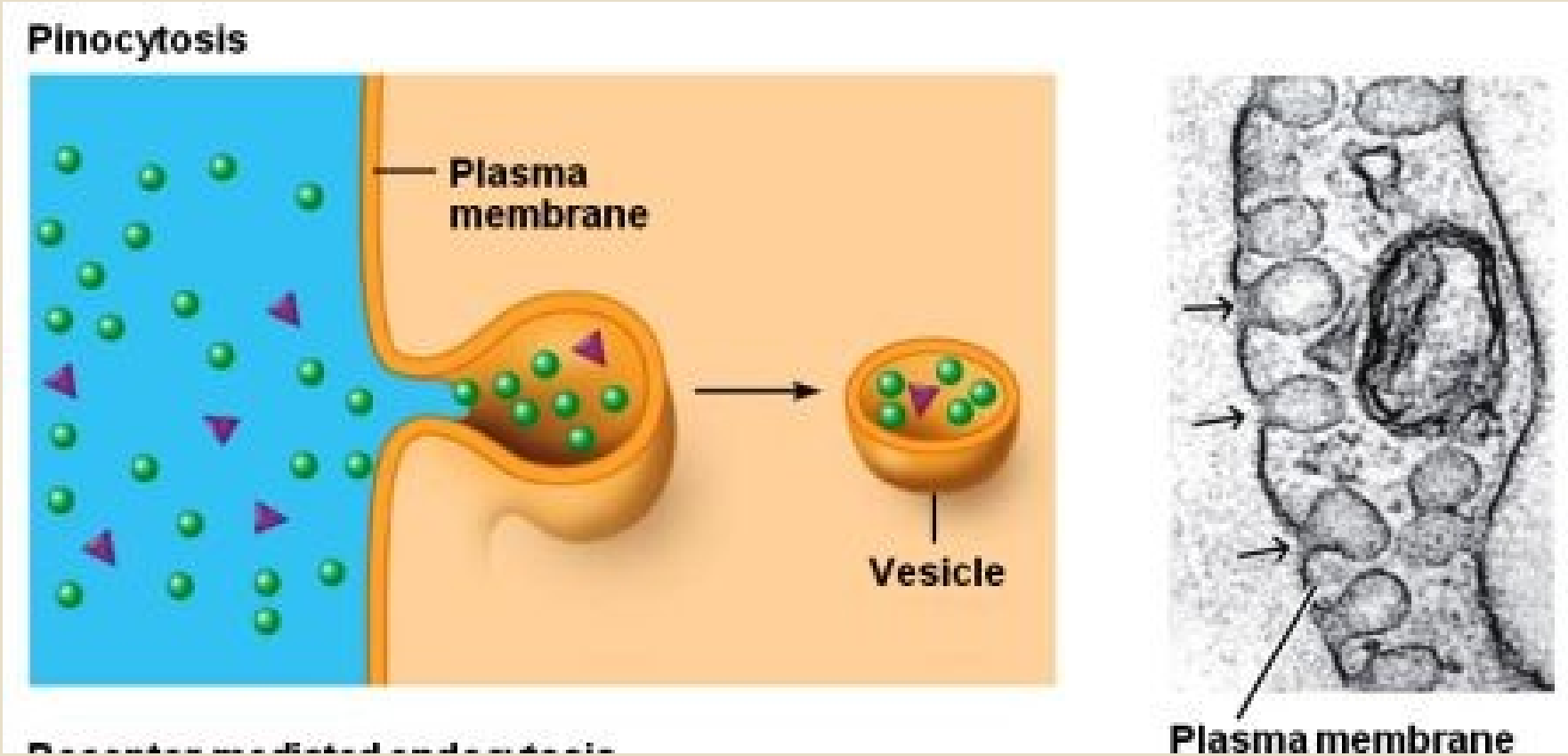
- In phagocytosis, a cell's plasma membrane expands around the particulate material, which may include whole pathogenic microorganisms, to form large vesicles called **phagosomes.**


1
Bacterium becomes attached to membrane evaginations called pseudopodia
2
Bacterium is ingested, forming phagosome
3
Phagosome fuses with lysosome
4
Lysosomal enzymes digest captured material
5
Digestion products are released from cell

- **Most phagocytosis is conducted by specialized cells**, such as blood monocytes, neutrophils, and tissue macrophages.

- Most cell types are capable of other forms of endocytosis, such as *receptor-mediated endocytosis*, in which extracellular molecules are internalized after binding by specific cellular receptors

- and *pinocytosis*, the process by which cells take up fluid from the surrounding medium along with any molecules contained in it.


Pinocytosis
Plasma membrane
Vesicle
Plasma membrane

Inflammation Represents a Complex Sequence of Events That Stimulates Immune Responses

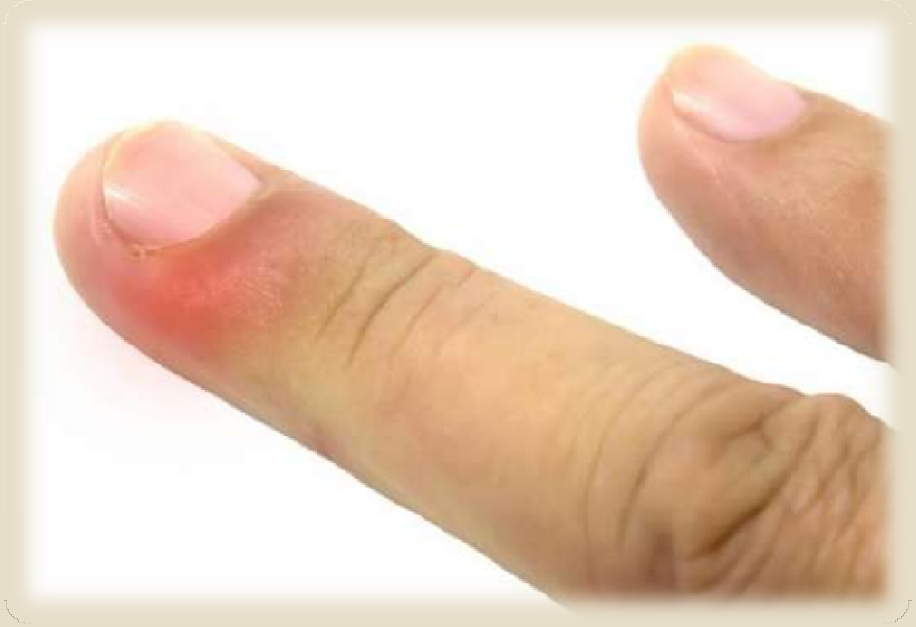
- **Tissue damage** caused by a **wound or by an invading pathogenic microorganism** induces a complex sequence of events collectively known as the **inflammatory response.**

- A molecular component of a microbe, such as LPS, may trigger an inflammatory response via interaction with cell surface receptors.

- The end result of inflammation may be the marshalling of a specific immune response to the invasion or clearance of the invader by components of the innate immune system.

"Four cardinal signs of inflammation" as

1. *rubor* (redness)
2. *tumor* (swelling)
3. *calor* (heat)
4. *dolor* (pain)



- In the second century AD, a physician Galen, added a fifth sign:

  5. *functio laesa* (loss of function).

- The cardinal signs of inflammation reflect the **three major events** of an inflammatory response

1. Vasodilation—an increase in the diameter of blood vessels.

2. An *increase in capillary permeability* facilitates an influx of fluid and cells from the engorged capillaries into the tissue.

The fluid that accumulates **(exudate)** has a much higher protein content than fluid normally released from the vasculature.

3. *Influx of phagocytes* from the capillaries into the tissues is facilitated by the increased permeability of the capillaries. The emigration of phagocytes is a multistep process.

- Adherence of the cells to the endothelial wall of the blood vessels **(margination)**
- Emigration between the capillary endothelial cells into the tissue **(extravasation)**
- Migration through the tissue to the site of the invasion **(chemotaxis)**.

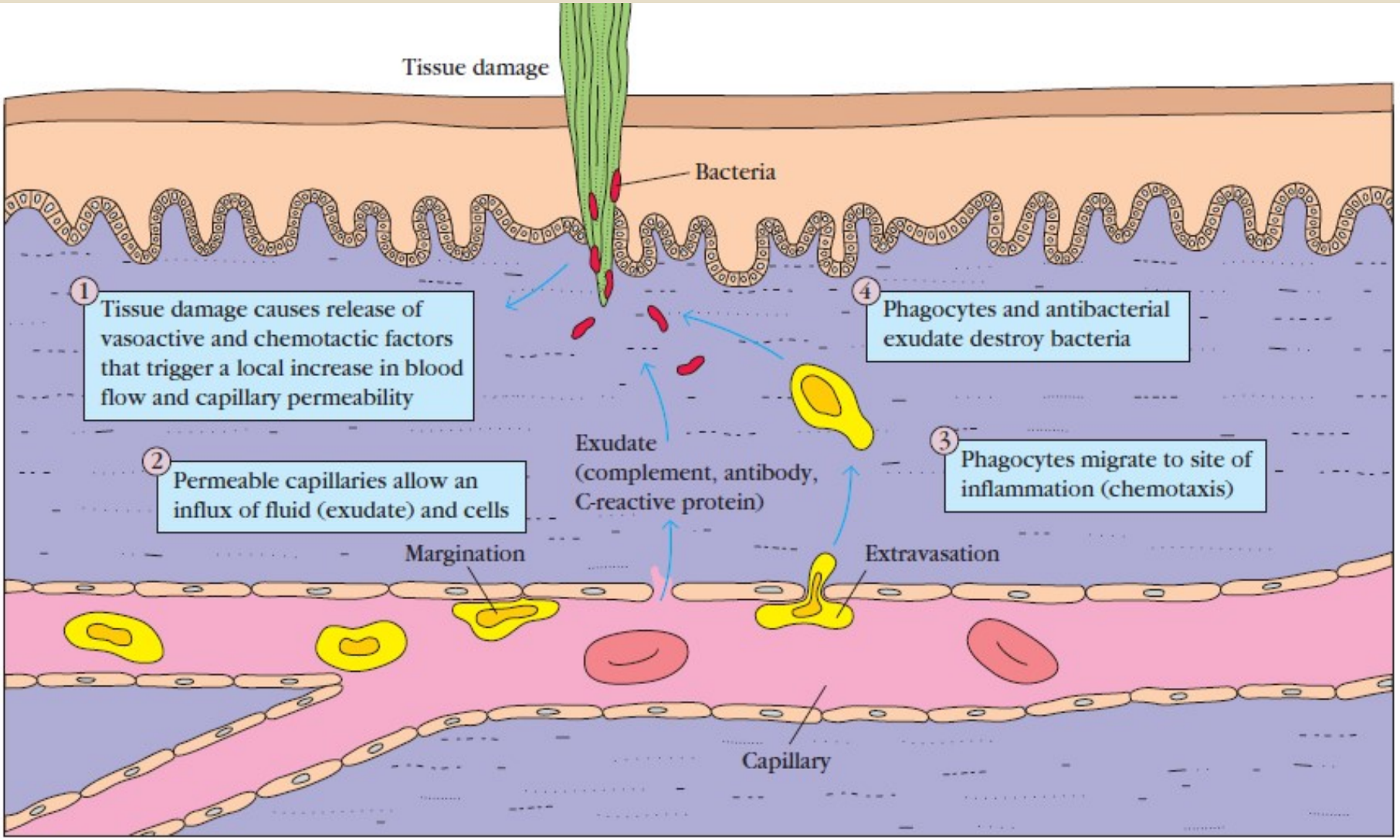


FIGURE 1-4 Major events in the inflammatory response. A bacterial infection causes tissue damage with release of various vasoactive and chemotactic factors. These factors induce increased blood flow to the area, increased capillary permeability, and an influx of white blood cells, including phagocytes and lymphocytes, from the blood into the tissues. The serum proteins contained in the exudate have antibacterial properties, and the phagocytes begin to engulf the bacteria, as illustrated in Figure 1-3.

- As phagocytic cells accumulate at the site and begin to phagocytose bacteria, they release lytic enzymes, which can damage nearby healthy cells. **The accumulation of dead cells, digested material, and fluid forms a substance called pus.**

- Among the chemical mediators released in response to tissue damage are various serum proteins called **acute-phase proteins.**

- The concentrations of these proteins increase dramatically in tissue-damaging infections.

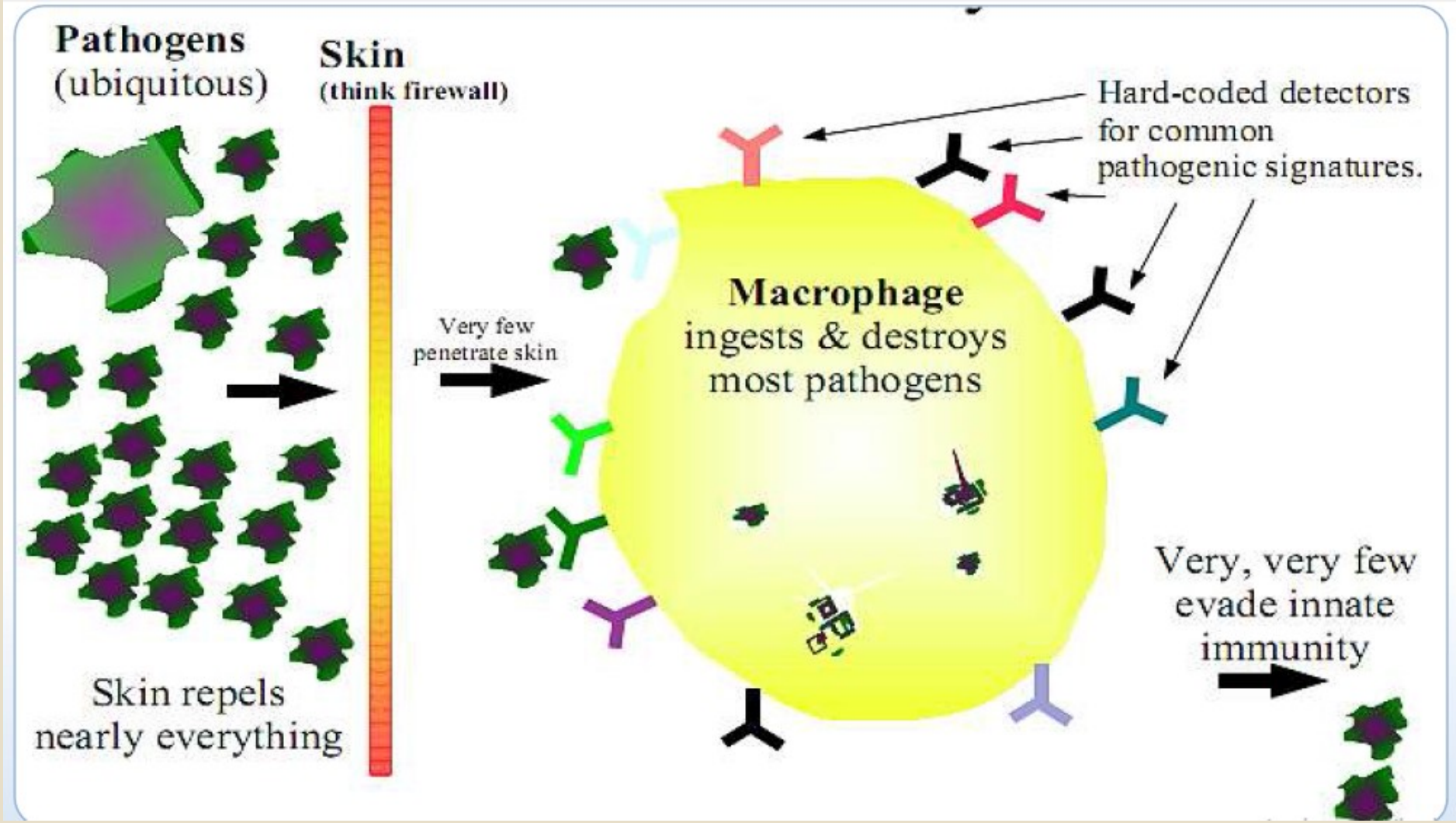
- C-reactive protein is a major acute-phase protein produced by the **liver in response to tissue damage**.

- Its name derives from its pattern recognition activity: C-reactive protein binds to the C-polysaccharide (capsular polysaccharide) cell-wall component found on a variety of bacteria and fungi.

- This binding activates the complement system, resulting in increased clearance of the pathogen either by complement-mediated lysis or by a complement mediated increase in phagocytosis.

- One of the **principal mediators of the inflammatory response** is **histamine,** a chemical released by a variety of cells in response to tissue injury. Histamine binds to receptors on nearby capillaries and venules, causing vasodilation and increased permeability.

- Another important group of inflammatory mediators, **small peptides** called **kinins,** are normally present in blood plasma in an inactive form. Tissue injury activates these peptides, which then cause vasodilation and increased permeability of capillaries.


Pathogens
(ubiquitous)
Skin
(think firewall)
Hard-coded detectors
for common
pathogenic signatures.
Very few
penetrate skin
Macrophage
ingests & destroys
most pathogens
Very, very few
evade innate
immunity
Skin repels
nearly everything

Common lymphoid progenitor cells give rise to

- **B cells**
- **T cells**
- **NK (natural killer) cells** and
- some **dendritic cells.**

Adaptive Immunity

- Adaptive immunity is capable of recognizing and selectively eliminating specific foreign microorganisms and molecules (i.e., foreign antigens).

Adaptive immunity displays four characteristic attributes:

- Antigenic specificity
- Diversity
- Immunologic memory
- Self/non-self recognition

- The **antigenic specificity** of the immune system permits it to distinguish subtle differences among antigens. Antibodies can distinguish between two protein molecules that differ in only a single amino acid.

Attribute	Innate immunity	Adaptive immunity
Soluble components of blood or tissue fluids – Humoral Immunity	Many antimicrobial peptides and proteins	Antibodies (Ab)
Major cell types – Cell Mediated Immunity (CMI)	Phagocytes (monocytes, macrophages, neutrophils), Natural Killer (NK) cells, dendritic cells	T cells, B cells, Antigen Presenting Cells (APC)

killing of target cells by cytotoxic T cells or natural killer cells.

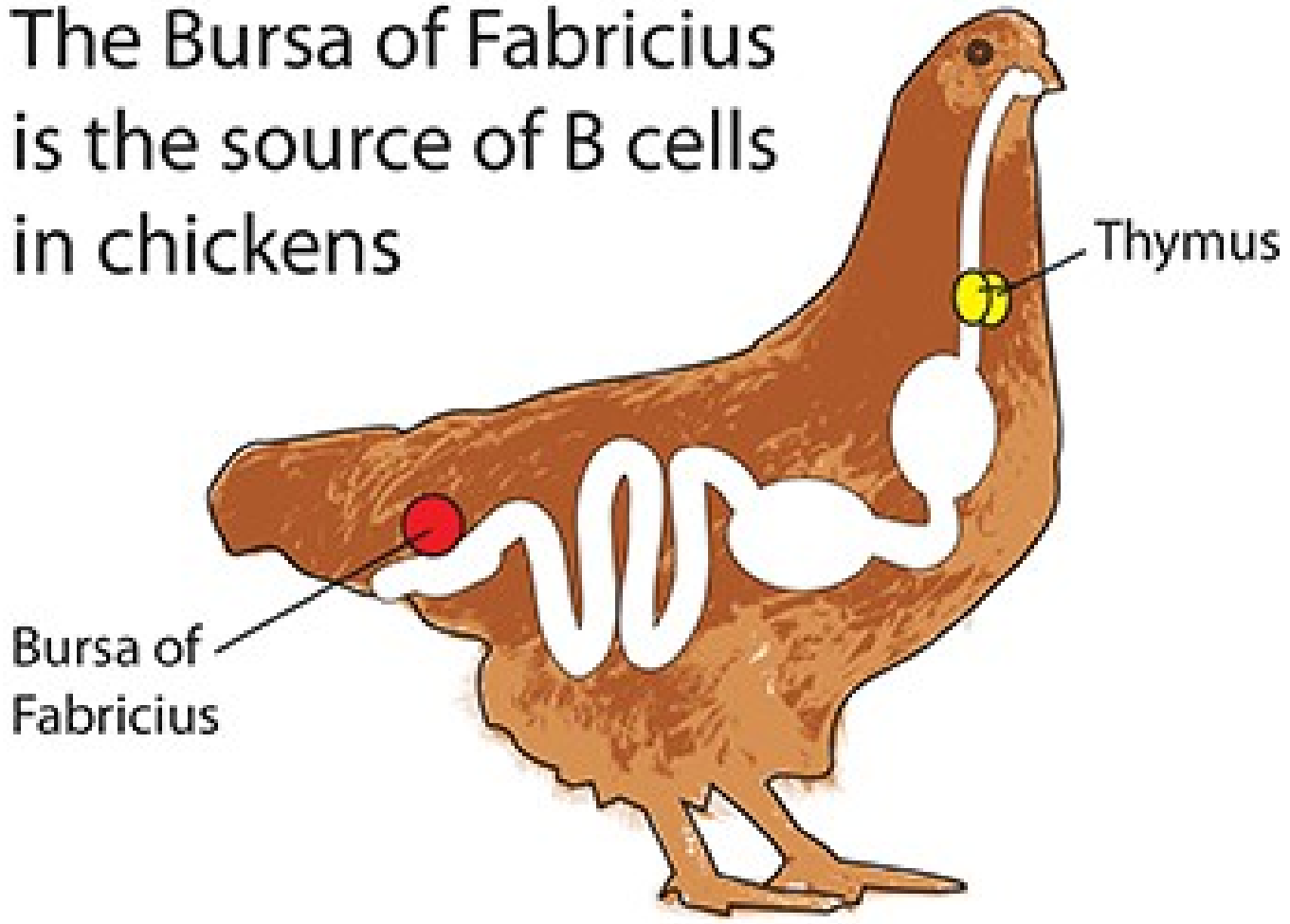
B and T lymphocytes

- Experiments with chickens pioneered by **Bruce Glick** at Mississippi State University indicated that there were two types of lymphocytes:

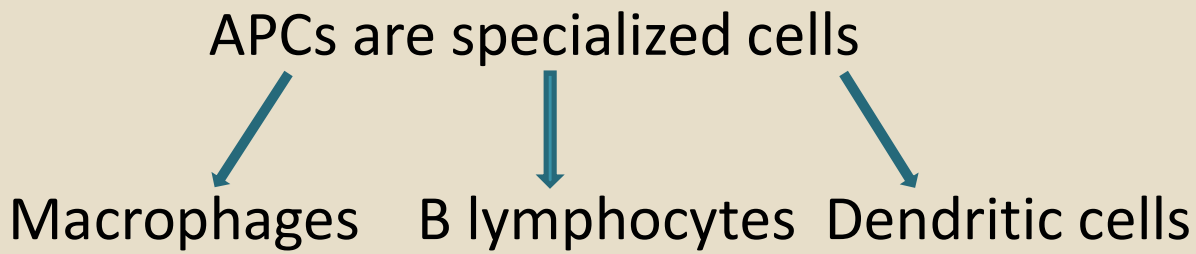
- **1. T lymphocytes** derived from the thymus mediated cellular immunity, and

- **2. B lymphocytes** from the bursa of Fabricius (an outgrowth of the cloaca in birds) were involved in humoral immunity.

The Bursa of Fabricius is the source of B cells in chickens



- 3. Antigen-presenting cells (APCs)



- APCs are distinguished by two properties:
- (1) they express class II MHC molecules on their membranes

- (2) they are able to deliver a co-stimulatory signal that is necessary for TH-cell activation.

- The lymphocytes can be broadly subdivided into three populations on the basis of function and cell-membrane components.

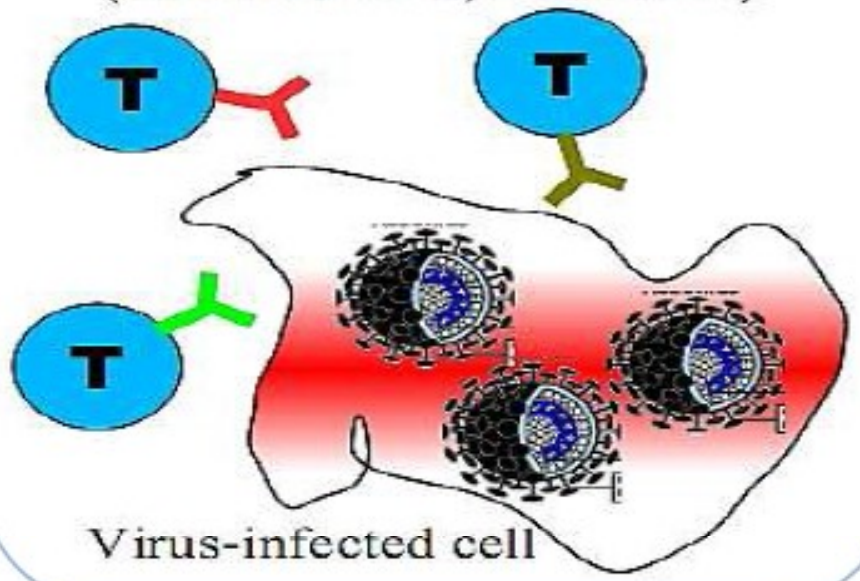
  B cells

  T cells, and

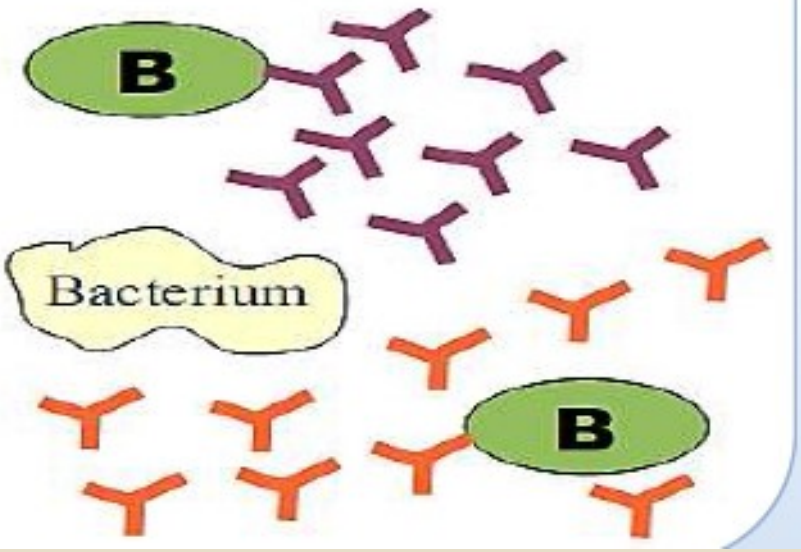
  Natural killer cells

- **Natural killer cells (NK cells) are large, granular lymphocytes that do** not express the set of surface markers typical of B or T cells.

T cells destroy infected cells
to eradicate intracellular pathogens.
(Some bacteria, all viruses)



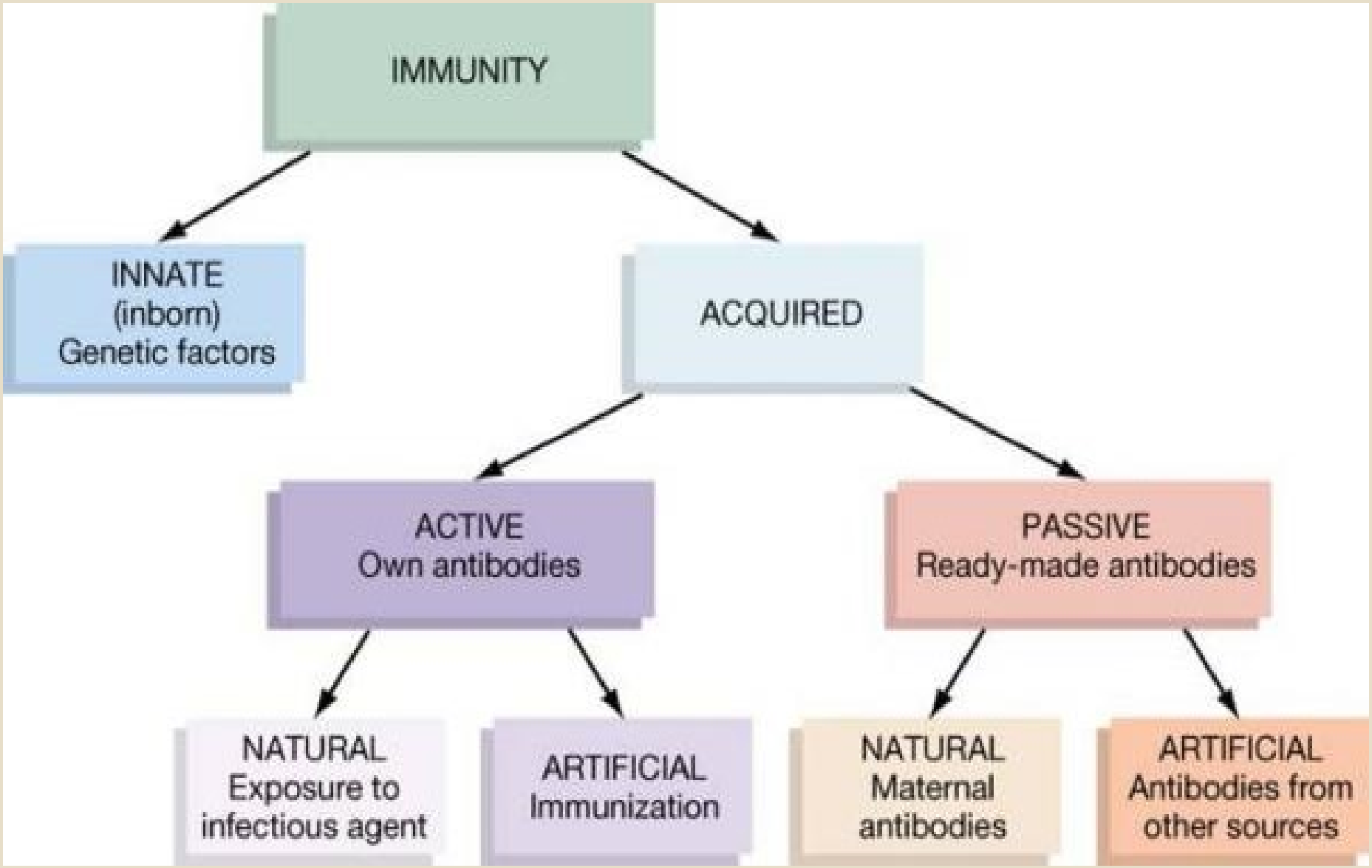
B cells secrete antibodies
to attack extracellular pathogens
(Most bacteria)

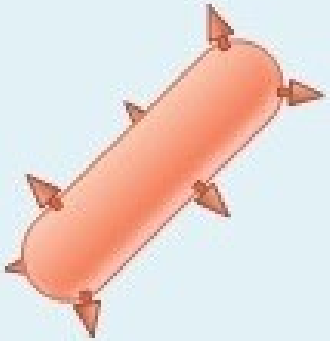
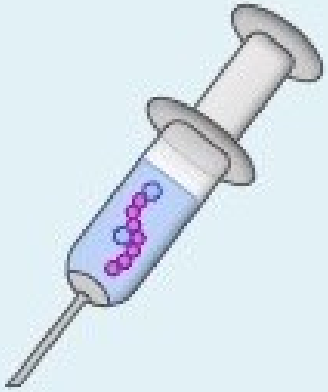
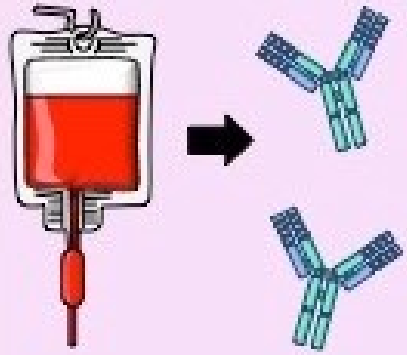


Active immunity & Passive immunity

- Active immunity – the immunity which results from the production of antibodies by the immune system in response to the presence of an antigen.

- Passive immunity – this is immunity received by a non-immune individual from an immune individual.

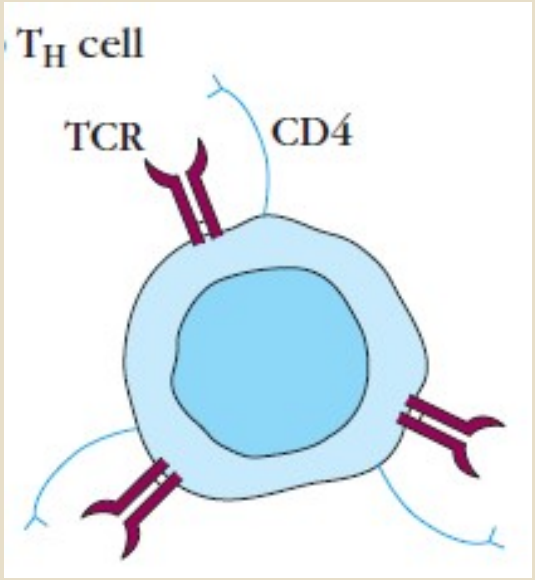

IMMUNITY
INNATE
(inborn)
Genetic factors
ACQUIRED
ACTIVE
Own antibodies
PASSIVE
Ready-made antibodies
NATURAL
Exposure to
infectious agent
ARTIFICIAL
Immunization
NATURAL
Maternal
antibodies
ARTIFICIAL
Antibodies from
other sources

ACTIVE IMMUNITY		PASSIVE IMMUNITY	
Natural	**Artificial**	**Natural**	**Artificial**
			
Infection	Vaccination	Maternal antibodies	Monoclonal antibodies

T lymphocyte

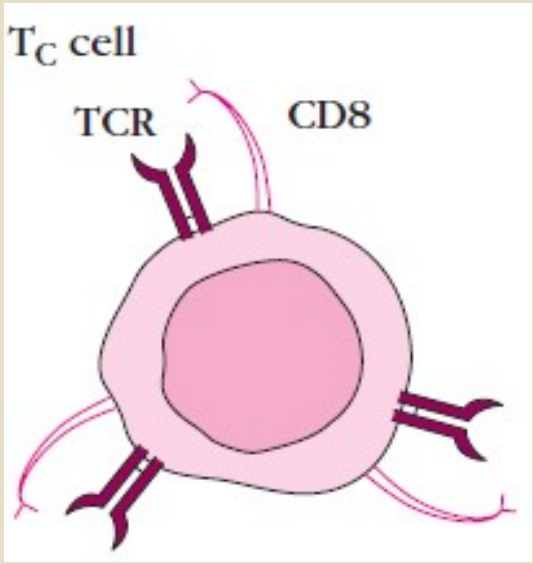
T helper cells

CD4

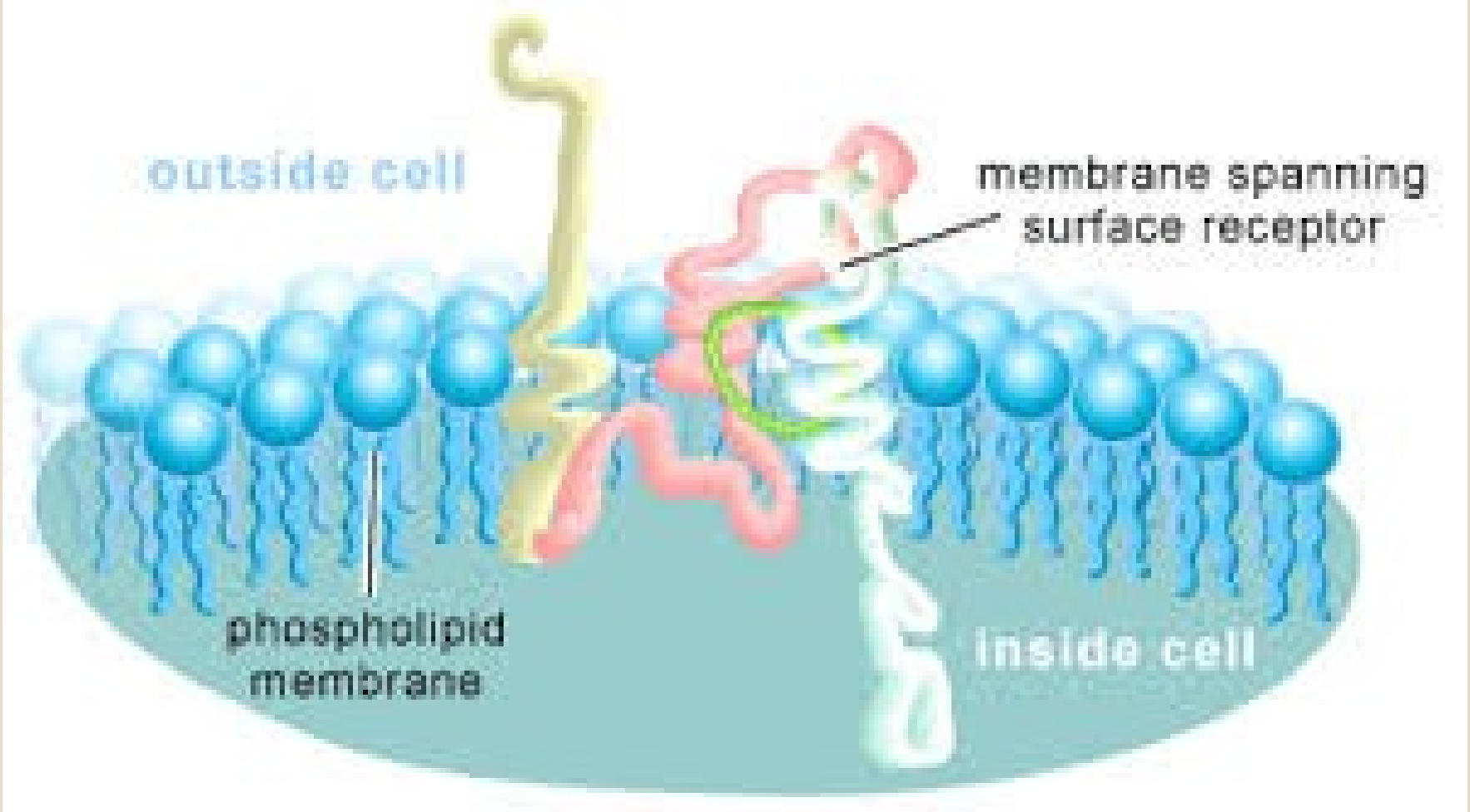


T cytotoxic cells

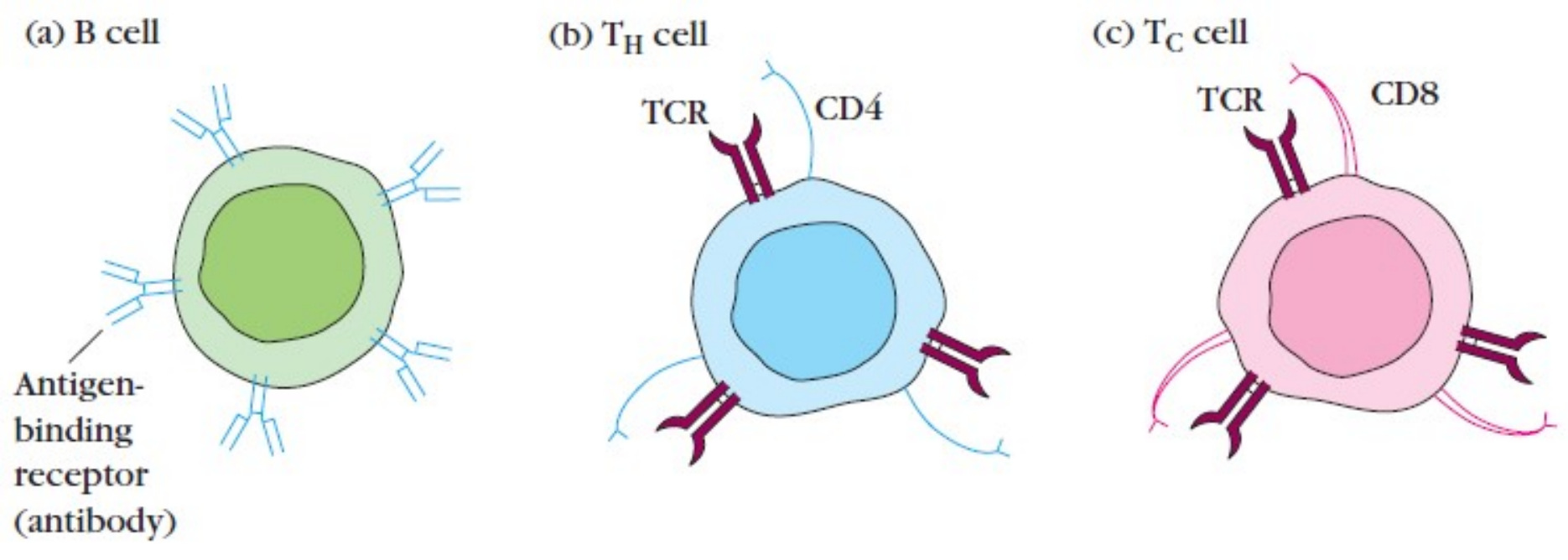
CD8



Cell surface receptors



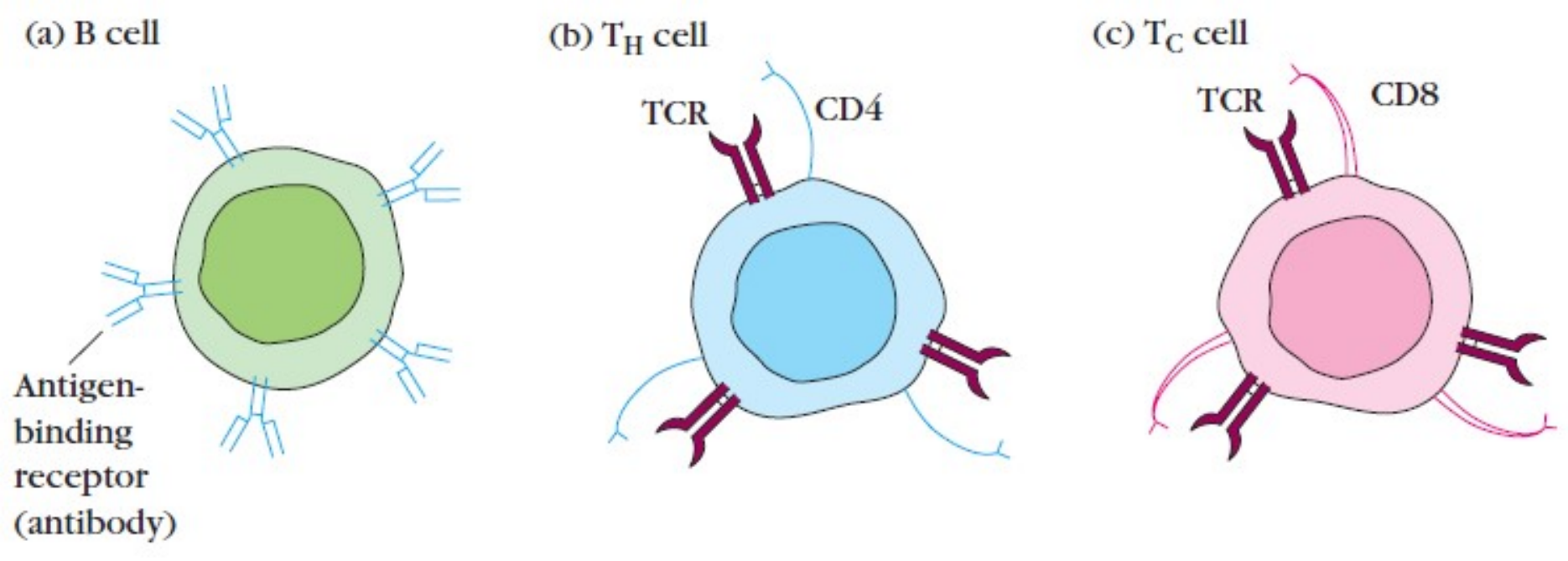
Distinctive membrane molecules on Lymphocytes



Cell

Cell surface receptors

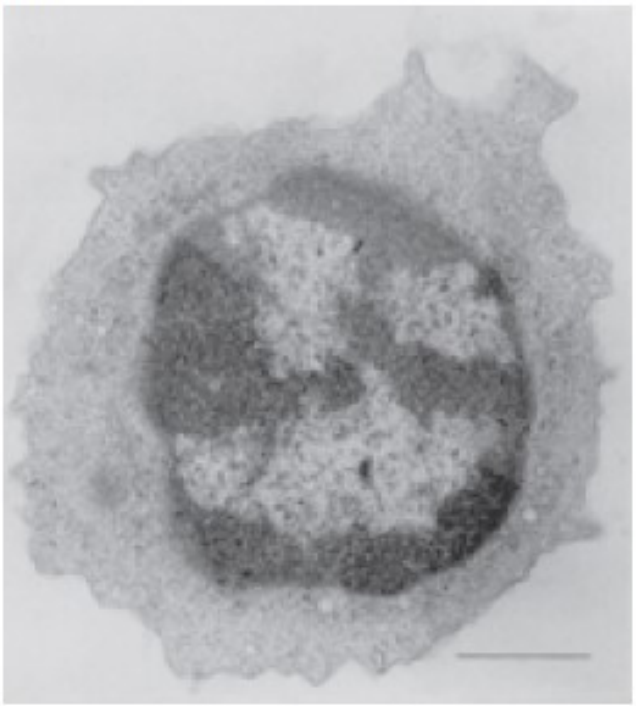
- B lymphocyte – B Cell Receptor (BCR)/ **Antibody/ I**mmunoglobulin
- T lymphocyte – T Cell Receptor (TCR)



- **Resting B and T lymphocytes** are small, motile, non-phagocytic cells, which cannot be distinguished morphologically.

- B and T lymphocytes that have not interacted with antigen—referred to as **naive, or unprimed—are resting cells in the G0** phase of the cell cycle.

- They are known as **small lymphocytes**.



Small lymphocyte (T or B)
6 µm diameter

- Some leukocytes, especially activated TH lymphocytes, secrete various proteinaceous growth factors/molecules known collectively as cytokines.

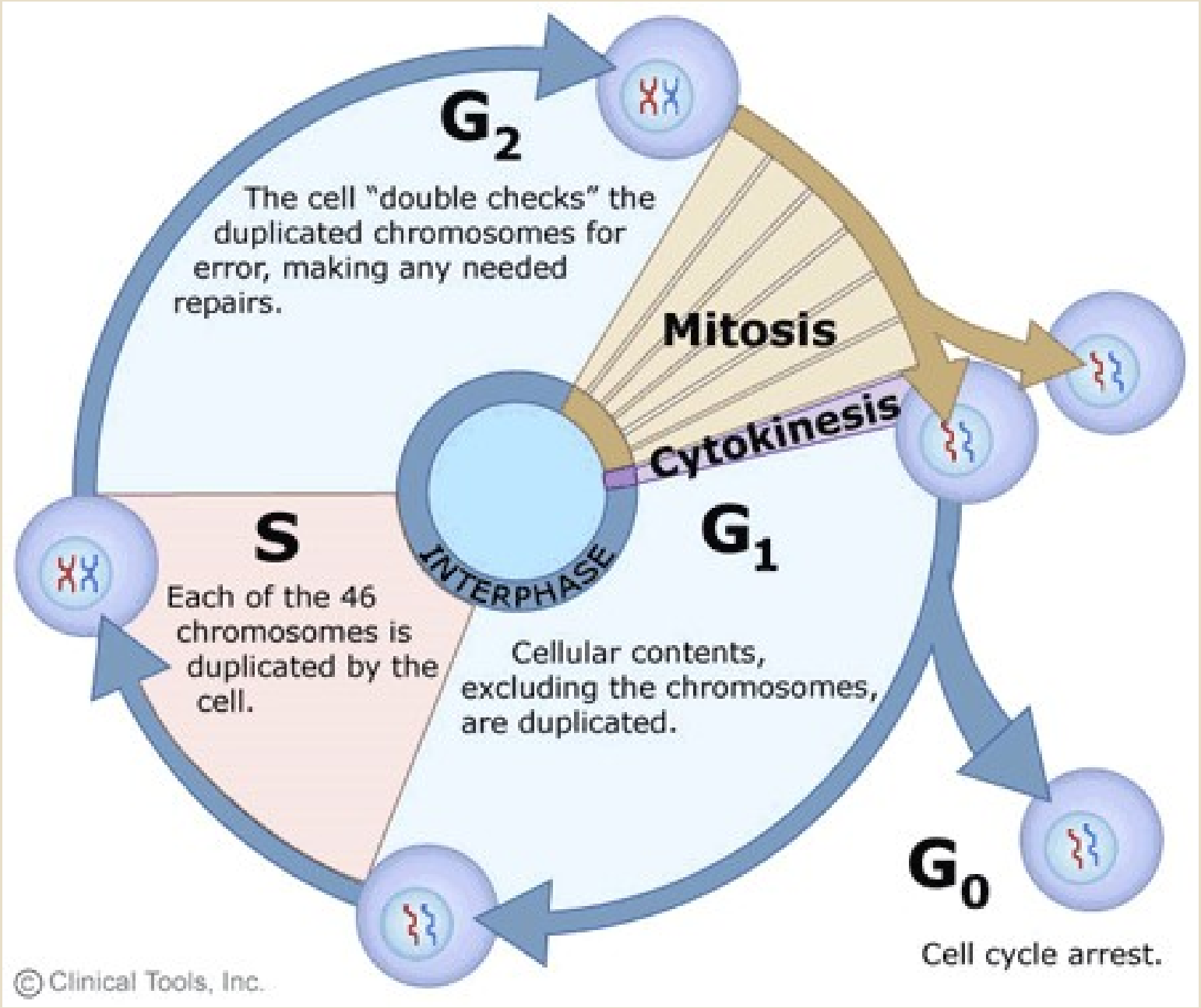
- These molecules act as **immunoregulatory hormones** and play important roles in the regulation of immune responses.

- The secreted cytokines play an important role in activating B cells, TC cells, macrophages, and various other cells that participate in the immune response.

- The naive lymphocyte is generally thought to have a **short life span.**

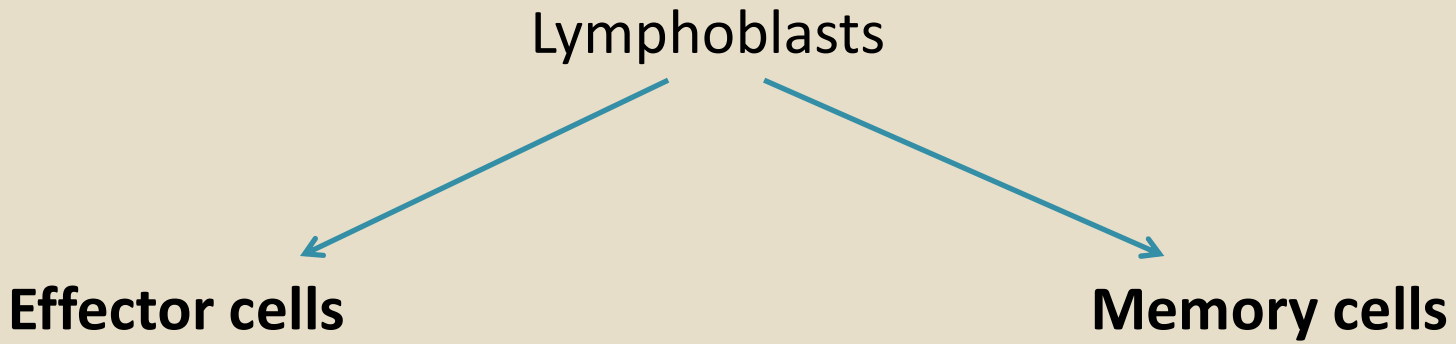
- Interaction of small lymphocytes with antigen, in the presence of certain cytokines, induces these cells to enter the cell cycle by progressing from G0 into G1 and subsequently into S, G2, and M.

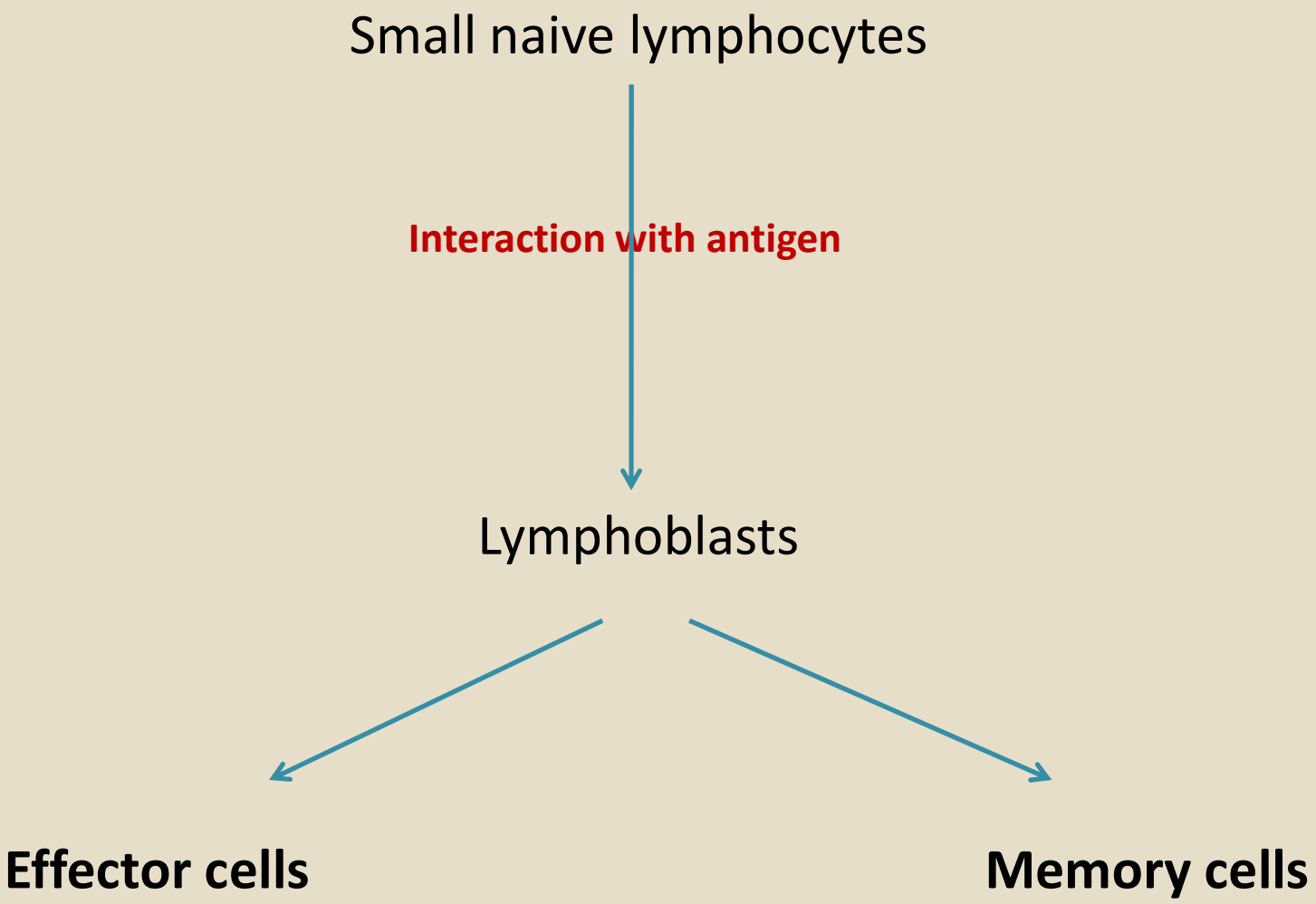
- As they progress through the cell cycle, lymphocytes enlarge into 15µ m-diameter blast cells, called **lymphoblasts**; these cells have a higher cytoplasm: nucleus ratio and more organellar complexity than small lymphocytes.


G2
The cell "double checks" the duplicated chromosomes for error, making any needed repairs.
Mitosis
Cytokinesis
INTERPHASE
G1
S
Each of the 46 chromosomes is duplicated by the cell.
Cellular contents, excluding the chromosomes, are duplicated.
G0
Cell cycle arrest.
© Clinical Tools, Inc.

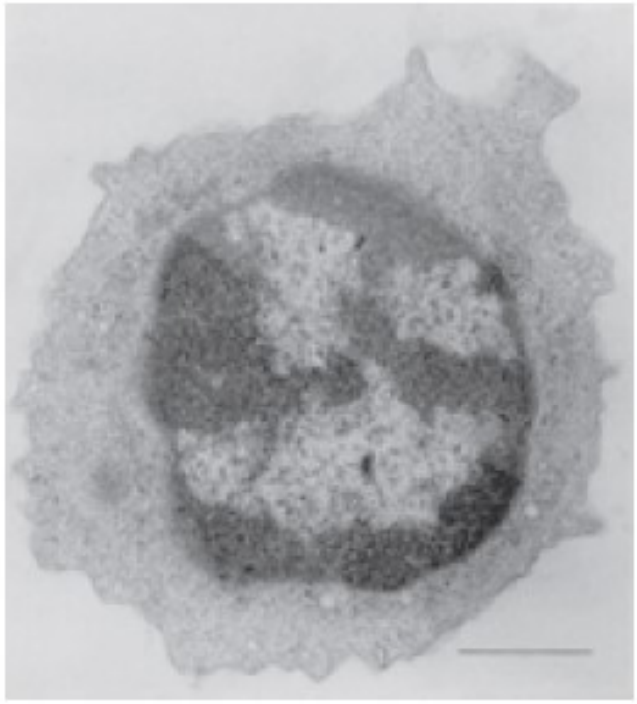
- Lymphoblasts proliferate and eventually differentiate into **effector cells or into memory cells.**

- **Effector cells function in** various ways to eliminate antigen. These cells have short life spans, generally ranging from a few days to a few weeks.

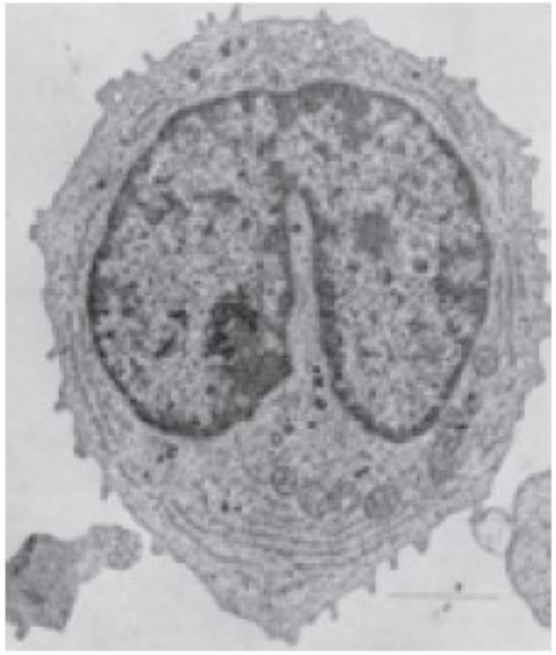



Small naive lymphocytes
Interaction with antigen
Lymphoblasts
Effector cells
Memory cells

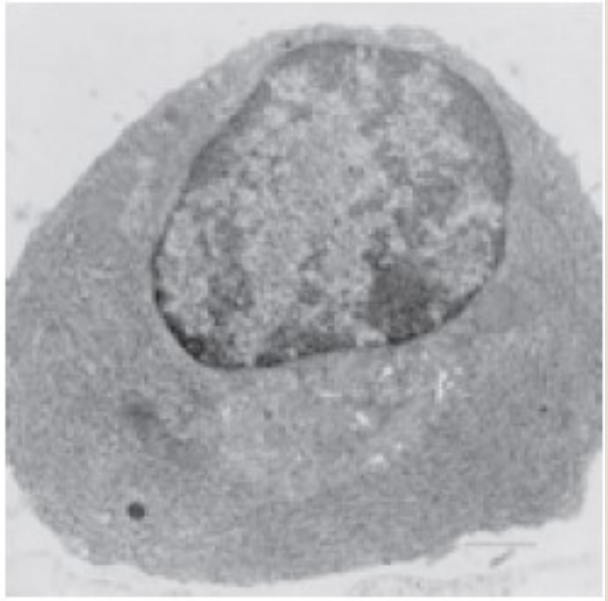
(b)



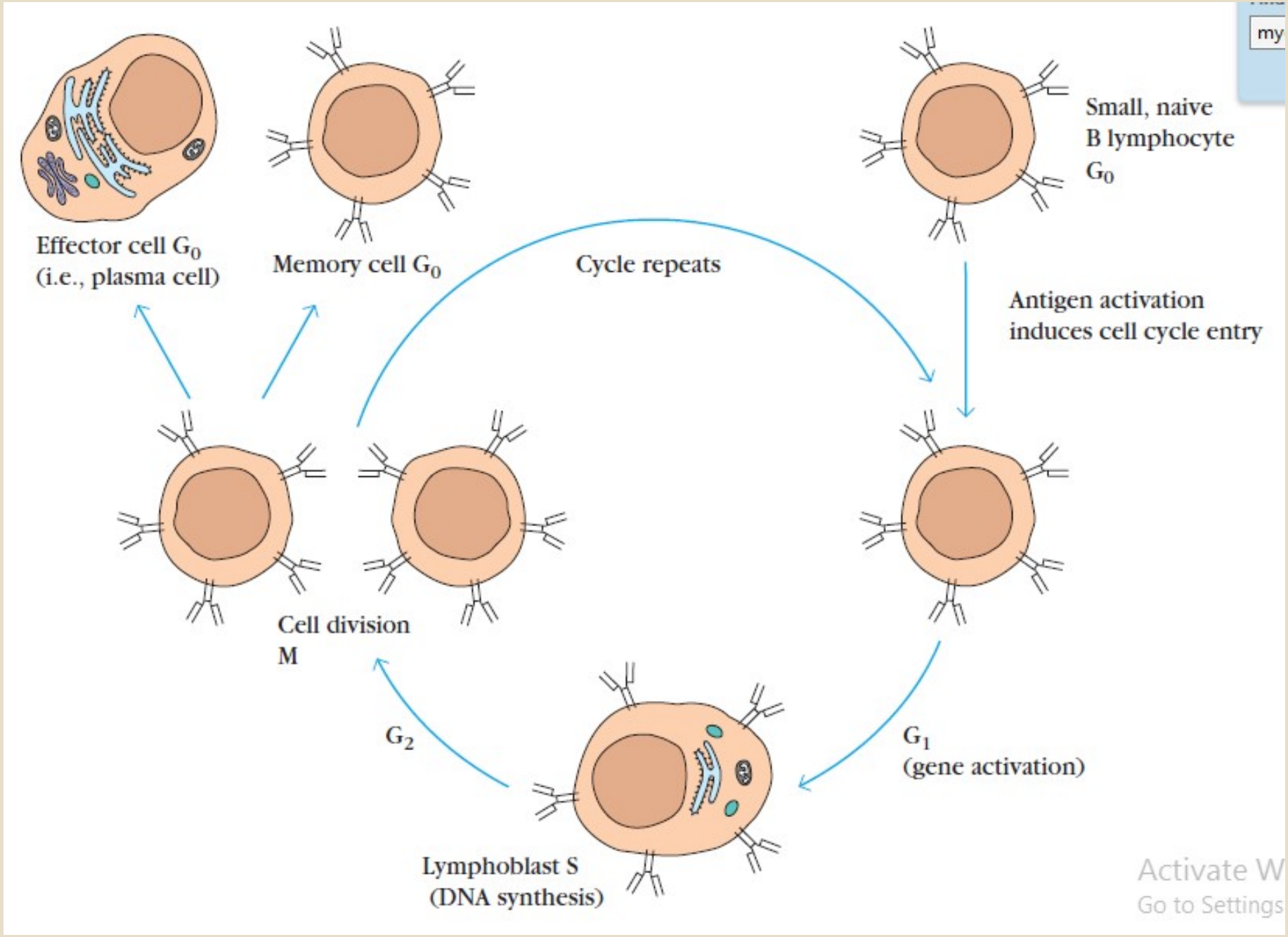
Small lymphocyte (T or B)
6 µm diameter



Blast cell (T or B)
15 µm diameter



Plasma cell (B)
15 µm diameter


Effector cell G_0
(i.e., plasma cell)
Memory cell G_0
Small, naive
B lymphocyte
G_0
Cycle repeats
Antigen activation
induces cell cycle entry
Cell division
M
G_2
G_1
(gene activation)
Lymphoblast S
(DNA synthesis)

Attribute	Innate immunity	Adaptive immunity
Soluble components of blood or tissue fluids	Many antimicrobial peptides and proteins	Antibodies
Major cell types	Phagocytes (monocytes, macrophages, neutrophils), Natural Killer (NK) cells, dendritic cells	T cells, B cells, Antigen Presenting Cells (APC)

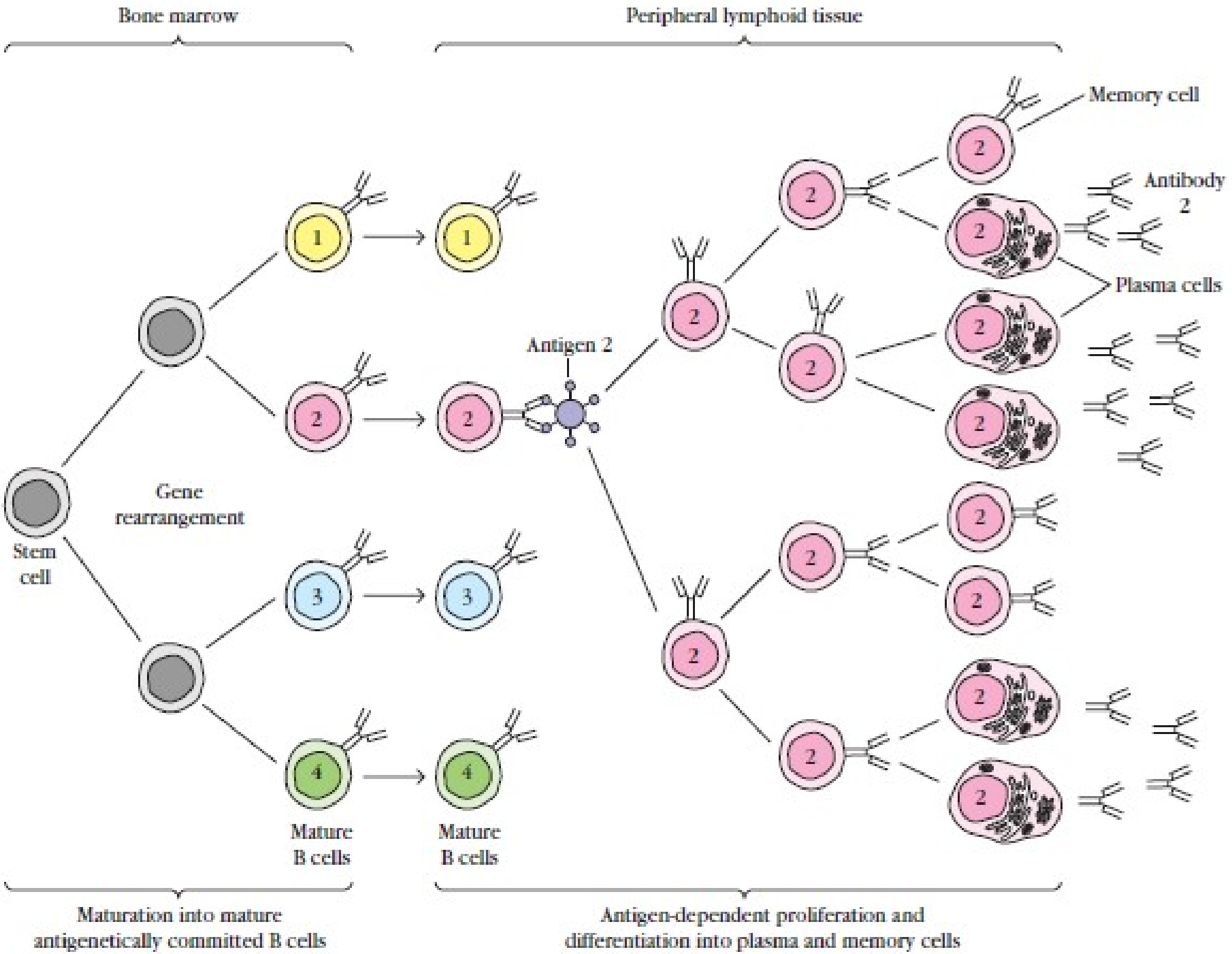
killing of target cells by cytotoxic T cells or natural killer cells.

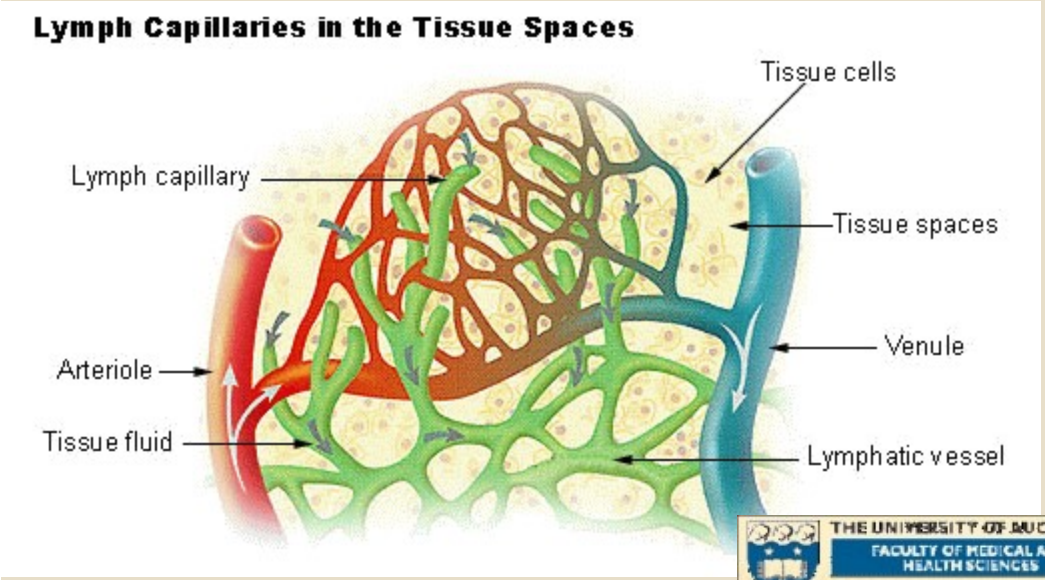
- **Plasma cells—the antibody-secreting effector cells of the B cell** lineage—have a characteristic cytoplasm that contains abundant endoplasmic reticulum (to support their high rate of protein synthesis) arranged in concentric layers and also many Golgi vesicles.

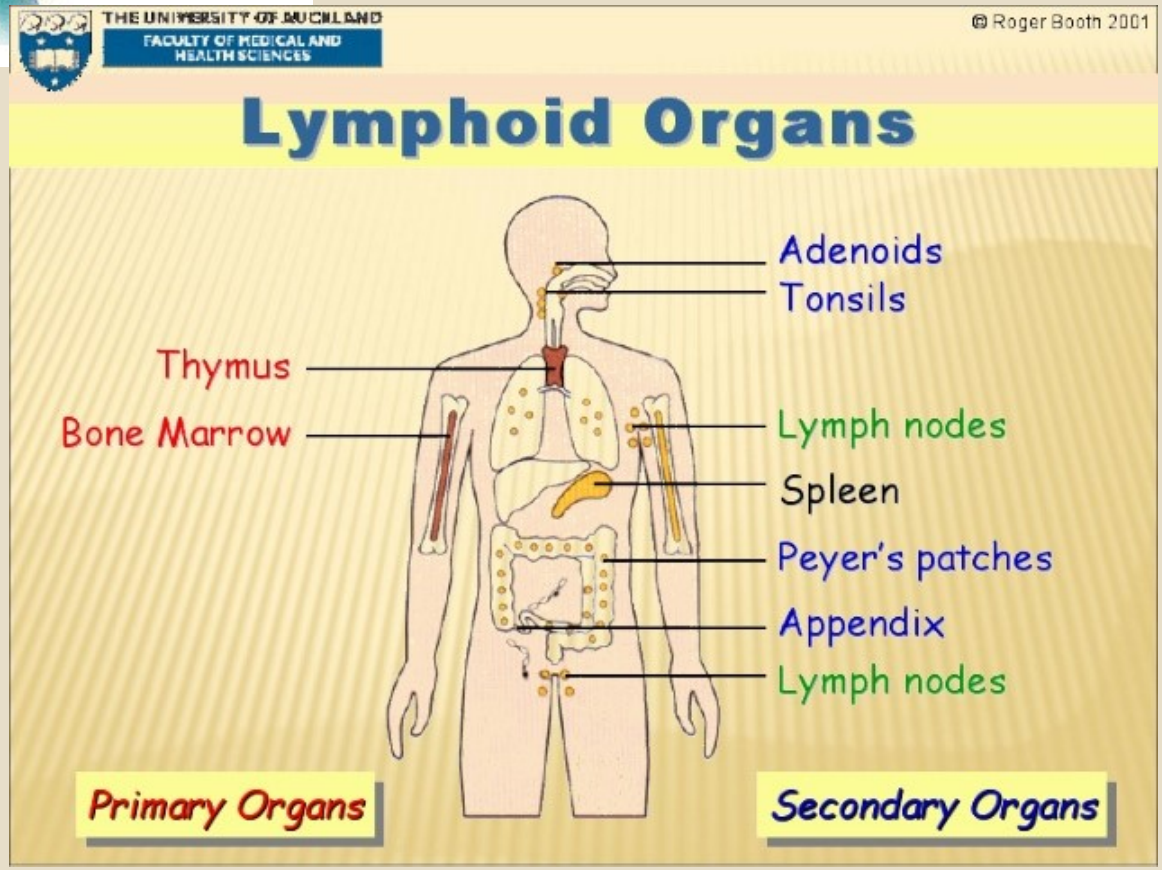
- The effector cells of the T-cell lineage include

1. The cytokine-secreting T helper cell (TH cell) and
2. The T cytotoxic lymphocyte (TC cell).

- Some of the progeny of B and T lymphoblasts differentiate into **memory cells**.


Bone marrow
Peripheral lymphoid tissue
Memory cell
Antibody 2
Plasma cells
Antigen 2
Gene rearrangement
Stem cell
Mature B cells
Mature B cells
Maturation into mature antigenetically committed B cells
Antigen-dependent proliferation and differentiation into plasma and memory cells


Lymph Capillaries in the Tissue Spaces
Tissue cells
Lymph capillary
Tissue spaces
Venule
Arteriole
Tissue fluid
Lymphatic vessel


THE UNIVERSITY OF AUCKLAND
FACULTY OF MEDICAL AND HEALTH SCIENCES
© Roger Booth 2001
Lymphoid Organs
Adenoids
Tonsils
Thymus
Bone Marrow
Lymph nodes
Spleen
Peyer's patches
Appendix
Lymph nodes
Primary Organs
Secondary Organs

Cell type	B lymphocyte	T lymphocyte
Effector cells	Plasma cell	The **cytokine-secreting** T helper cell (TH cell)
		The T cytotoxic lymphocyte (TC cell)
Memory cell	Memory B cells	Memory T cells

T helper cell ($\mathbf{T_H}$) ⟹ The **cytokine-secreting** T helper cell (TH cell)

T cytotoxic cells ($\mathbf{T_C}$) ⟹ Cytotoxic T lymphocyte (CTL)

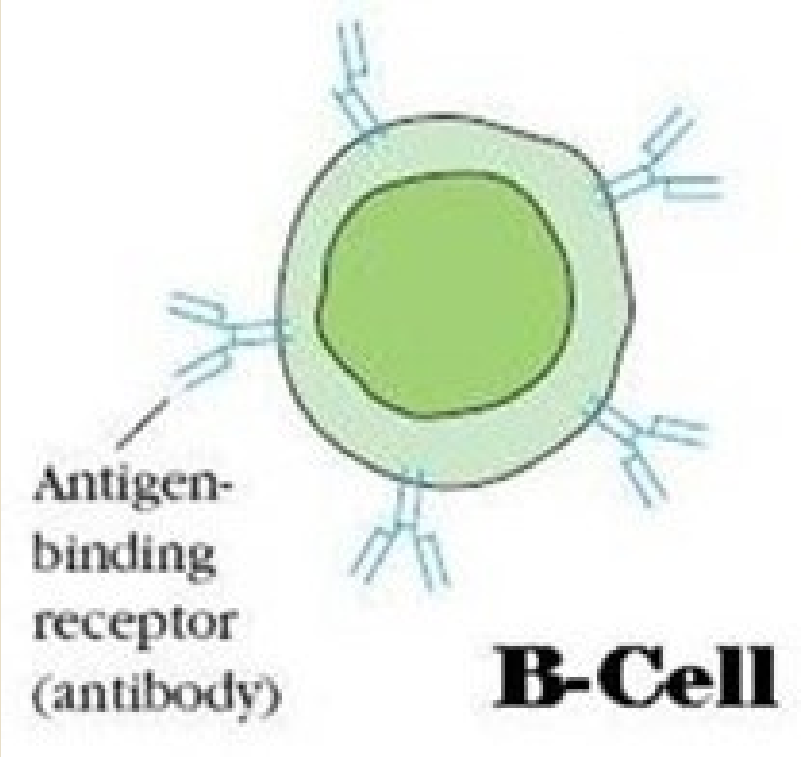
- In contrast to the T_C cell, the CTL generally does not secrete many cytokines and instead exhibits cell-killing or cytotoxic activity. The CTL has a vital function in monitoring the cells of the body and eliminating any that display antigen, such as virus-infected cells, tumor cells, and cells of a foreign tissue graft.

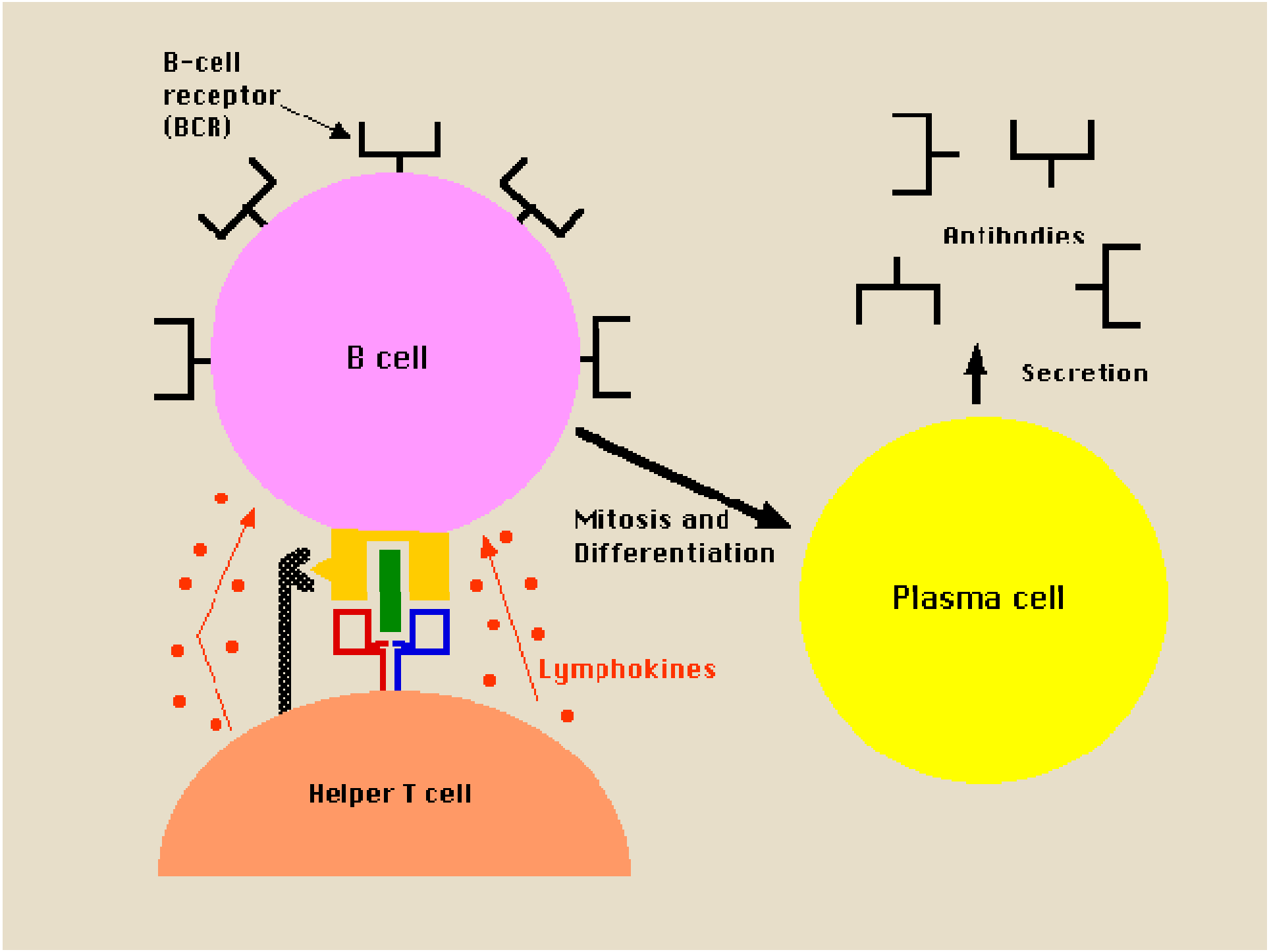
- The persistence of this population of cells is responsible for life-long immunity to many pathogens.

- Memory cells look like small lymphocytes but can be distinguished from naive cells by the **presence or absence of certain cell membrane molecules.**

B LYMPHOCYTES

- The B lymphocyte derived its letter designation from its site of maturation, in the *bursa of Fabricius* in birds; the name turned out to be apt, for *bone marrow is its major site of maturation* in a number of mammalian species, including humans and mice.




B-cell
receptor
(BCR)
B cell
Antibodies
Secretion
Mitosis and
Differentiation
Plasma cell
Lymphokines
Helper T cell

- Mature B cells are definitively distinguished from other lymphocytes by their synthesis and display of membrane-bound **immunoglobulin (antibody) molecules** which serve as receptors for antigen.

- Among the other molecules expressed on the membrane of mature B cells; the important is **Class II MHC molecules permit the B cell to function as** an antigen-presenting cell (APC).

- Interaction between antigen and the membrane-bound antibody on a mature naive B cell, as well as interactions with T cells and macrophages, selectively induces the activation and differentiation of B-cell clones of corresponding specificity.

- In this process, the B cell divides repeatedly and differentiates over a 4- to 5-day period, generating a population of plasma cells and memory cells.

- Plasma cells, which have lower levels of membrane-bound antibody than B cells, **synthesize and secrete antibody.**

- All clonal progeny from a given B cell secrete antibody molecules with the same antigen-binding specificity.

- Plasma cells are terminally differentiated cells, and many die in 1 or 2 weeks.

T LYMPHOCYTES

- T lymphocytes derive their name from their site of maturation in the *thymus.*

- Like B lymphocytes, these cells have **membrane receptors for antigen.**

- Although the antigen binding **T-cell receptor is structurally distinct from immunoglobulin,** it does share some common structural features with the immunoglobulin molecule, most notably in the structure of its antigen-binding site.

- Unlike the membrane- bound antibody on B cells, though, the **T-cell receptor (TCR) does not recognize free antigen.**

- Instead the **TCR recognizes only antigen that is bound to particular classes of self-molecules.**

- Most T cells recognize antigen only when it is bound to a self-molecule encoded by genes within the major histocompatibility complex (MHC).

- A fundamental difference between the humoral and cell-mediated branches of the immune system is that the **B cell is capable of binding soluble antigen, whereas the T cell is restricted to binding antigen displayed on self-cells.**

- To be recognized by most T cells, this antigen must be displayed together with MHC molecules on the surface of

- Antigen-Presenting Cells (APC) or
- on virus-infected cells
- cancer cells, and
- grafts.

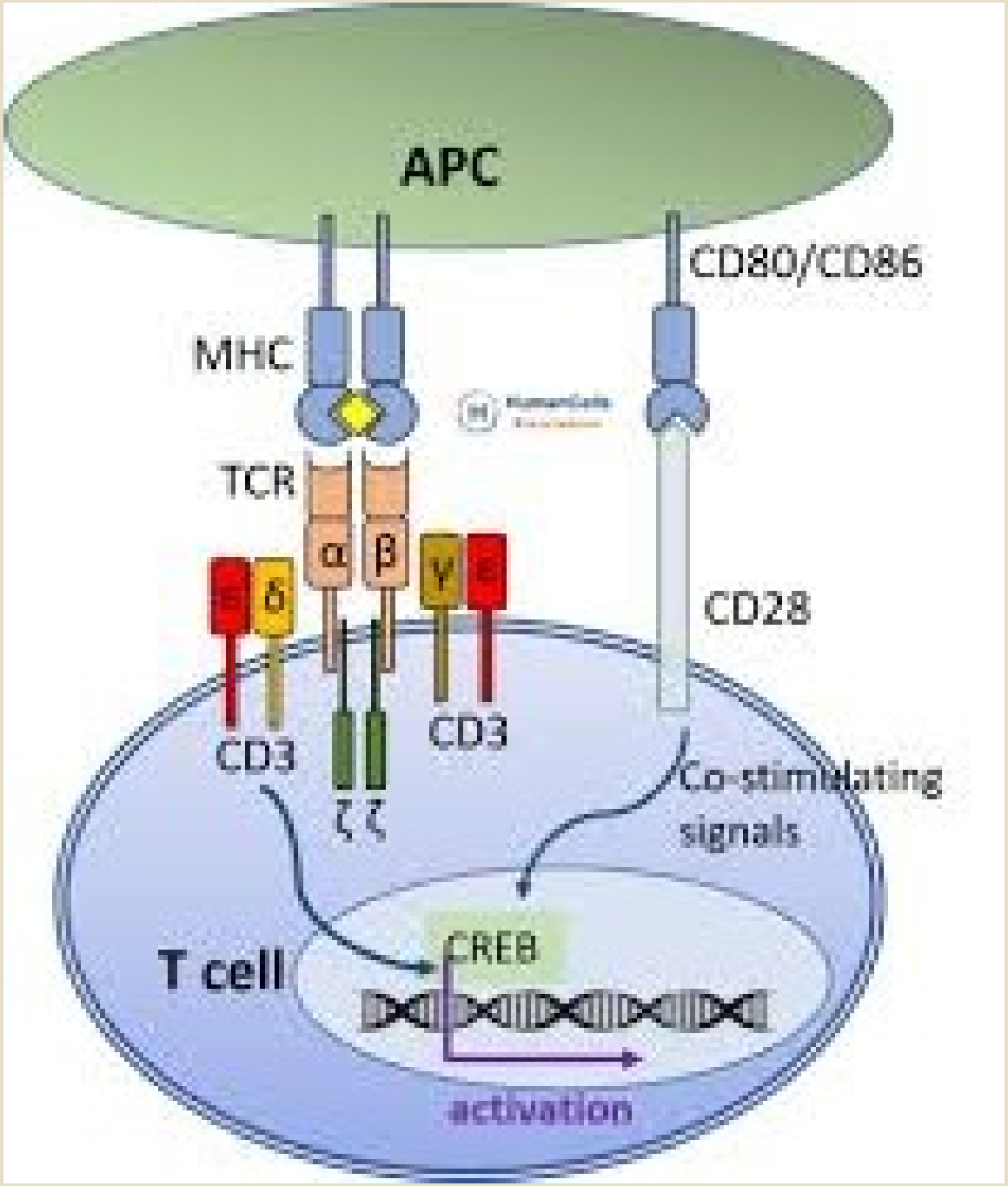
- The T-cell system has developed to eliminate these altered self-cells, which pose a threat to the normal functioning of the body.

- Like B cells, T cells express distinctive membrane molecules.

- All T-cell subpopulations express the T-cell receptor, a complex of polypeptides that includes CD3; and most can be distinguished by the presence of one or the other of two membrane molecules, **CD4 and CD8.**

- In addition, most mature T cells express the following membrane molecules:

- **CD28 - a receptor for the co-stimulatory B7 family of** molecules present on B cells and other antigen presenting cells
- **CD45 -** a signal-transduction molecule


APC
CD80/CD86
MHC
TCR
α
β
γ
ε
δ
CD28
CD3
CD3
ζ ζ
Co-stimulating
signals
T cell
CREB
activation

- T cells that express the membrane glycoprotein molecule CD4 are restricted to recognizing antigen bound to class II MHC molecules, whereas T cells expressing CD8, a dimeric membrane glycoprotein, are restricted to recognition of antigen bound to class I MHC molecules.

- Thus the expression of CD4 versus CD8 corresponds to the MHC restriction of the T cell.

- In general, expression of CD4 and of CD8 also defines two major functional subpopulations of T lymphocytes. CD4 T cells generally function as T helper (TH) cells and are class-II restricted; CD8 T cells generally function as T cytotoxic (TC) cells and are class-I restricted.

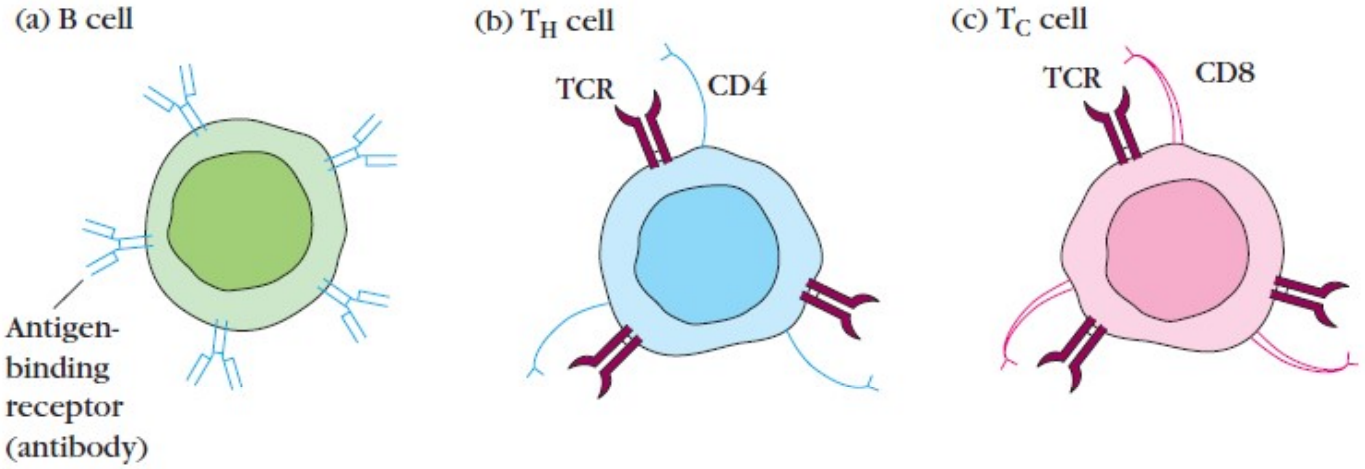
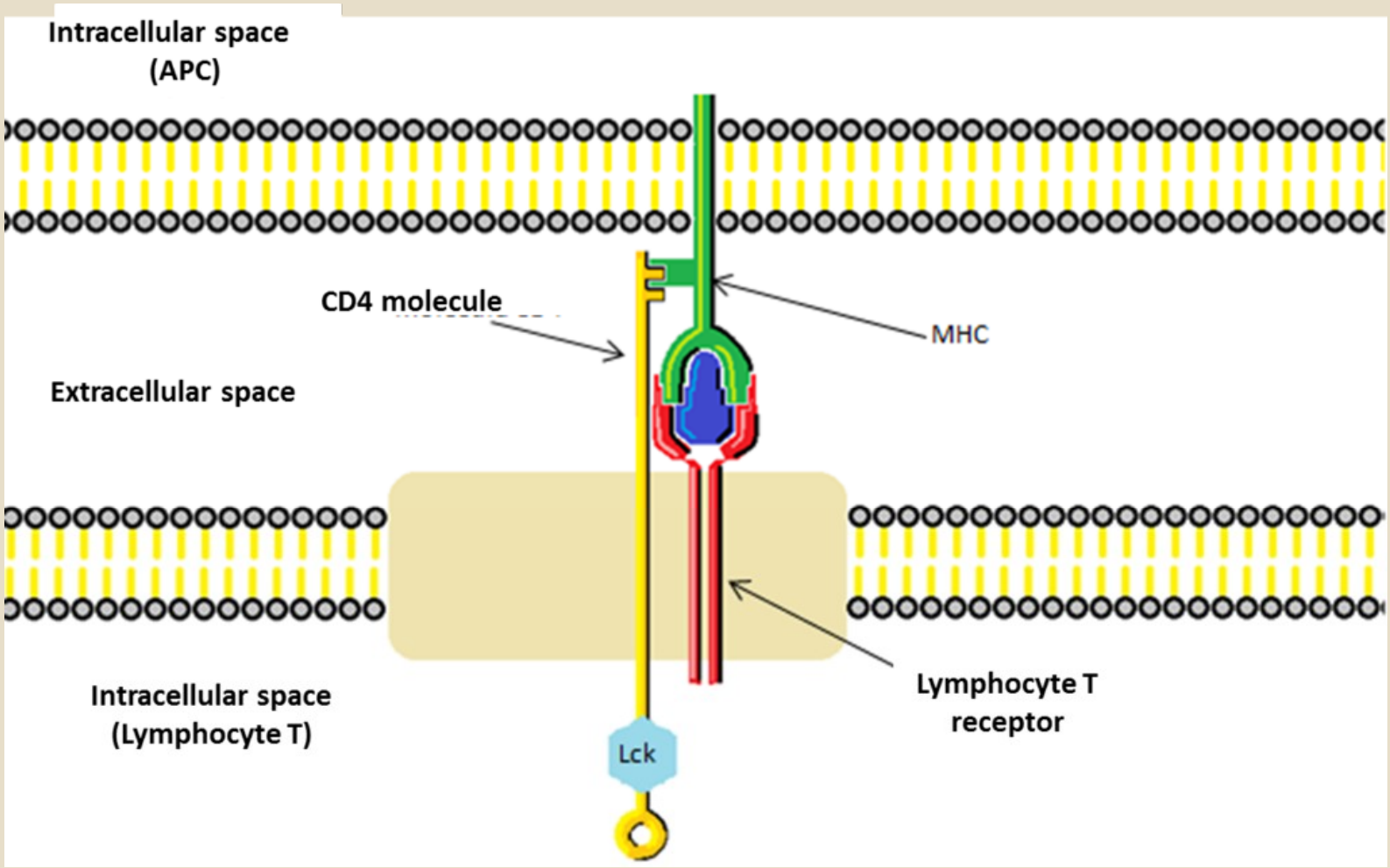


FIGURE 1-5 Distinctive membrane molecules on lymphocytes. (a) B cells have about 10^5 molecules of membrane-bound antibody per cell. All the antibody molecules on a given B cell have the same antigenic specificity and can interact directly with antigen. (b) T cells bearing CD4 ($CD4^+$ cells) recognize only antigen bound to class II MHC molecules. (c) T cells bearing CD8 ($CD8^+$ cells) recognize only antigen associated with class I MHC molecules. In general, $CD4^+$ cells act as helper cells and $CD8^+$ cells act as cytotoxic cells. Both types of T cells express about 10^5 identical molecules of the antigen-binding T-cell receptor (TCR) per cell, all with the same antigenic specificity.

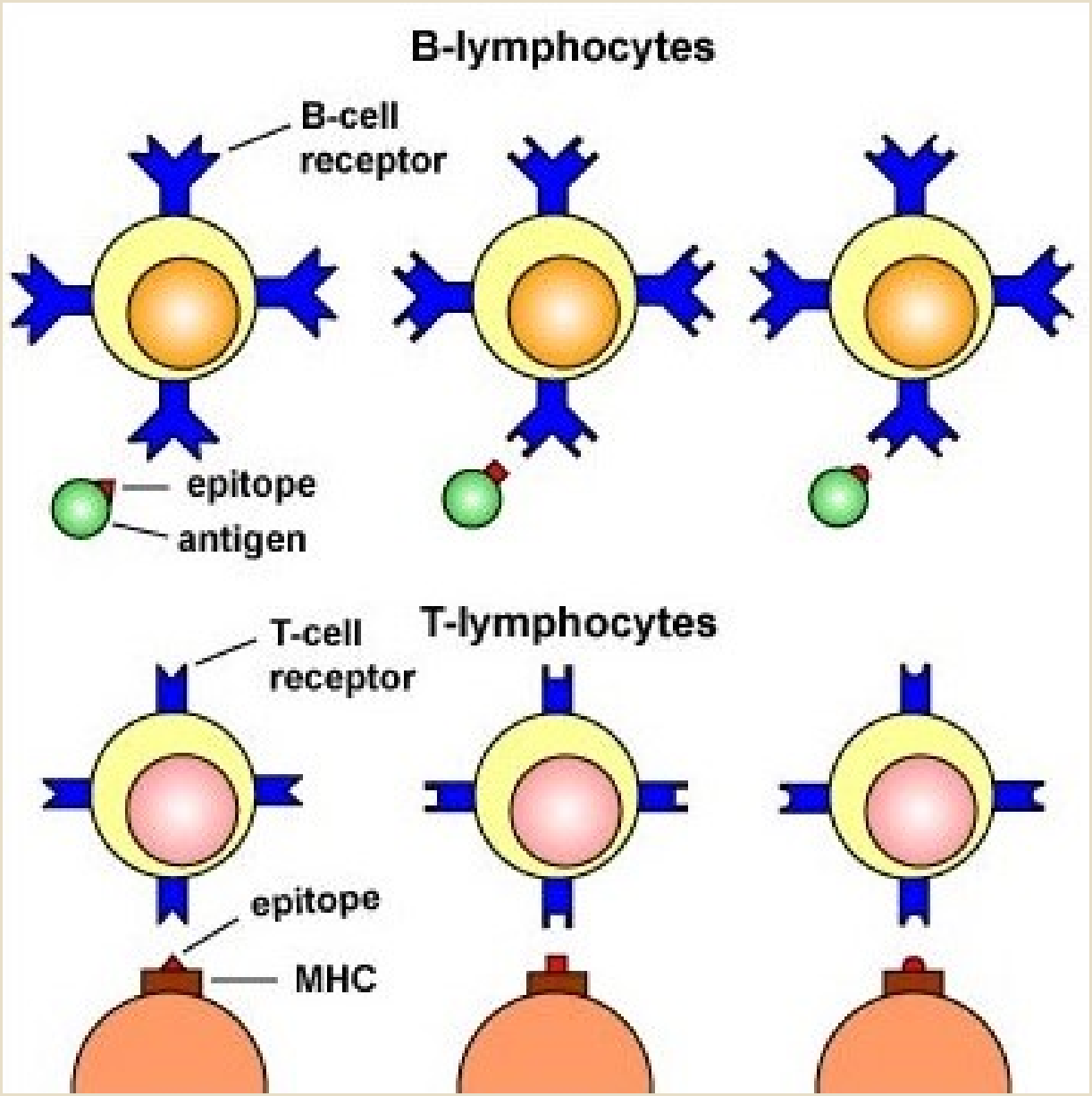
Table 1: Specificities of antigen interaction with T and B lymphocytes

Parameter	B lymphocyte	T lymphocyte
Chemical nature of antigen	Protein, polysaccharide or lipid	Mostly proteins
Interaction with antigen	Involves binary complex of membrane Ig and Ag	Involves ternary complex of TCR, Ag and MHC molecules
Binding with soluble antigen	Yes	No
MHC molecule requirement	None required	Required to display processed antigen
Properties of Epitope	Hydrophilic mobile peptides containing sequential or non sequential amino acids	Internal linear peptides processed and bound to MHC molecules

- A linear or a **sequential** epitope is an epitope that is recognized by antibodies by its linear **sequence** of **amino acids**, or primary structure.
- In contrast, most antibodies recognize a **conformational epitope** that has a specific three-dimensional shape and its protein structure.



- Image of CD4 co-receptor binding to MHC (Major Histocompatibility Complex) non-polymorphic region.

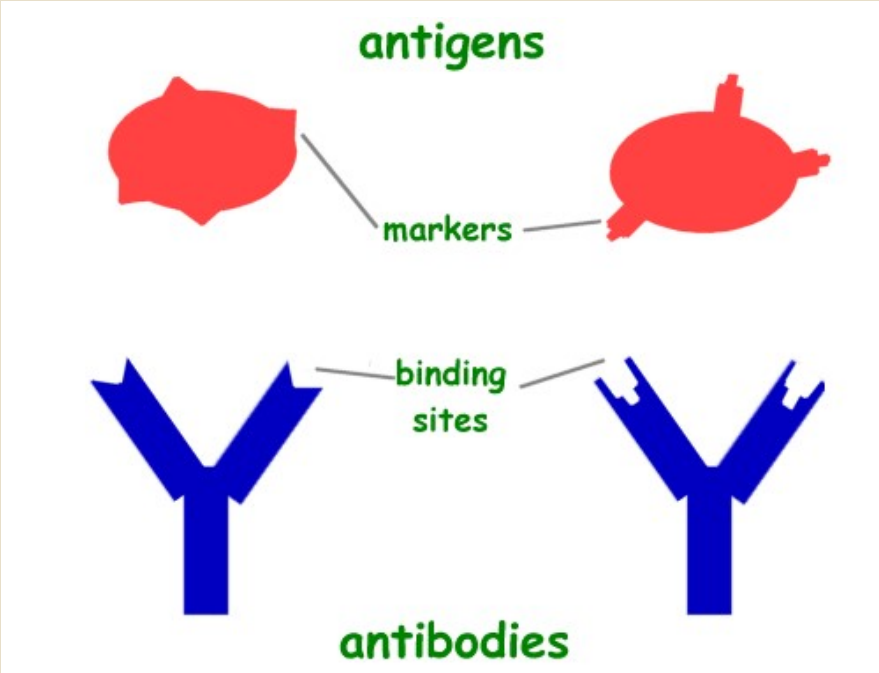

B-lymphocytes
B-cell receptor
epitope
antigen
T-lymphocytes
T-cell receptor
epitope
MHC

Antigens

- A substance that induces a specific immune response is usually called an antigen.

or

- Substances that can be recognised by immunoglobulin receptor of B cells, or by the T cell receptor when complexed with MHC, are called **antigens**.

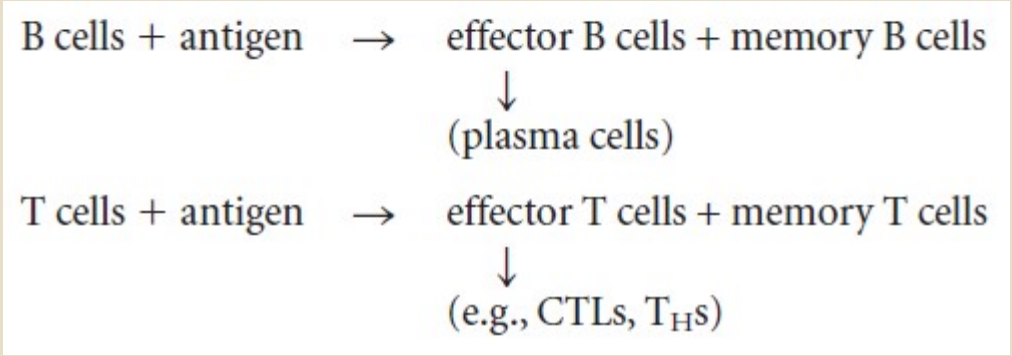


(Immunoglobulins)

Immunogenicity Versus Antigenicity

- Immunogenicity and antigenicity are related but distinct immunologic properties that sometimes are confused.

- **Immunogenicity** is the ability to induce a humoral and/or cell mediated immune response:



- Although a substance that induces a specific immune response is usually called an antigen, it is more appropriately called an **immunogen.**

- **Antigenicity** is the ability to combine specifically with the final products of the above responses (i.e., antibodies and/or cell-surface receptors).

Epitopes/antigenic determinants.

- Immune cells do not interact with, or recognize, an entire immunogen molecule; instead, lymphocytes recognize discrete sites on the macromolecule called **epitopes,** or **antigenic determinants.**

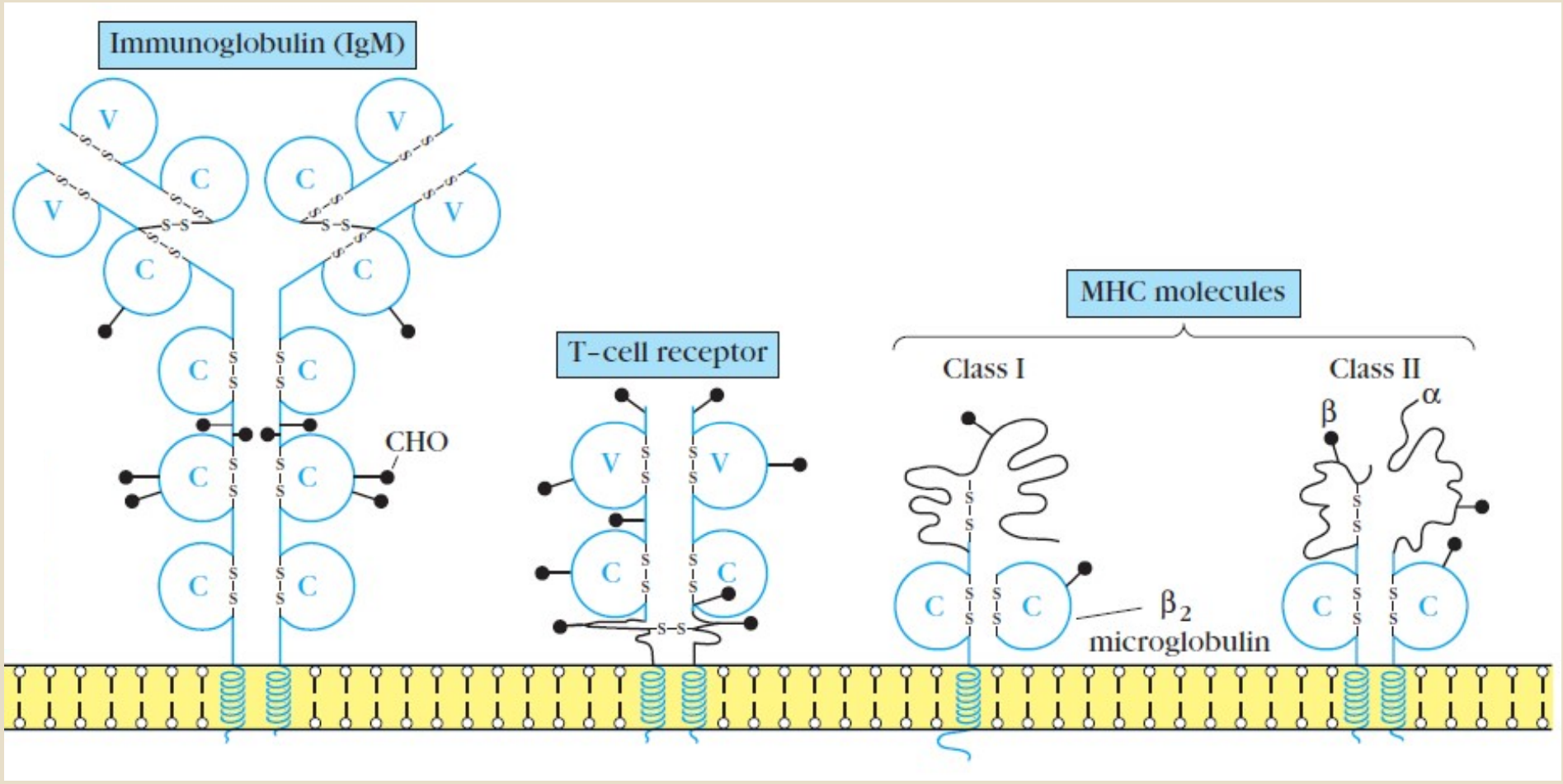
- Epitopes are the immunologically active regions of an immunogen that bind to antigen-specific membrane receptors on lymphocytes or to secreted antibodies.

- Studies with small antigens have revealed that B and T cells recognize different epitopes on the same antigenic molecule.

Major Histocompatibility Complex (MHC) molecules

- The **Major Histocompatibility Complex** (**MHC**) molecules are a set of cell surface proteins essential for the acquired immune system to recognize foreign molecules in vertebrates, which in turn determines **histocompatibility**.

- The function of **MHC** molecules is to bind peptide fragments derived from pathogens and display them on the cell surface for recognition by the appropriate T cells


Immunoglobulin (IgM)
V
C
S–S
CHO
T-cell receptor
MHC molecules
Class I
Class II
β
α
β_2
microglobulin

- Four related but **distinct *cell-membrane molecules that are responsible for antigen recognition*** by the immune system:

1. Membrane-bound antibodies on B cells

2. T-cell receptors

3. Class I MHC molecules

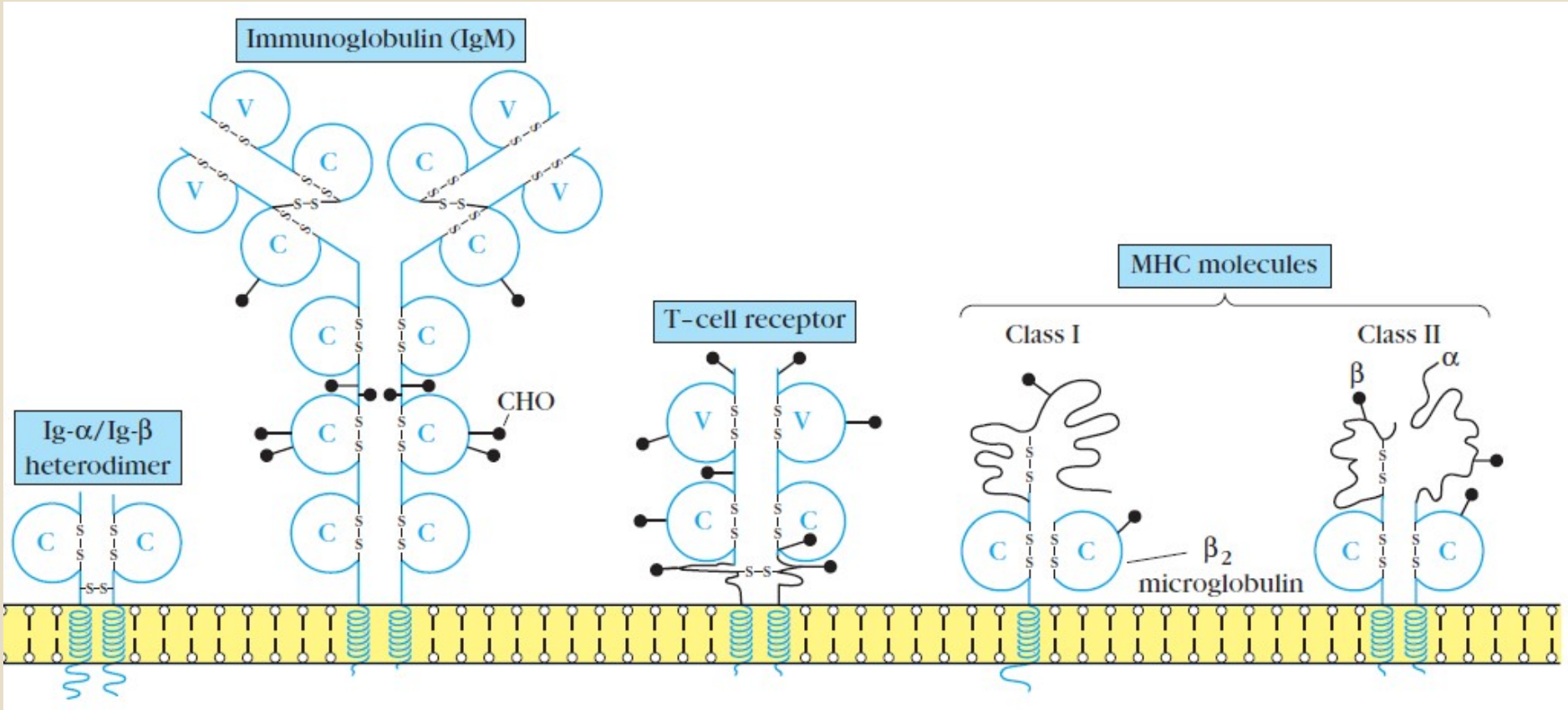
4. Class II MHC molecules

Each of these molecules plays a unique role in antigen recognition, ensuring that the immune system can recognize and respond to the different types of antigen that it encounters.

MHC (Major histocompatibility complex)

The major histocompatibility complex (MHC) is a large genetic complex with multiple loci.

- Every mammalian species studied to date possesses a tightly linked cluster of genes, the **major histocompatibility complex (MHC),** whose products play roles in intercellular recognition and in discrimination between self and nonself.


Immunoglobulin (IgM)
V
C
S–S
CHO
Ig-α/Ig-β
heterodimer
T-cell receptor
MHC molecules
Class I
Class II
β
α
β_2
microglobulin

- The **MHC participates in the development of both humoral and cell mediated immune responses.**

- While antibodies may react with antigens alone, most T cells recognize antigen only when it is combined with an MHC molecule.

- Furthermore, because MHC molecules act as antigen-presenting structures, the particular set of MHC molecules expressed by an individual influences the selection of antigens to which that individual's TH and TC cells can respond.

- The major histocompatibility complex is *a collection of genes arrayed within a long continuous stretch of DNA on chromosome* ***6 in humans*** and on chromosome 17 in mice.

- The MHC is referred to as the **HLA complex (Human Leukocyte Antigen)** in humans and as the **H-2 complex** in mice.

- Although the arrangement of genes is somewhat different, in both cases the MHC genes are organized into regions encoding three classes of molecules.

Types

- **Class I MHC genes** encode glycoproteins expressed on the surface of nearly **all nucleated cells**; the major function of the class I gene products is **presentation of peptide antigens to TC cells.**

- **Class II MHC genes** encode glycoproteins expressed primarily on antigen-presenting cells (macrophages, dendritic cells, and B cells), where they **present processed antigenic peptides to TH cells.**

- **Class III MHC genes** encode, in addition to other products, various secreted proteins that have **immune functions, including components of the complement system and molecules involved in inflammation.**

Important points…

- Class I and class II MHC molecules are membrane-bound glycoproteins that are closely related in both structure and function.

- Both types of membrane glycoproteins function as ***highly specialized antigen-presenting molecules*** that form unusually stable complexes with antigenic peptides, displaying them on the cell surface for recognition by T cells.

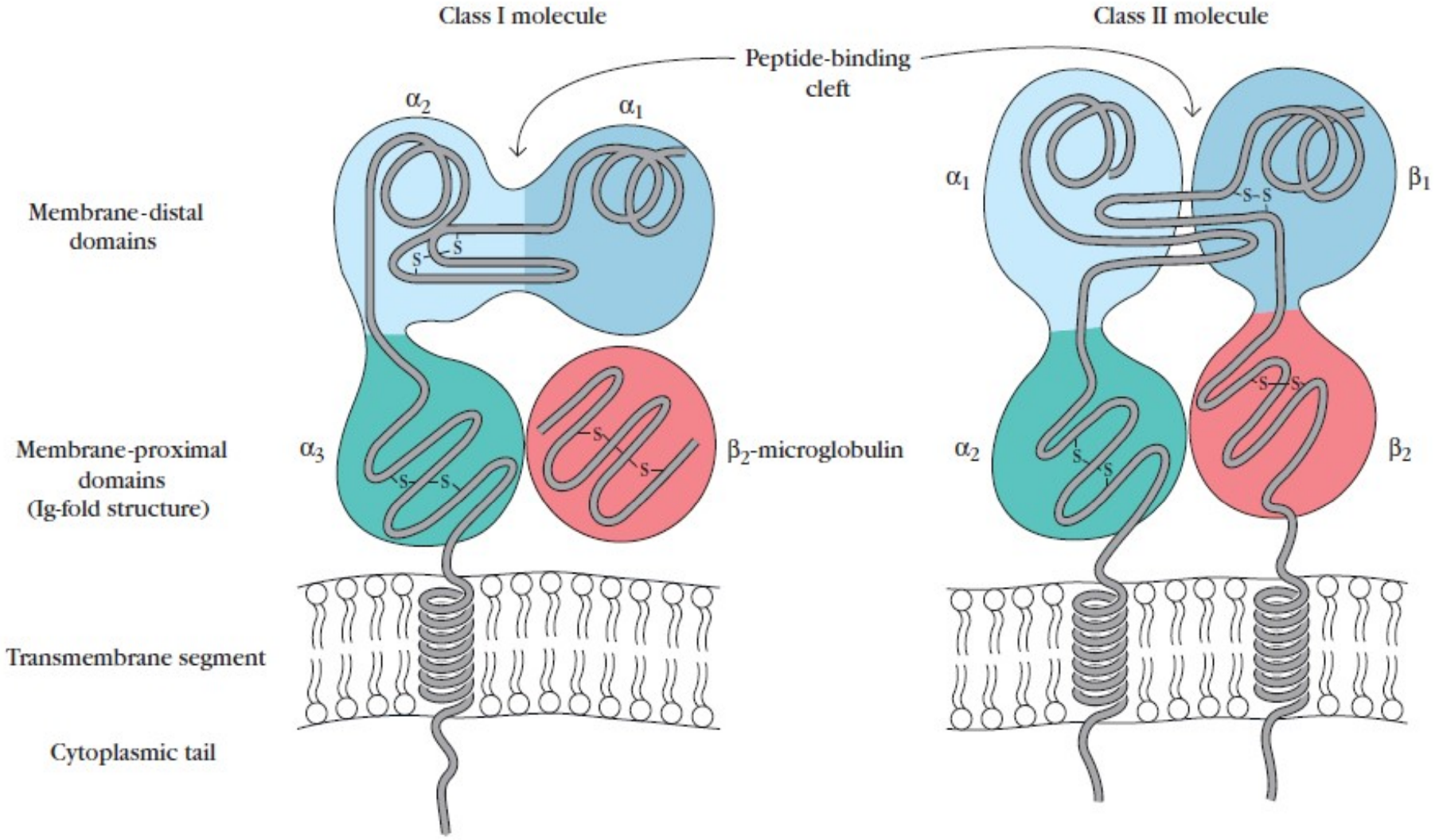


FIGURE 7-5 Schematic diagrams of a class I and a class II MHC molecule showing the external domains, transmembrane segment, and cytoplasmic tail. The peptide-binding cleft is formed by the membrane-distal domains in both class I and class II molecules. The membrane-proximal domains possess the basic immunoglobulin-fold structure; thus, class I and class II MHC molecules are classified as members of the immunoglobulin superfamily.

- **MHC class I molecules** are one of two primary classes of major histocompatibility complex (MHC) molecules (the other being MHC class II) and are **found on the cell surface of all nucleated cells** in the bodies of jawed vertebrates.

- They also occur on platelets, but not on red blood cells.

- **Class I MHC molecules** contain a 45-kilodalton (kDa) α chain associated noncovalently with a 12-kDa β_2 **microglobulin** molecule.

- The α chain is a transmembrane glycoprotein.

- Structural analyses have revealed that the α chain of class I MHC molecules is organized into **three external domains** (α1, α2, and α3).

- The β_2-microglobulin is similar in size and organization to the α3 domain; it does not contain a transmembrane region and is non-covalently bound to the class I glycoprotein.

- The *peptide-binding cleft is located on the top surface of the* class I MHC molecule, and it is large enough to bind a peptide of 8–10 amino acids.

- The great surprise in the x-ray crystallographic analysis of class I molecules was the finding of small peptides in the cleft that had co-crystallized with the protein.

- These peptides are, in fact, processed antigen and self-peptides bound to the 1 and 2 domains in this deep groove.

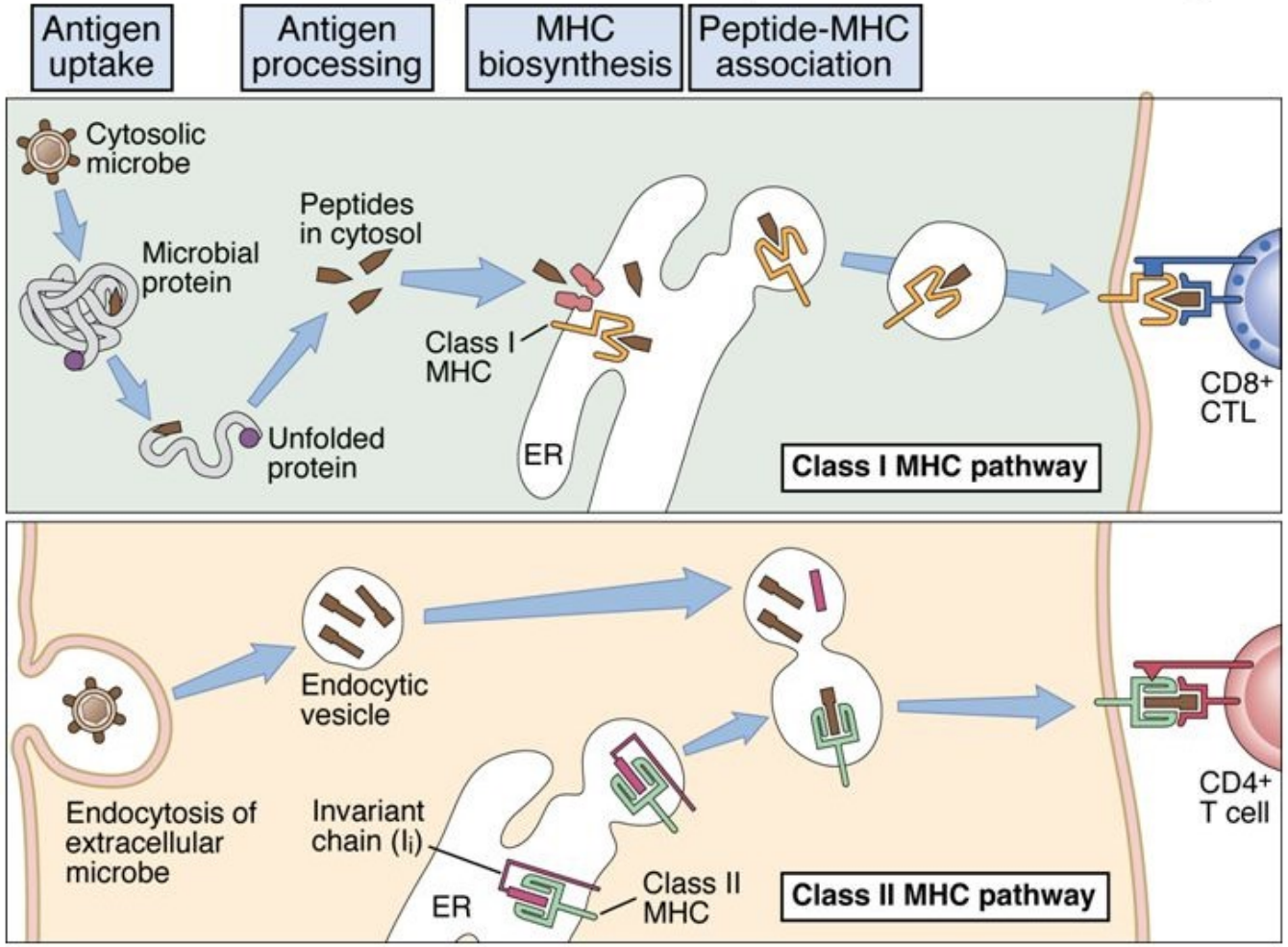
- Because MHC class I molecules present peptides derived from cytosolic proteins, the pathway of MHC class I presentation is often called *cytosolic* or *endogenous pathway*.

- Class I MHC molecules bind peptides generated mainly from degradation of cytosolic proteins by the proteasome. The MHC I:peptide complex is then inserted via endoplasmic reticulum into the external plasma membrane of the cell.

- The epitope peptide is bound on extracellular parts of the class I MHC molecule. Thus, the function of the class I MHC is to display intracellular proteins to cytotoxic T cells (CTLs).

- Essentially, the MHC-peptide complex is a complex of autoantigen/alloantigen.
- Upon binding, T cells should in principle tolerate the auto-antigen, but activate when exposed to the allo-antigen.
- Disease states occur when this principle is disrupted.

Pathways of antigen processing



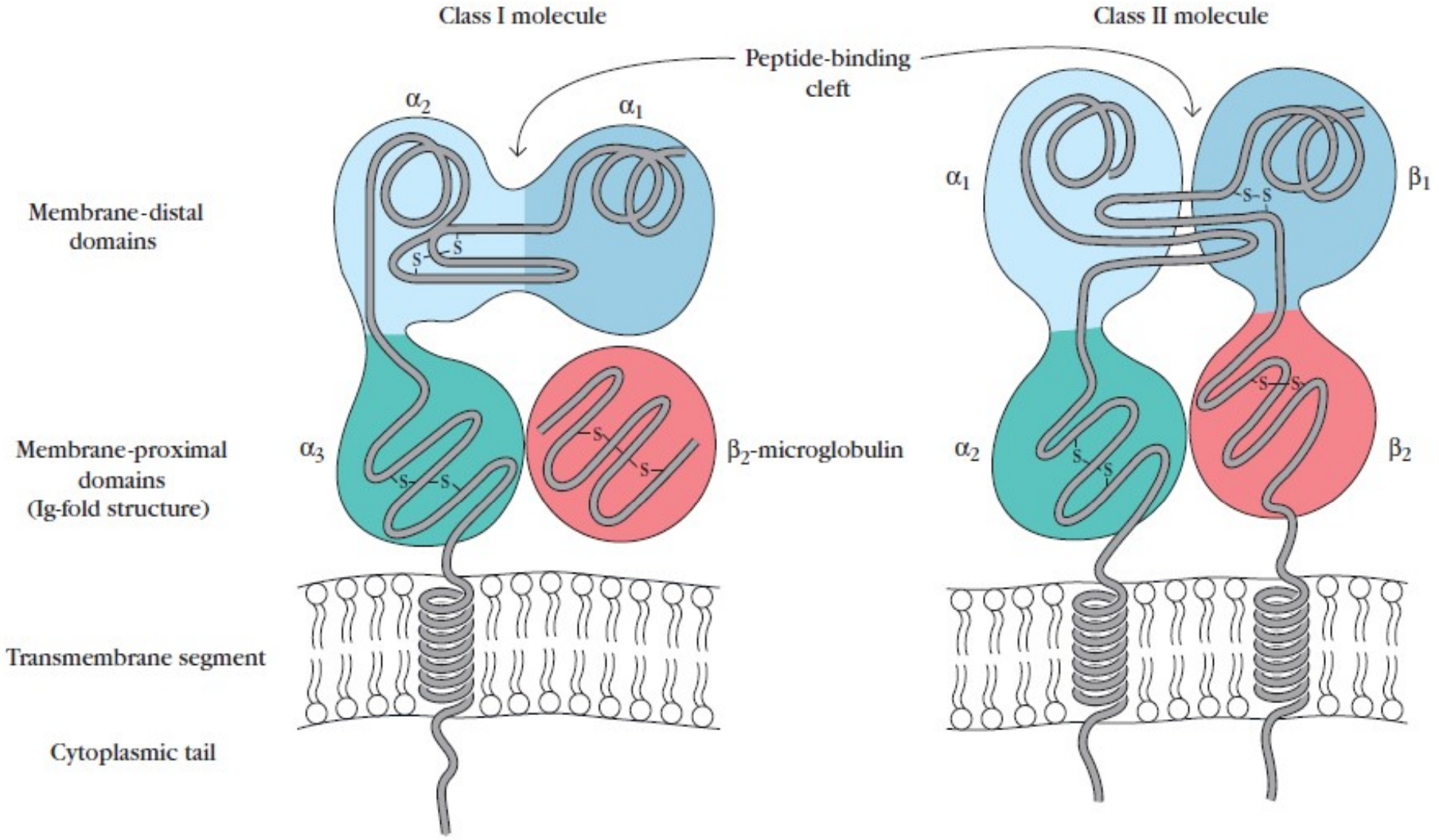
Protein antigen in cytosol (cytoplasm) --> class I MHC pathway
Protein antigen in vesicles --> class II MHC pathway

Abbas & Lichtman. Cellular and Molecular Immunology, 5th ed. W. B. Saunders 2003

- However, class I MHC can also present peptides generated from exogenous proteins, in a process known as cross-presentation.

- A normal cell will display peptides from normal cellular protein turnover on its class I MHC, and CTLs will not be activated in response to them due to central and peripheral tolerance mechanisms.

- When a cell expresses foreign proteins, such as after viral infection, a fraction of the class I MHC will display these peptides on the cell surface. Consequently, CTLs specific for the MHC:peptide complex will recognize and kill presenting cells.



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MHC class II

- **Class II MHC molecules** contain two different polypeptide chains, a 33-kDa α chain and a 28-kDa β chain, which associate by non-covalent interactions.

- Like class I α chains, class II MHC molecules are membrane-bound glycoproteins that contain
- external domains
- a transmembrane segment, and
- a cytoplasmic anchor segment.

- Each chain in a class II molecule contains two external domains: α1 and α2 domains in one chain and β1 and β2 domains in the other.

- MHC class II can be conditionally expressed by all cell types, but normally **occurs only on professional antigen-presenting cells (APCs):** macrophages, B cells, and especially dendritic cells (DCs).

- An APC takes up an antigen, performs antigen processing, and returns a molecular fraction of it—a fraction termed the epitope—to the APC's surface, coupled within an MHC class II molecule mediating antigen presentation by displaying this epitope.

- On surfaces of helper T cells are CD4 receptors, as well as T cell receptors (TCRs). When a naive helper T cell's CD4 molecule docks to an APC's MHC class II molecule, its TCR can meet and be imprinted by the epitope coupled within the MHC class II.

- This event primes the naive helper T cell.

- According to the local environment, that is, the balance of cytokines secreted by APCs in the microenvironment, the naive helper T cell (Th_0) polarizes into either a memory Th cell or an effector Th cell or regulatory/suppressor (T_{reg}), as so far identified, the Th cell's terminal differentiation.

- MHC class II thus mediates immunization to—or, if APCs polarize Th_0 cells principally to T_{reg} cells, immune tolerance of—an antigen. The polarization during primary exposure to an antigen is key in determining a number chronic diseases, such as inflammatory bowel diseases and asthma, by skewing the immune response that memory Th cells coordinate when their memory recall is triggered upon secondary exposure to similar antigens.

- (B cells express MHC class II to present antigen to Th_0, but when their B cell receptors bind matching epitopes, interactions which are not mediated by MHC, these activated B cells secrete soluble immunoglobulins: antibody molecules mediating humoral immunity.)

Thank you