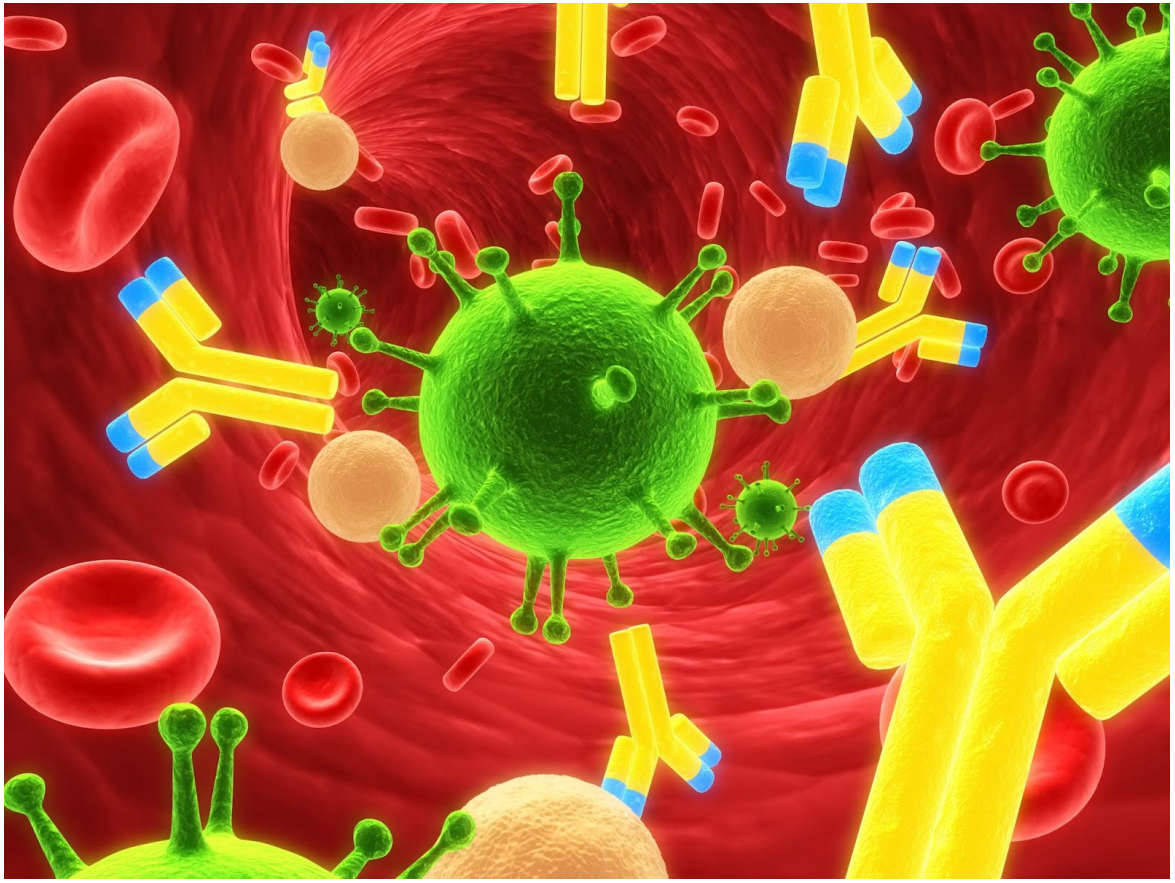
Overview of immune system



Functions of the Immune System

What is the primary function?

To maintain good health and to protect the body from harmful substances including:

- *Pathogens*

disease-producing microorganisms ex. Bacteria, viruses, parasites

- *Allergens*

substances that produce allergic reactions ex. Pollen, dust, animal dander

- *Toxins*

poisonous or harmful substances ex. Venom

- *Malignant cells*

*potentially life-threatening **cancer** cells*

Immune system performs three basic functions

Defense - identification and protection against pathogenic microorganisms and their toxins

Autotolerance – recognition of own tissues and keeping tolerance to them

Immune surveillance - identifying and removing the old , damaged and otherwise changed cells

↓

(Such as Malignant cells or cancerous cells)

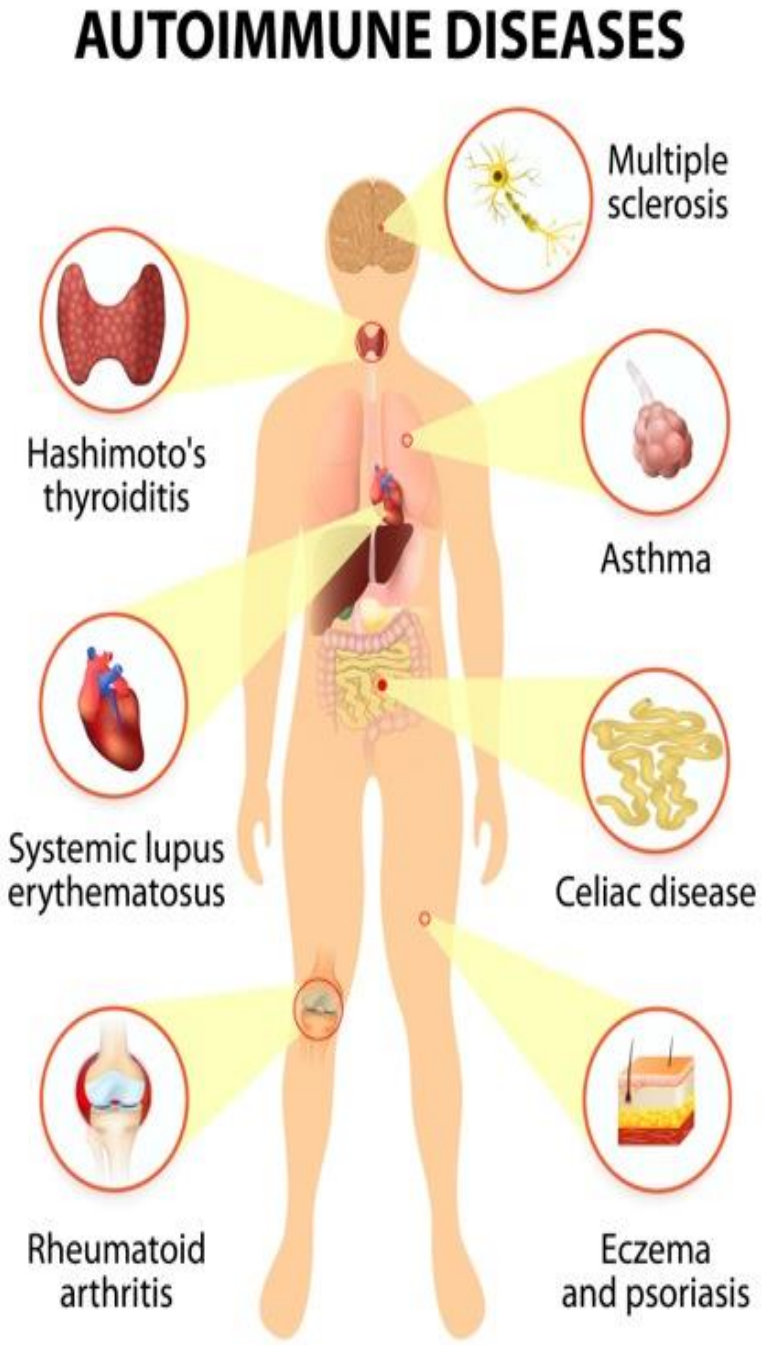
When there are

Immunologic "mistakes:"

1. Incorrect responses: autoimmunity
2. Overactive responses: allergy
3. Lack of response: immune deficiency

What is Autoimmunity? **Immune system creates antibodies that attack their own cells.**

What is Immunodeficiency? **Immune system's ability to fight infectious diseases is completely absent or compromised**

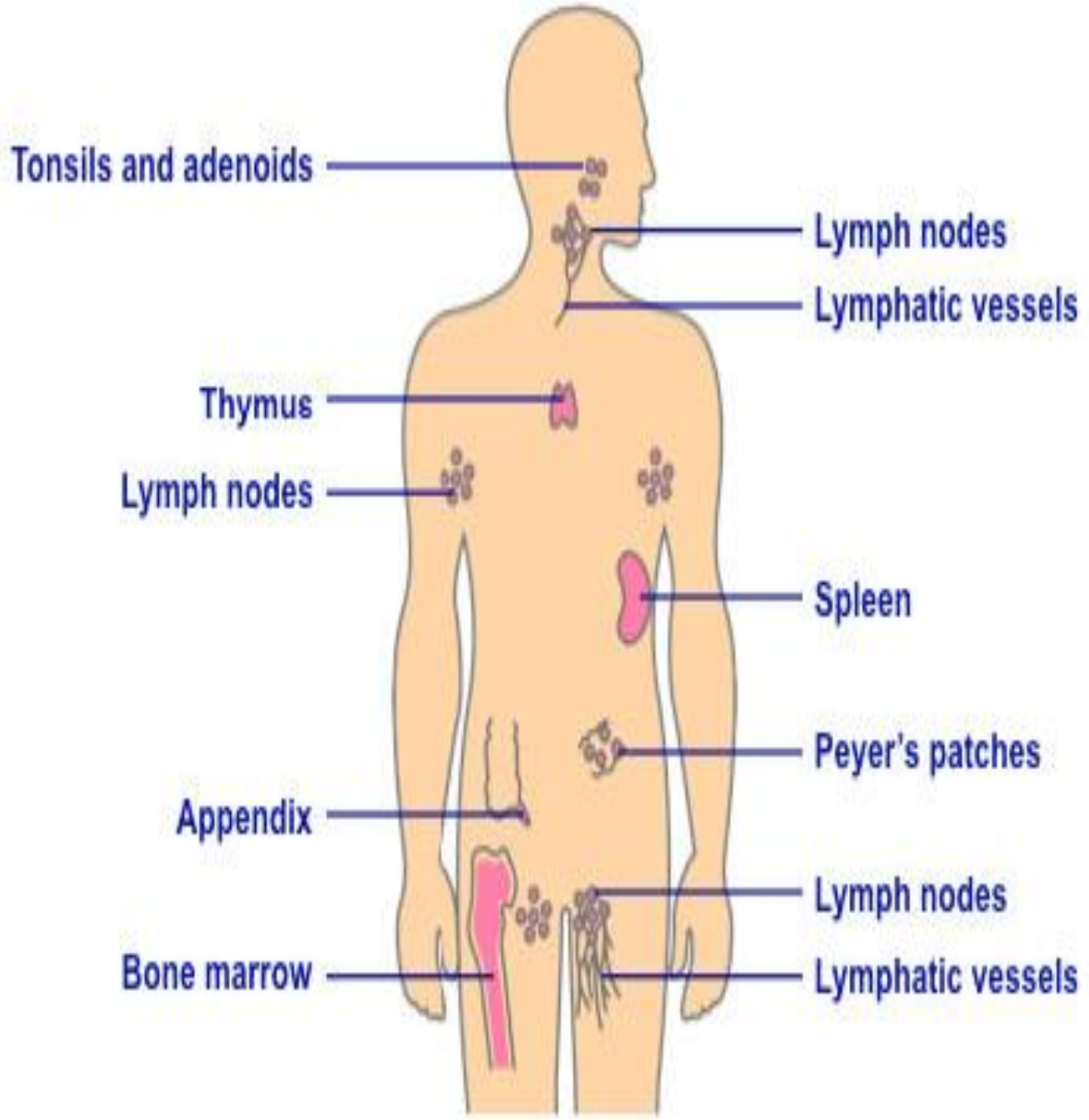


Immunodeficiency syndromes

Immune Component	Example of Diseases
T lymphocyte deficiency	DiGeorge's syndrome
	AIDS/HIV infection (secondary Immunodeficiency)
B lymphocyte deficiency	X-linked agammaglobulinemia
	CVID **(Common variable immune deficiency)**
	Selective IgA deficiency

Organs / Lymphoid organs of immune system

- *Tonsils and adenoids*
- *Lymphatic vessels*
- *Bone marrow*
- *Lymph nodes*
- *Thymus*
- *Spleen*
- *Appendix and Peyer's patches*



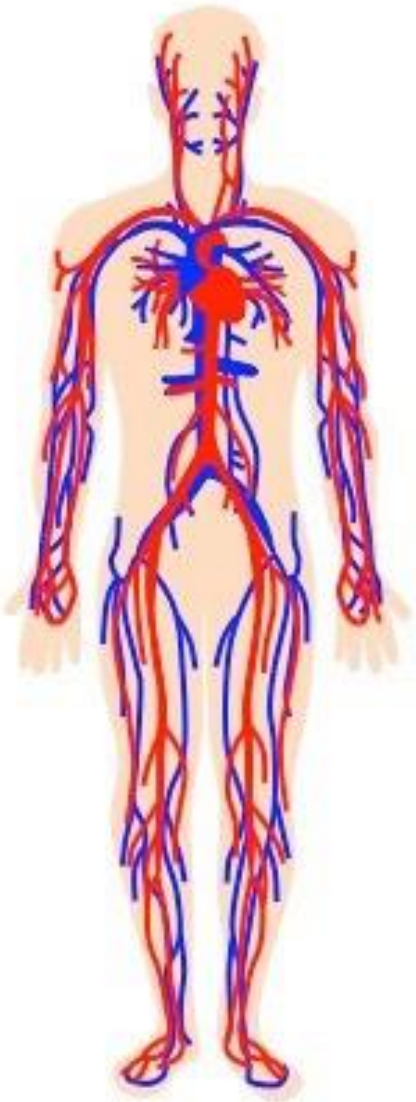
Lymphatic System

Overview

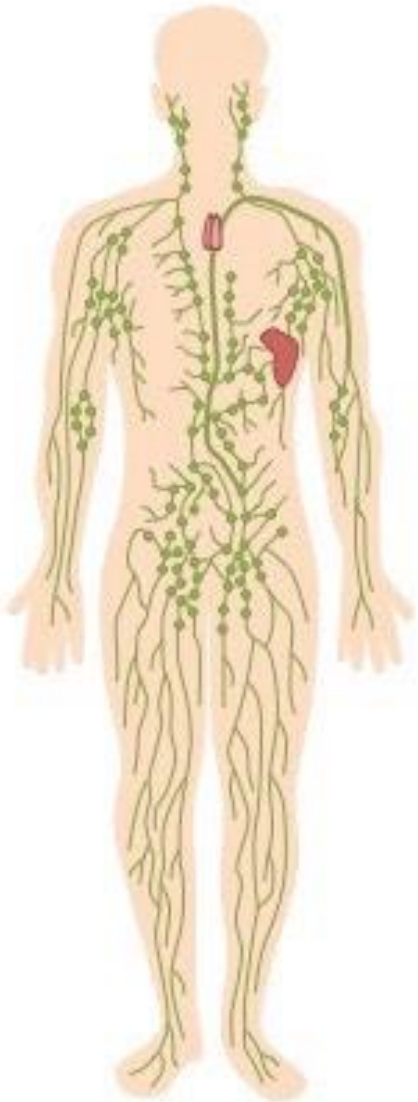
The Lymphatic system is a network of vessels and organs that filters and returns interstitial fluid to blood circulation.

- It prevents fluid build-up (edema)
- It protects the body against pathogens.
- It absorbs fats from the intestine and transports them to the bloodstream

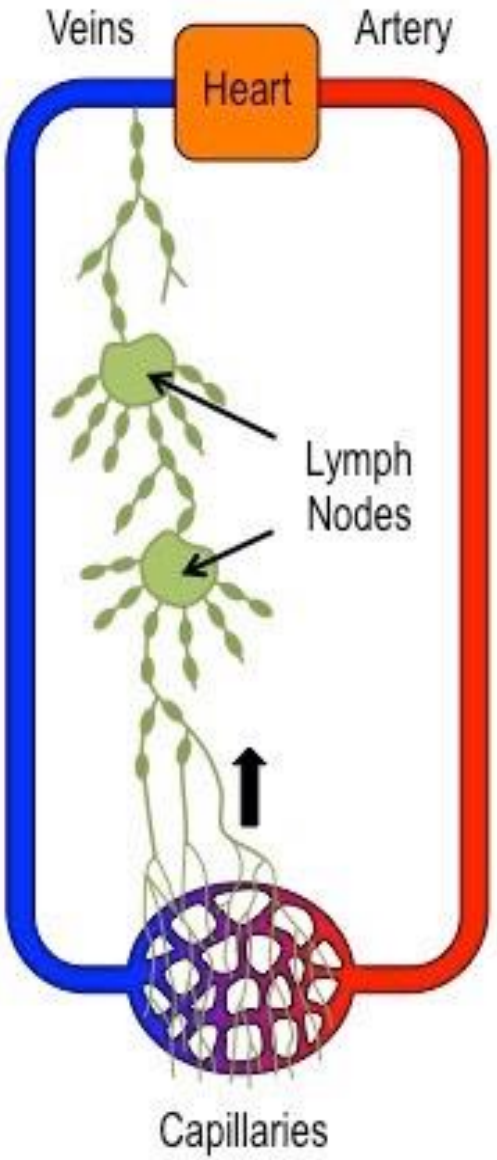
Circulatory System



Lymphatic System

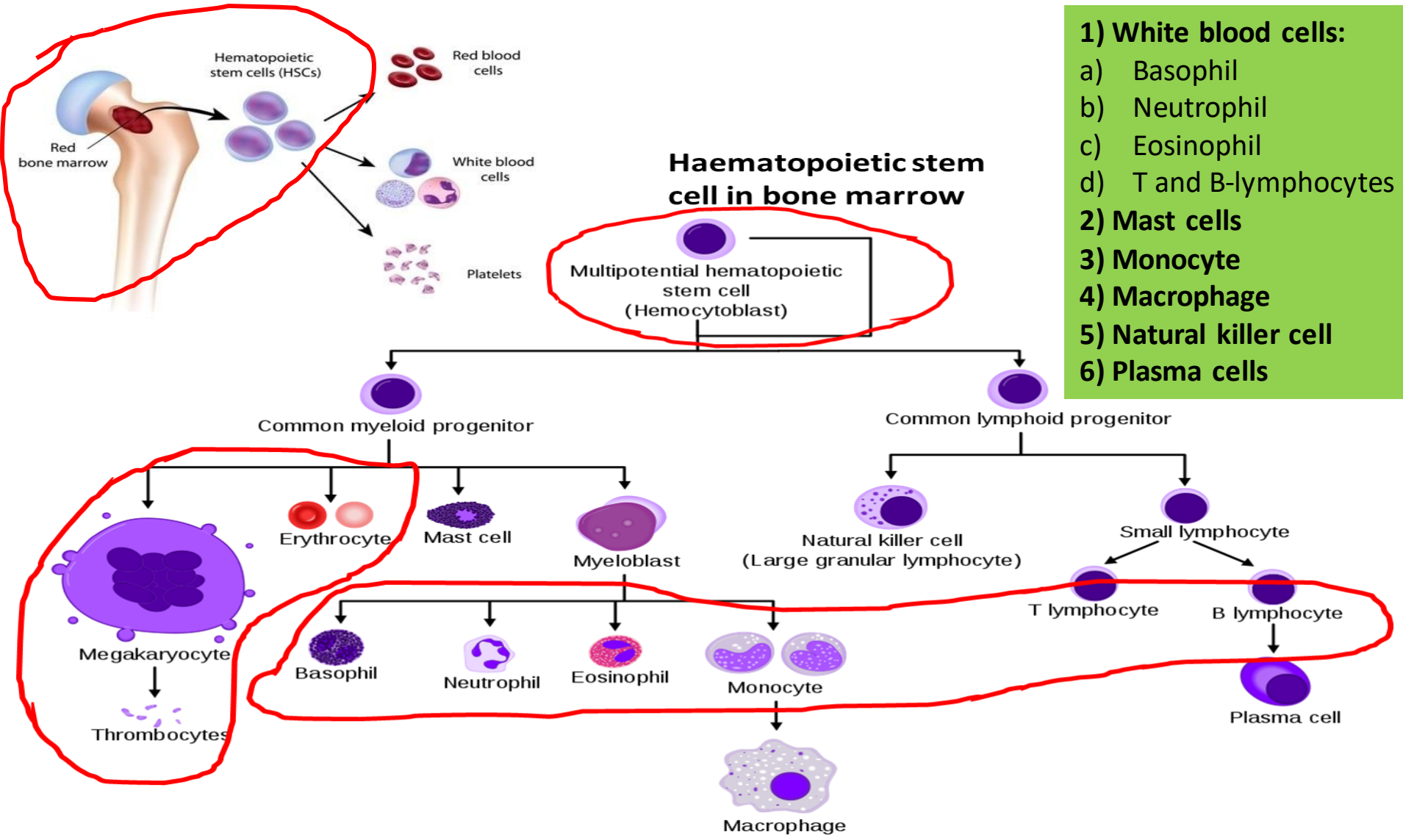


Inter-relationship between systems



Lymphoid organs of the immune system	Main functions
Tonsils and adenoids	specialized lymph nodes containing immune cells that protect the body against invaders of the respiratory system
Lymphatic vessels	constitute a network of channels that transport the lymph (fluid that carries lymphatic cells and exogenous antigens) to the immune organs and blood
Bone marrow	soft tissue contained in the inside part of the longest bones, **responsible for the generation of the immune cells;**
Lymph nodes	act as convergence sites of the lymphatic vessels, where each node stores immune cells, including B and T cells (site where the adaptive immune response takes place)
Thymus	from the bone marrow, a few cells migrate into the thymus**, where they multiply and mature, transforming themselves into T cells**, capable of producing an immune response;
Spleen	site where the leukocytes destroy the organisms that invaded the blood stream;
Appendix and Peyer's patches	specialized lymph nodes containing the immune cells destined to protect the digestive system.

Haematopoietic stem cells in bone marrow give rise to immune cells



1) White blood cells:

a) Basophil
b) Neutrophil
c) Eosinophil
d) T and B-lymphocytes

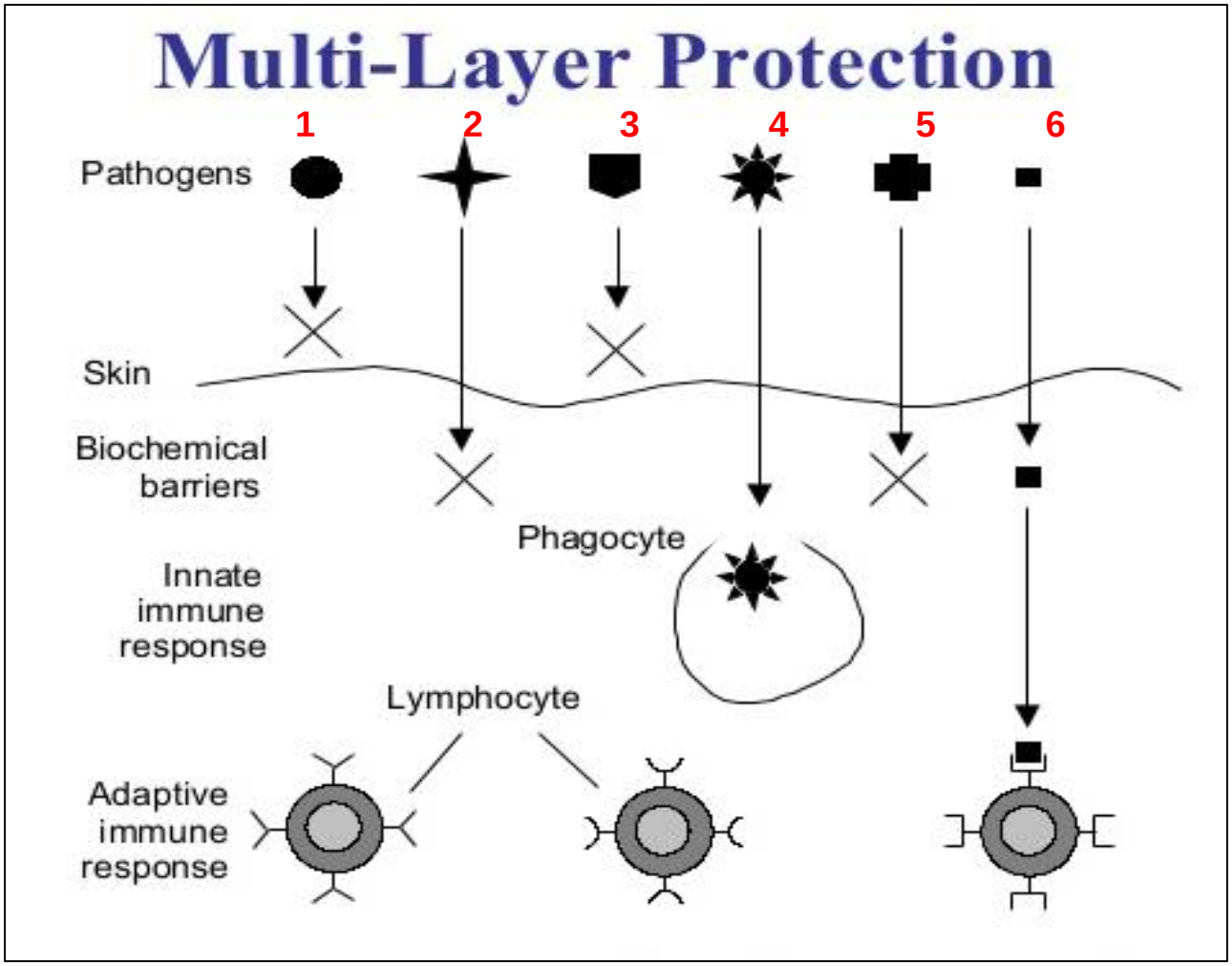
2) Mast cells
3) Monocyte
4) Macrophage
5) Natural killer cell
6) Plasma cells

What is Haematopoiesis??

production of all types of blood cells including formation, development, and differentiation of blood cells.

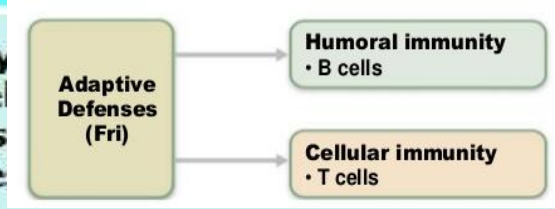
The 1st, 2nd and 3rd line of defense as a multilayer protection

- **1, 2, 3, 5 pathogen** are defended by **first line of defense.**
- **4 pathogen** is defended by **second line of defense.**
- **6 pathogen** is defended by **third line of defense**



Immune System: 3 Lines of Defense

Innate Immunity (Non-specific Defense Mechanisms)		Adaptive Immunity (Specific Defense Mechanisms)
Timeline: 0 to 12 hours		Timeline: 1 to 7 Days
1st Line of Defense	2nd Line of Defense	3rd Line of Defense
• Skin • Mucous membranes • Secretions of skin • Secretions of mucous membranes	• Macrophages • Other Phagocytes (i.e. neutrophils, NK cells) • Antimicrobial proteins • The Inflammatory response (e.g. redness, fever)	• Lymphocy (B & T Ce • Antigen-s • Antibodie • Memory



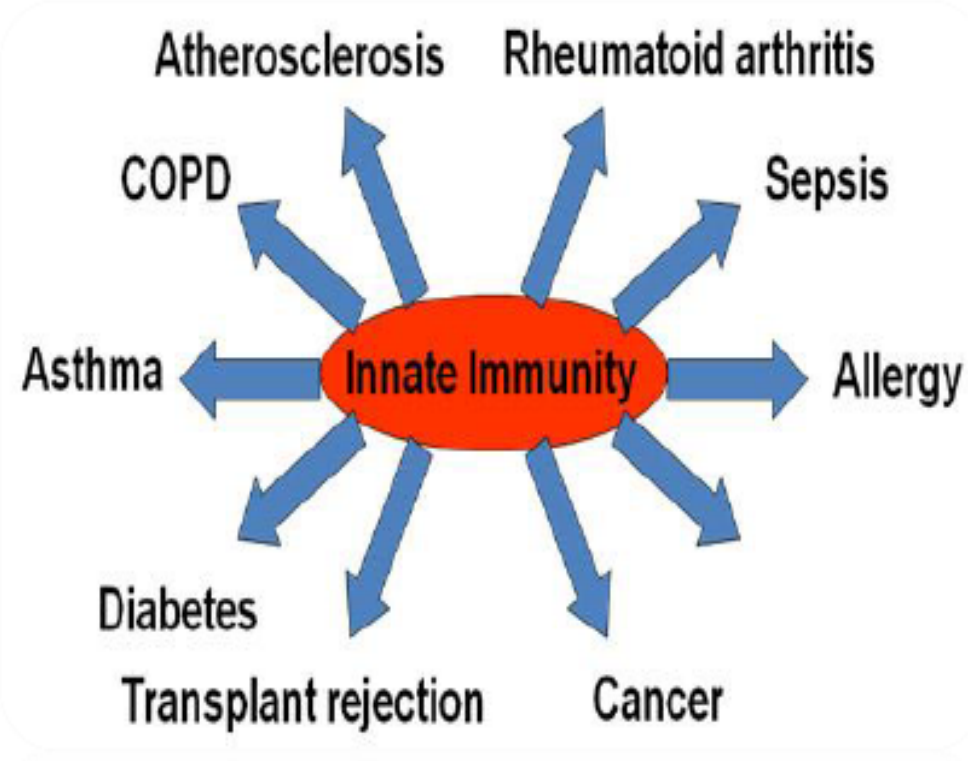
The First line of defense is the physical barriers: skin, mucous membranes, hair within nose, cilia in the upper respiratory tract, saliva in mouth that contains digestive enzymes, stomach gastric juice and sebum.

The second line of defense is internal barriers: inflammatory response, phagocytic cells (they are WBCs capable of ingesting pathogens), Complement proteins, Natural killer cells, antimicrobial substances such as interferons, iron-binding proteins, antimicrobial proteins

The third line of defense are T-cells and B-cells: B-cells produce antibodies and called as humoral immune response, whereas T-cells kills pathogens and called cell-mediated immune response or cellular immunity

Innate immunity / non-specific defense mechanism

- Nonspecific host defenses that exist prior to exposure to an antigen. Involves the following components:
  - Anatomic
  - Physiologic
  - Phagocytic
  - Inflammatory



Pathogen recognition

Most microorganisms express repeating patterns of molecular structures termed **Pathogen Associated Molecular Patterns (PAMPs).**

Innate immune system has evolved mechanisms capable of recognising these repeating patterns termed **Pattern Recognition Receptors (PRRs).**

Ex. of pattern recognition receptors:

- **Mannose-Binding Lectin (MBL)**
- **Macrophage Mannose Receptor**
- **Scavengers receptors**
- **Toll-like receptors (TLRs)**
- **Nod-like receptors**
- **RNA helicases (RIG-I, MDA-5)**

Table 12.1 Summary of Innate (Nonspecific) Body Defenses

Category and associated elements	Protective mechanism
Surface membrane barriers—first line of defense	
Intact skin (epidermis)	Forms mechanical barrier that prevents entry of pathogens and other harmful substances into body.
• Acid mantle	Skin secretions make epidermal surface acidic, which inhibits bacterial growth; sebum also contains bacteria-killing chemicals.
• Keratin	Provides resistance against acids, alkalis, and bacterial enzymes.
Intact mucous membranes	Form mechanical barrier that prevents entry of pathogens.
• Mucus	Traps microorganisms in respiratory and digestive tracts.
• Nasal hairs	Filter and trap microorganisms in nasal passages.
• Cilia	Propel debris-laden mucus away from lower respiratory passages.
• Gastric juice	Contains concentrated hydrochloric acid and protein-digesting enzymes that destroy pathogens in stomach.
• Acid mantle of vagina	Inhibits growth of bacteria and fungi in female reproductive tract.
• Lacrimal secretion (tears); saliva	Continuously lubricate and cleanse eyes (tears) and oral cavity (saliva); contain lysozyme, an enzyme that destroys microorganisms.
Antimicrobial chemicals	
• Complement	Group of plasma proteins that lyses microorganisms, enhances phagocytosis by opsonization, and intensifies inflammatory response.
• Interferons	Proteins released by virus-infected cells that protect uninfected tissue cells from viral takeover; mobilize immune system.
• Fluids with acid pH	Normally acid pH inhibits bacterial growth; urine cleanses the lower urinary tract as it flushes from the body.
Fever	Systemic response triggered by pyrogens; high body temperature inhibits multiplication of bacteria and enhances body repair processes.

ACQUIRED IMMUNITY

- Adaptive immunity /Specific
- sub-divided into two major types depending on how the immunity was introduced:
- **Naturally acquired immunity** occurs through contact with a disease causing agent, when the contact was not deliberate
- **Artificially acquired immunity** develops only through deliberate actions such as vaccination.

N/B:

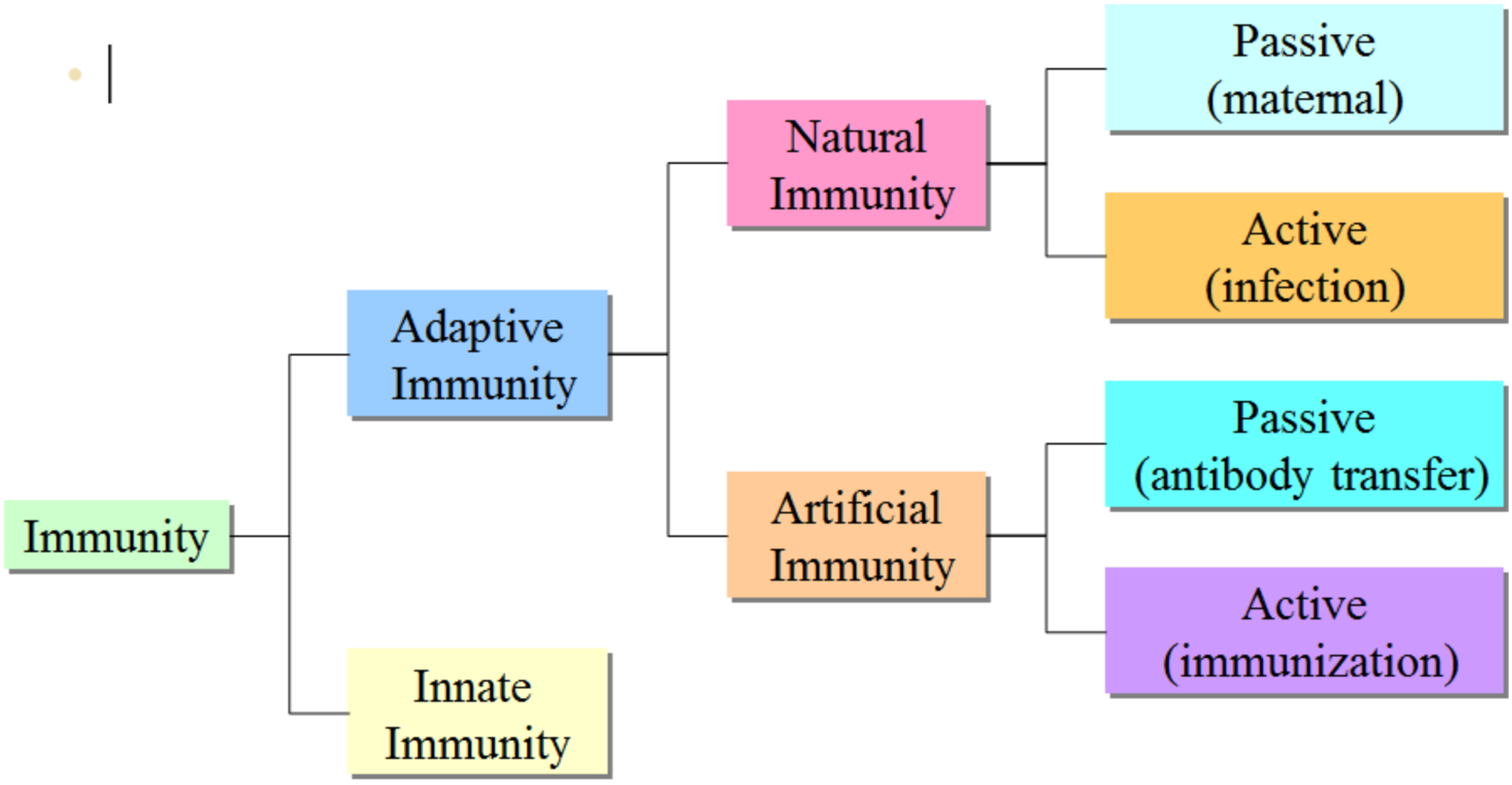
Memory cells are only produced in active immunity.

Protection for active immunity is permanent whereas in passive immunity it is only temporary.

Antigens are only encountered in active immunity.

Active immunity takes several weeks to become active but passive is immediate.

Adaptive/acquired immunity



IN ACQUIRED IMMUNITY, LYMPHOCYTE RECEPTORS PROVIDE PATHOGEN-SPECIFIC RECOGNITION

- White blood cells called **lymphocytes** recognize and respond to antigens, foreign molecules
- Lymphocytes that mature in the **thymus** above the heart are called **T cells**, and those that mature in bone marrow are called **B cells**
- Lymphocytes contribute to immunological memory, an enhanced response to a foreign molecule encountered previously
- **Cytokines** are secreted by macrophages and dendritic cells to recruit and activate lymphocytes
- The acquired immune system has three important properties:
- Receptor diversity
- A lack of reactivity against host cells
- Immunological memory

Adaptive immunity / Acquired immunity / Specific defense mechanism

- It is not present at birth time but becomes part of our immune system as the lymphoid system develops.

Two ways :

1) Humoral immunity / humoral immune response: Activation of B-Lymphocytes or B-cells.

2) Cellular immunity / cell-mediated immune response: Activation of T-Lymphocytes or T-cells

- **Cell-mediated immune response** (CMIR)
  - T-lymphocytes
  - eliminate intracellular microbes that survive within phagocytes or other infected cells
- **Humoral immune response (HIR)**
  - B-lymphocytes
  - mediated by antibodies
  - eliminate extra-cellular microbes and their toxins

Plasma cell
(Derived from B-lymphocyte, produces antibodies)

Terminologies in understanding immune system

Antigens are any substance that can activate the immune system and induces specific immune response.

Epitopes are the specific sites on an antigenic molecule that interacts with an antibody. Any given antigen may have several epitopes and is recognized by different antibodies.

Immunogenicity: The ability of antigens to induce a humoral and or cell-mediated immune response. Antigens are able to combine specifically with the components of these response (antibodies or cell-surface receptors).

Antibody is a protein used by the immune system to identify and neutralize foreign objects like bacteria and viruses. Each antibody recognizes a specific antigen unique to its target.

Monoclonal antibodies are antibodies that are identical because they were produced by single type of immune cell, all clones of a single parent cell. It is derived against from single epitope of antigen.

Polyclonal antibodies are antibodies that derived against different epitopes of antigens.

Pathogenic microorganisms: microorganisms capable of causing infection or disease.

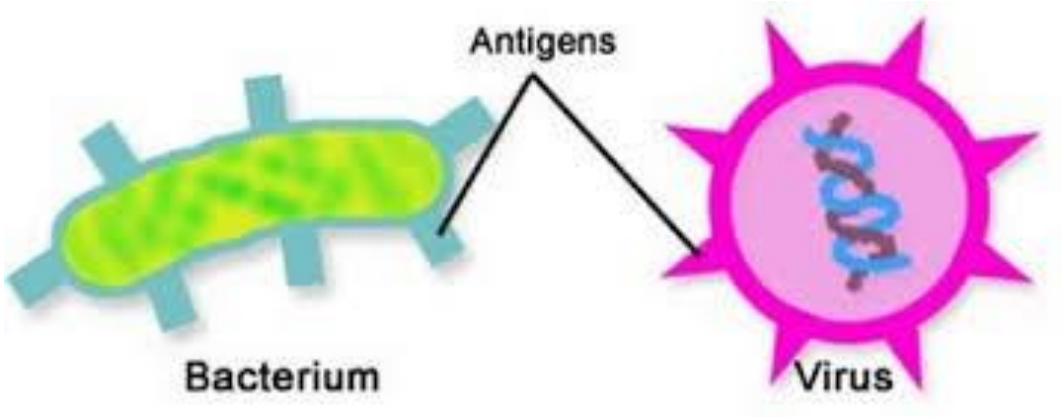
Infection: Ability of pathogen to enter host, multiply and stimulate an immune response.

Disease: clinical manifestations associated with infection.

What do you understand by ANTIGENS and EPITOPES ?

Antigens are any substance that can activates the immune system and induces specific immune response.

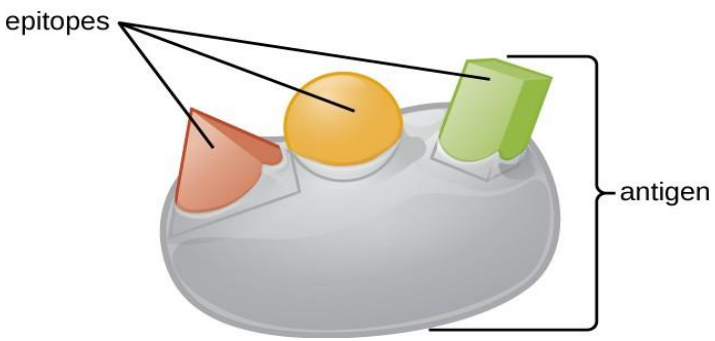
- Proteins, nucleic acids, lipids, polysaccharides.
- Pathogenic microbes or molecules from pathogens such as capsules, cell walls, toxins
- Non-microbes such as pollen, red blood cell surface receptors, surface molecules from transplant tissue, egg white etc.

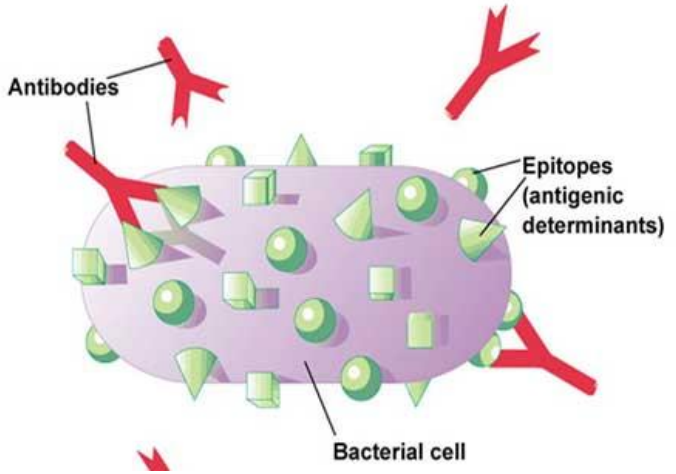


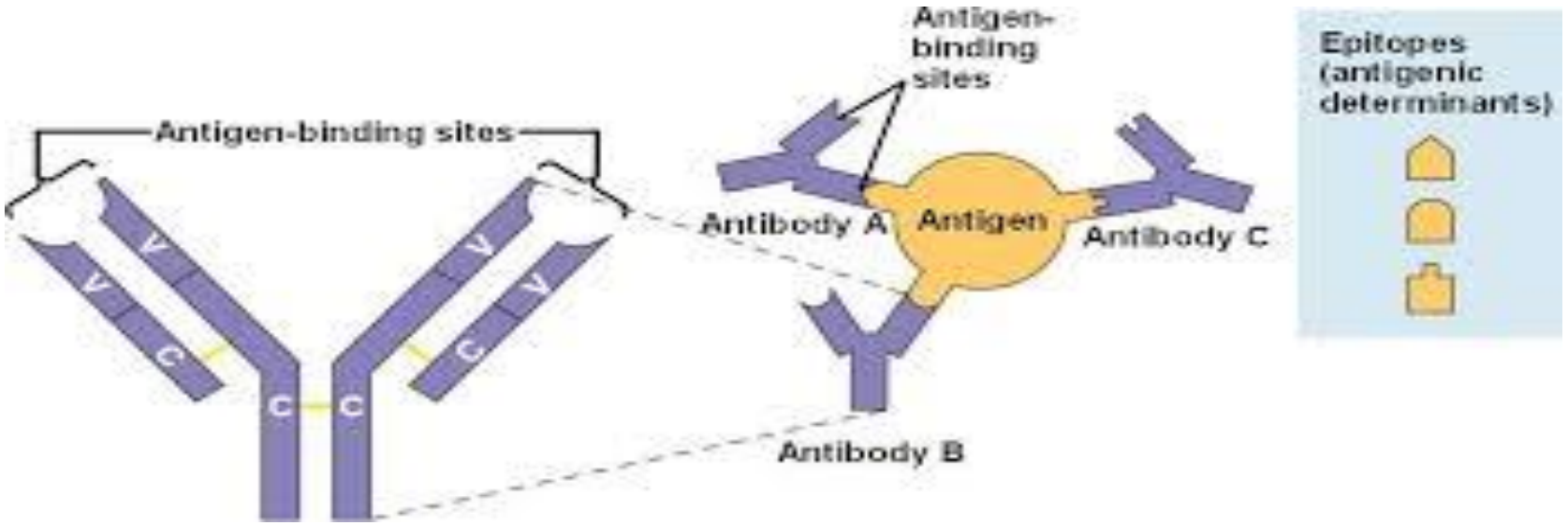
What are the epitopes found in antigens?

Epitopes are the specific sites on an antigenic molecule that interacts with an antibody.

Any given antigen may have several epitopes and is recognized by different antibodies.



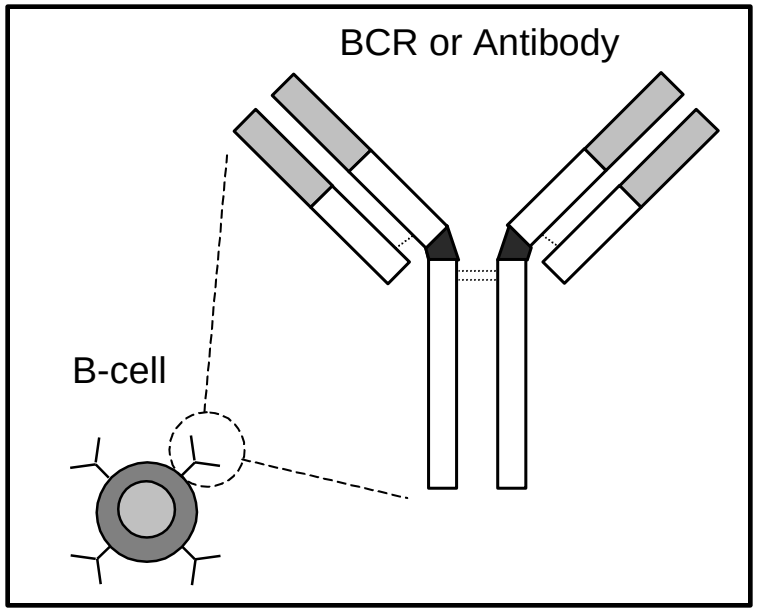


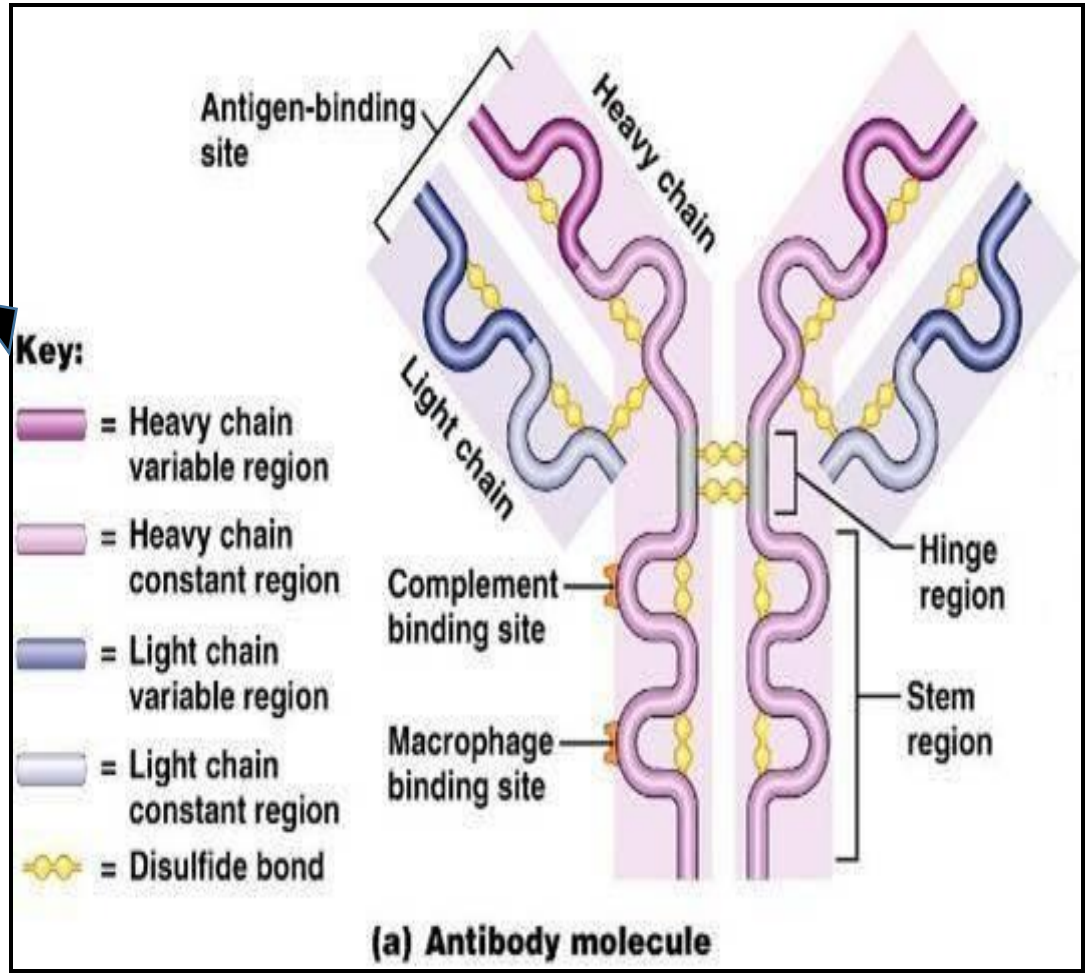


Antibody and its structure

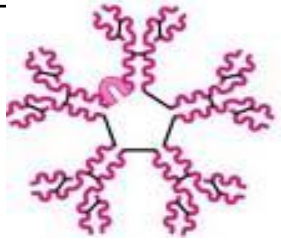
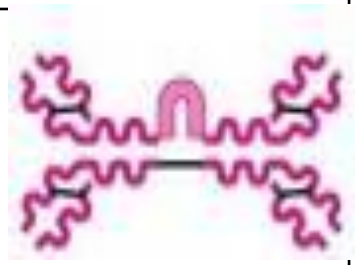
Antibody is a protein used by the immune system to identify and neutralize foreign objects like bacteria and viruses. Each antibody recognizes a specific antigen unique to its target.

- Constant (C) region defines antibody class
- Determines chemical & cellular interactions
- Determines how class functions to eliminate antigens



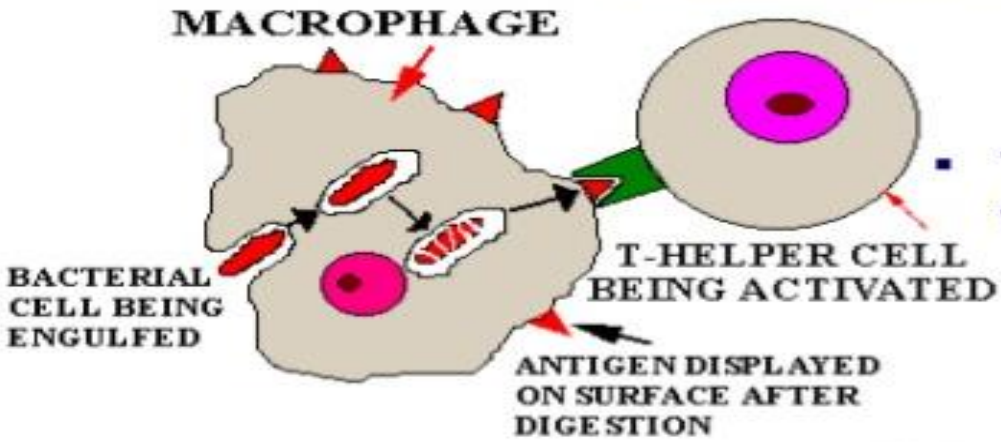


Various types of antibodies

Antibody class	Function	Structure
IgG	Exist as Monomer; 80%; found in placental transfer and protects fetus and new born	
IgM	Exist as Pentamer as circulating antibody; 5-10% of serum antibodies; 1st antibody that is produced during infection. Effective against microbes.	
IgA	Exist as Dimer; 10 -15% of serum antibodies: mostly found in **tears, saliva, intestinal secretions, milk, blood and lymph.** Localized protection of mucosal surfaces, **provides immunity to infant digestive tract**.	
IgD	Exist as monomer; 0.2%; found in B-cell surfaces, blood and lymph	
IgE	Exist as monomer; 0.002%, levels become high **during allergic reactions**; bound to mast cells, basophils, combats **parasitic infections.**	

Concept of Antigen presenting cells (APCs)

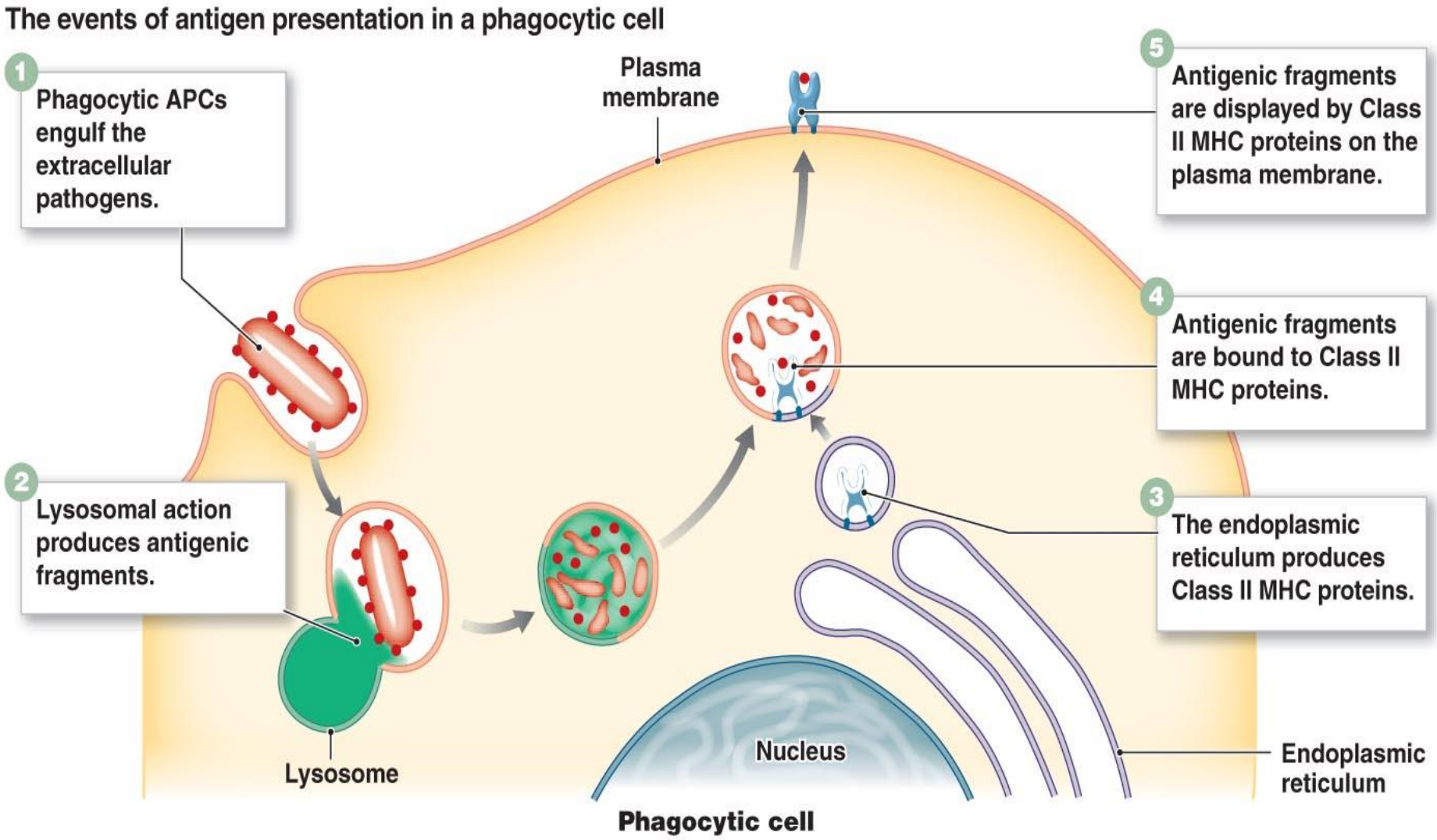
- APCs ingest foreign material, then present antigenic fragments on their cell surface where they are recognized by T-cells.
- T-cells respond to antigen only if it is displayed on plasma membrane along with MHC molecules.



- **These specialized cells include:**
  - **macrophages,**
  - **B lymphocytes, and**
  - **dendritic cells.**
- **They are distinguished by two properties:**
  - **they express class II MHC molecules on their membranes, and**
  - **they are able to deliver a co-stimulatory signal that is necessary for T_H-cell activation.**

MHC-Major histocompatibility complex

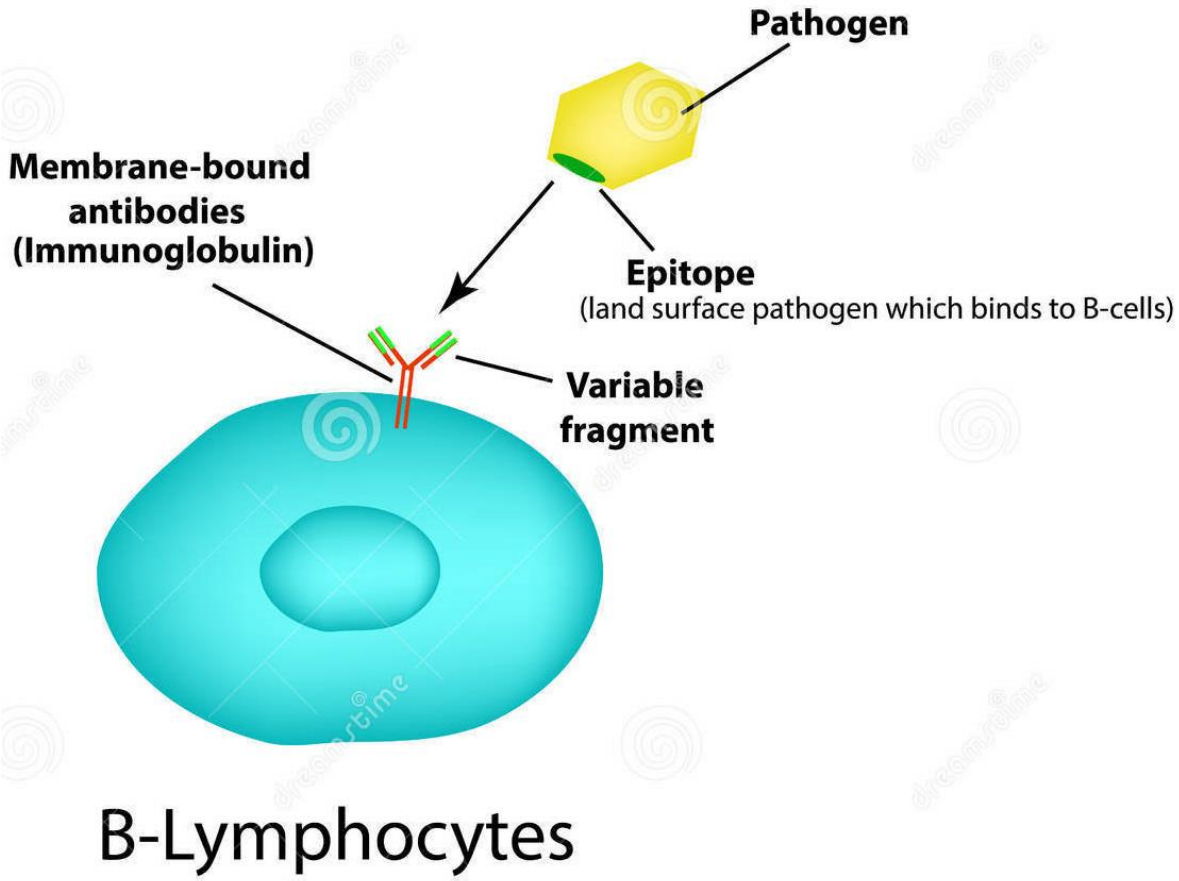
Phagocytic cell-events of antigen presentation



Humoral immunity- B-cells and antibodies

Antibody mediated immunity is called Humoral immunity

B-cells	Antibodies on their plasma membrane; express MHC-II molecule on surface	Generates humoral immune response. Clonal selection is the process of humoral response.



Humoral immune response - Clonal selection of B-cells

Adaptive defenses → Humoral immunity

Primary Response
(initial encounter with antigen)

Antigen

Antigen binding to a receptor on a specific B lymphocyte (B lymphocytes with non-complementary receptors remain inactive)

Proliferation to form a clone

B lymphoblasts

Plasma cells

Memory B cell

Secreted antibody molecules

Secondary Response
(can be years later)

Clone of cells identical to ancestral cells

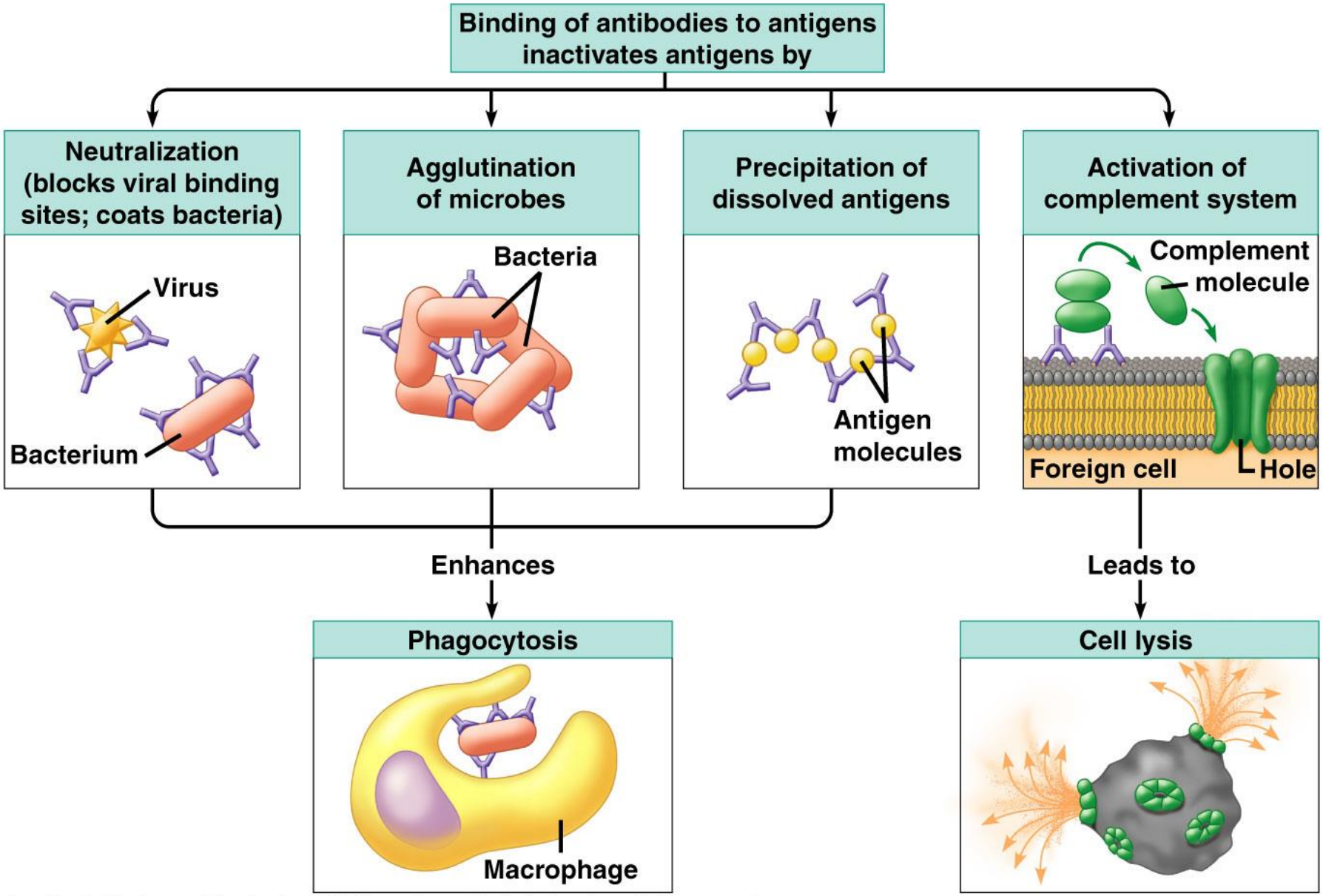
Subsequent challenge by same antigen

Plasma cells

Secreted antibody molecules

Memory B cells

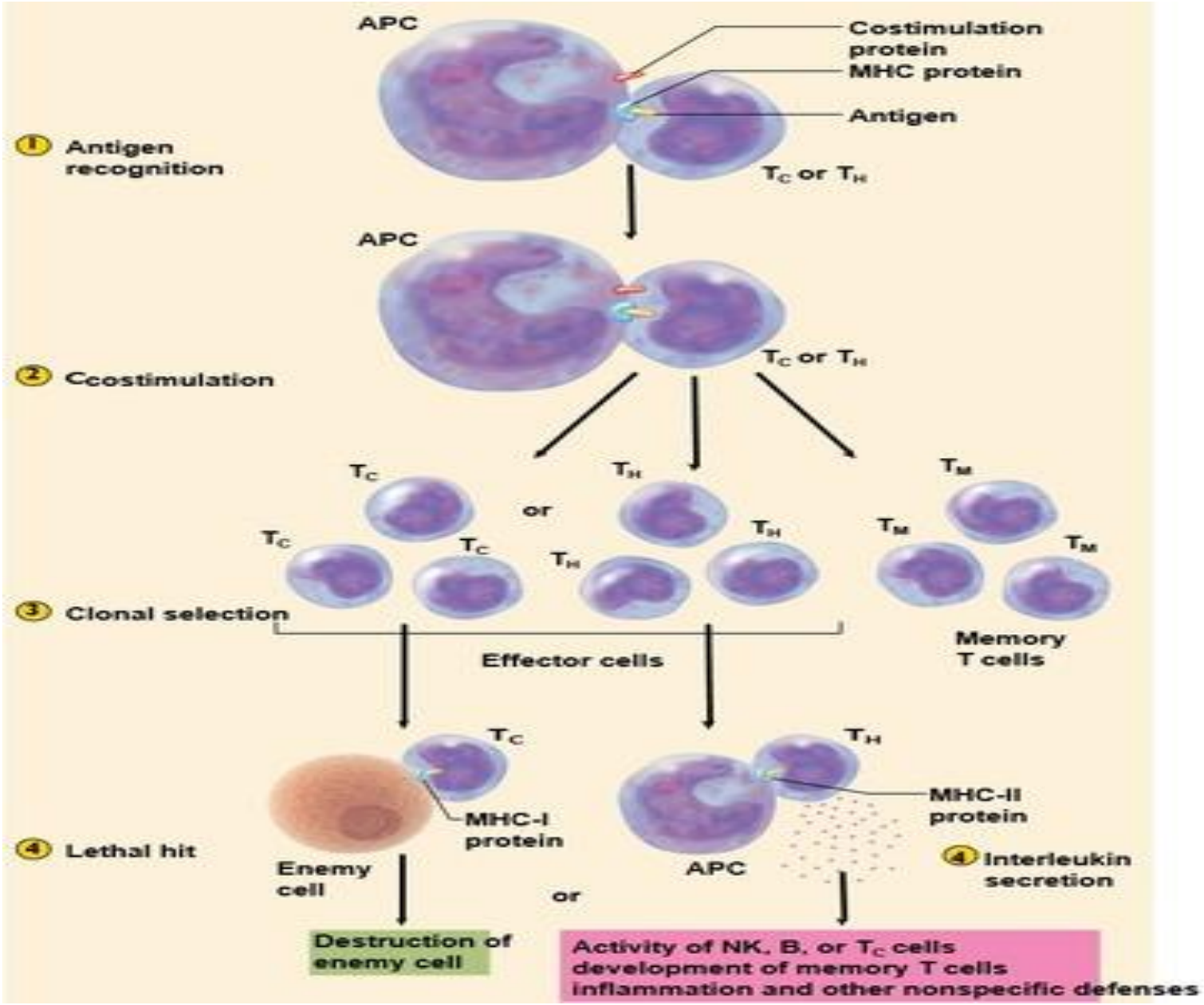
How antibodies inactivate antigens



T cells and their roles in defense

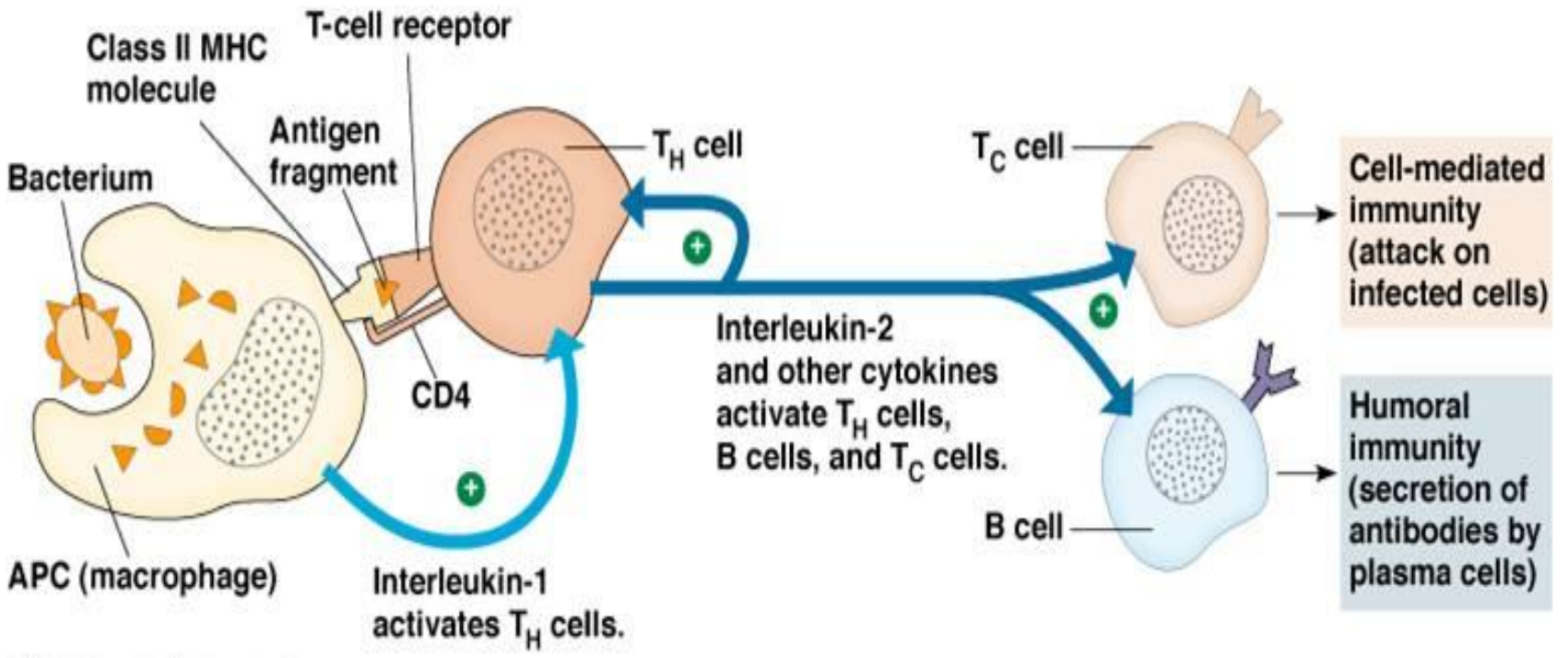
Lymphocytes	Surface markers	Functions
T-cells	T-cell receptor on the plasma membrane, **CD4+** surface marker on T-helper cell (T_H), **CD8+** surface marker on cytotoxic T cell (Tc)	Generates **cell mediated immune** response. **Their function include the regulation of other cells' actions and directly attack the host infected cells.**
1. Helper T cell	T-cell receptor , **CD4+** surface marker, interacts with the MHC-II molecule of APC	T_H cell stimulate other components of immune system by secreting signaling molecules that activate B cells, cytotoxic cells, and Phagocytes. **HIV** destroys helper T cells and therefore makes HIV infected people with opportunistic infections.
2. Cytotoxic T cell	**CD8+** surface marker, interacts with the MHC-I molecule of APC	Tc cells are cytotoxic or killer cell and recognizes pathogens more specifically. They kill virus infected cells, and cancerous cells by secreting proteins that damage their membranes and makes pores.
3. Suppressor T cell	Without their activity, immunity would certainly loose control and results in allergic reactions and autoimmune diseases.	Turn off the immune response once the pathogen is defeated.

Cell-mediated immune response - Clonal selection of T-cells

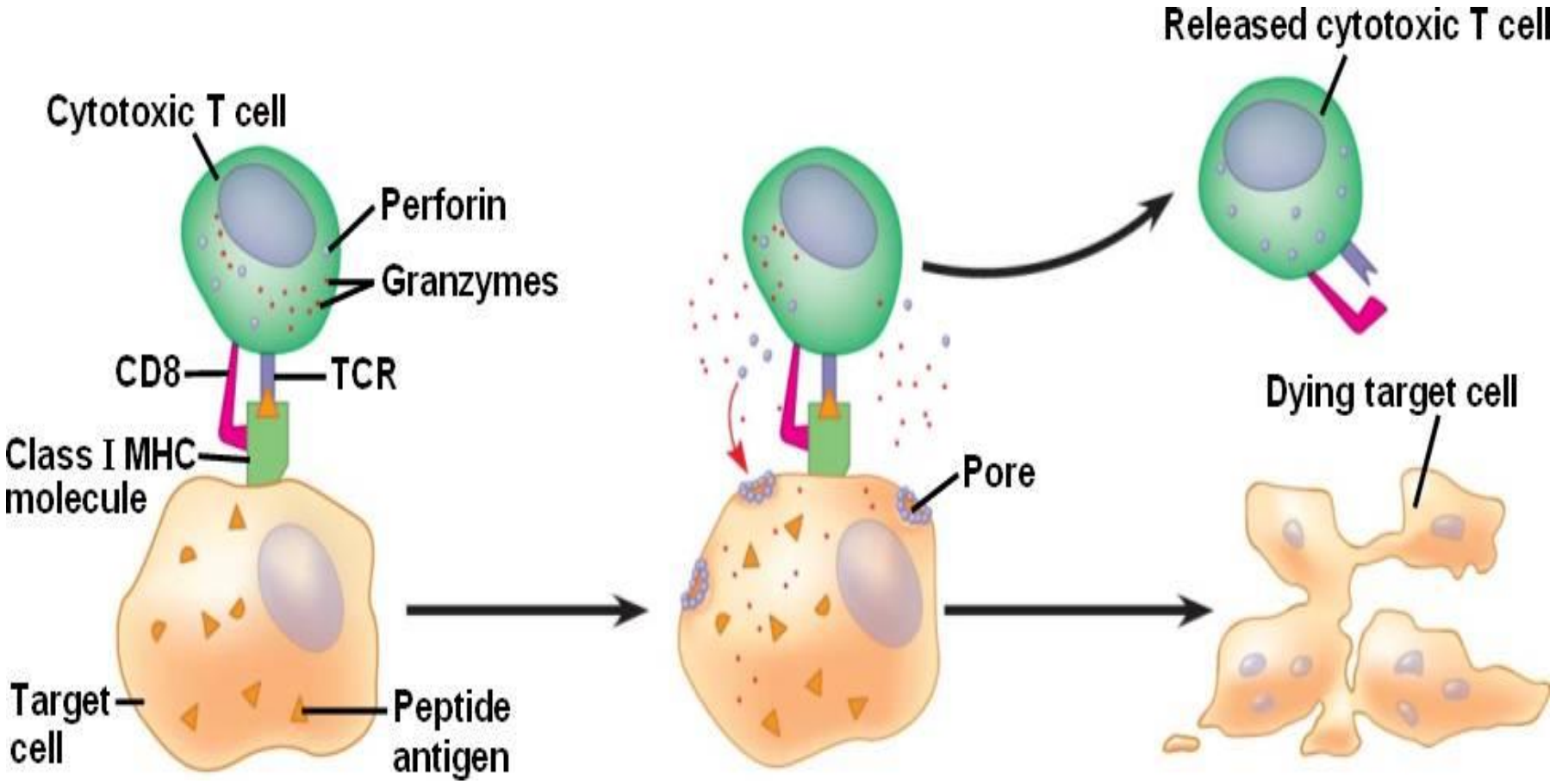


How helper T cell help in cell mediated immunity- Activating cytotoxic T-cell

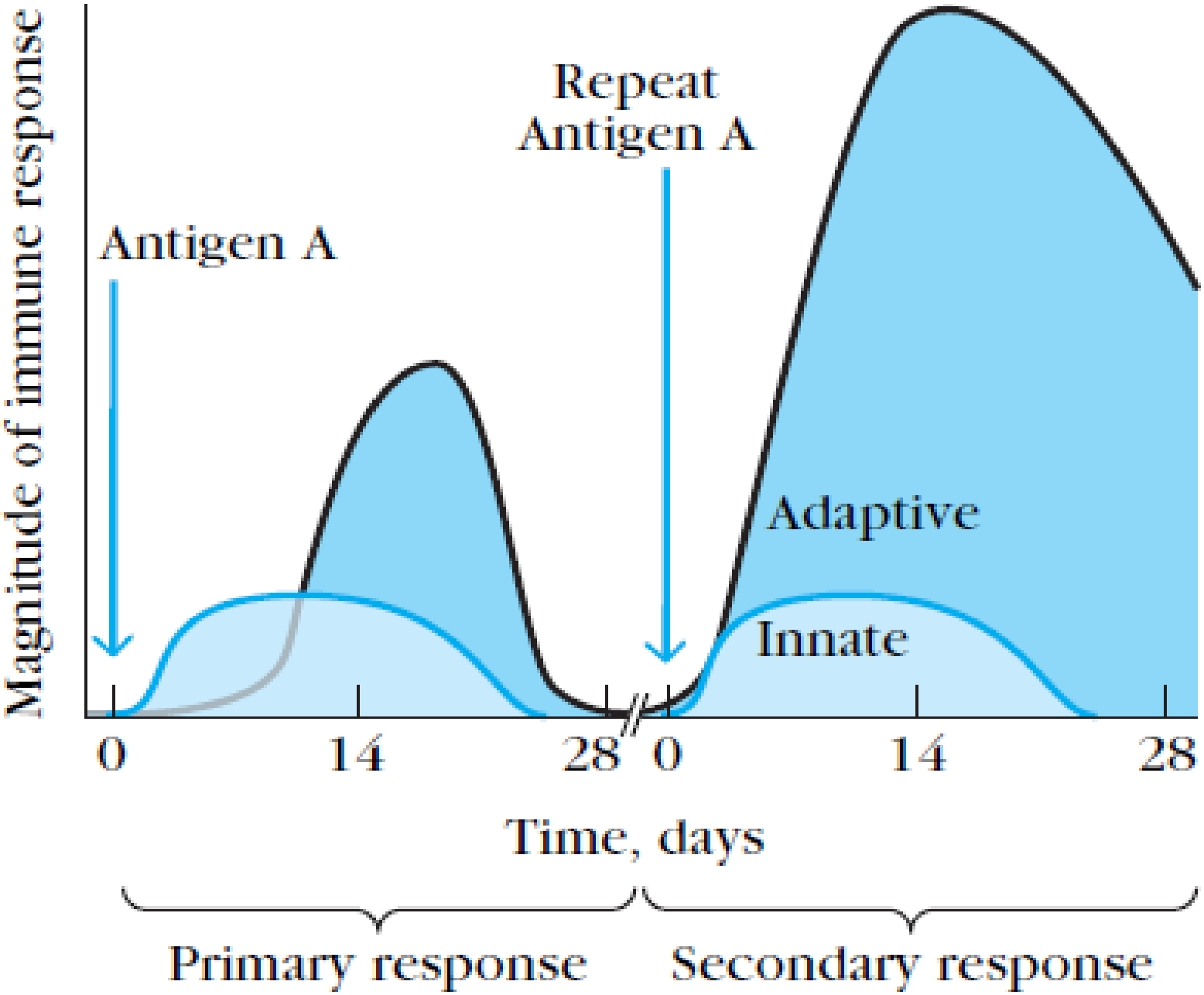
- **Helper T cells** are arguably the most important **cells** in adaptive **immunity**, as they are required for almost all adaptive **immune** responses.
- They not only **help** activate B **cells to** secrete antibodies and macrophages **to** destroy ingested microbes, but they also **help** activate **cytotoxic T cells (to kill infected target cells) and B cells (to secrete antibodies)**.

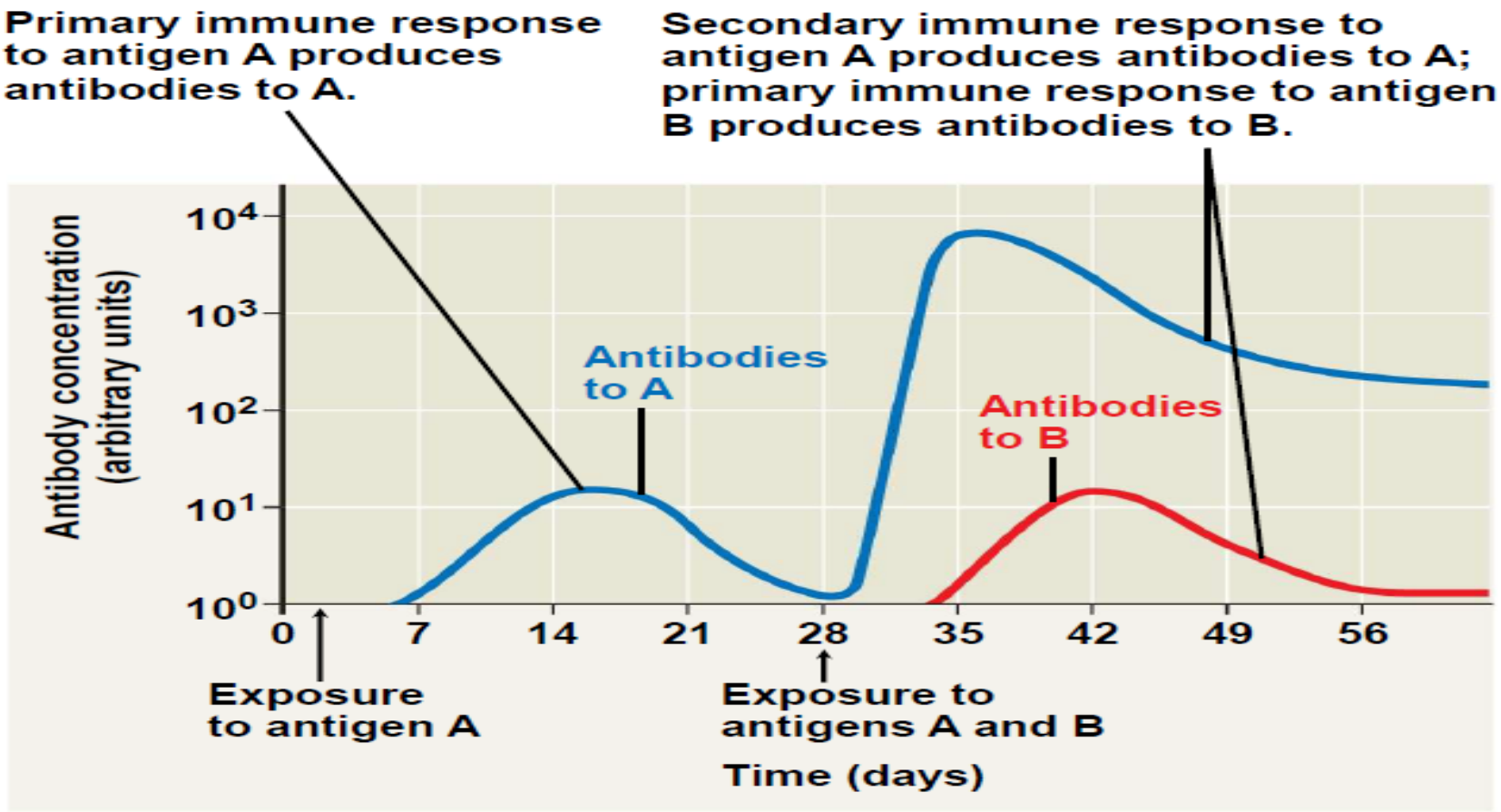


Cytotoxic Tc cell mediated immune response



Adaptive Immunity has Memory





Primary Immune Response

- This occurs when an antigen enters the body for the first time.
- It takes 5 days for the body to recognize the antigen and start production of antibodies.
- It takes another 10 to 15 days for the antibodies to build up.
- Most likely will get sick for a time

Secondary Immune Response

- This occurs if an antigen that has entered the body before
  - Same pathogen enters a second time.
- There is a shorter response time of only 1 to 2 days for antibody production
- May or may not get sick depending on the pathogen

Difference between innate and adaptive immunity

Innate immune system *

Physical barriers – skin, gastrointestinal tract, respiratory tract, nasopharynx, cilia, eyelashes, other body hair

Defence mechanisms – secretions, mucus, bile, gastric acid, saliva, tears, sweat

General immune responses – inflammation, complement, non-specific cellular responses

- Leukocytes – phagocytes, macrophages, mast cells, neutrophils, eosinophils, basophils, natural killer cells, dendritic cells
- Complement system [a] – opsonisation, chemotaxis, cell lysis, agglutination

Non-specific (will defend against anything that is identified as foreign or 'non-self') and **fast** (minutes or hours)

Adaptive ('acquired') immune system **

B cells – mature in bone marrow; contribute to antibodies that bind directly with specific antigens; contribute to humoral immunity [b]

T cells – mature in the thymus; express T cell receptors and CD4 or CD8 (not both); contributes to cell-mediated immunity [c]

- T cell receptors only recognise antigens bound to certain receptor molecules (major histocompatibility complex [MHC] class I or II)
- CD4 and CD8 contribute to T cell recognition and activation by binding to either MHCI or MHCII

Highly specific (identifies pathogens and differences in molecular structures) and **slow** (days)