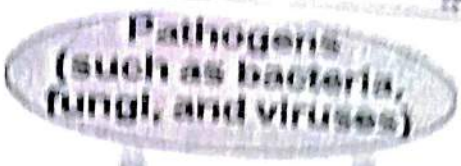
Animal Defenses Against Infection

-**Pathogens**, agents that cause disease, infect a wide range of animals, including humans.

-Two major kinds of defense have evolved to counter threats **innate immunity** and **acquired immunity**

1. Innate Immunity: present before any exposure to pathogens and is effective from the time of birth and involves nonspecific responses to pathogens

2. Acquired immunity (adaptive immunity): develops only after exposure to inducing agents such as microbes, toxins, or other foreign substances and involves a very specific response to pathogens



INNATE IMMUNITY **(all animals)** • Recognition of traits shared by broad ranges of pathogens, using a small set of receptors • Rapid response	**Barrier defenses:** Skin Mucous membranes Secretions **Internal defenses:** Phagocytic cells Natural killer cells Antimicrobial proteins Inflammatory response
ADAPTIVE IMMUNITY **(vertebrates only)** • Recognition of traits specific to particular pathogens, using a vast array of receptors • Slower response	**Humoral response:** Antibodies defend against infection in body fluids. **Cell-mediated response:** Cytotoxic cells defend against infection in body cells.

In Innate Immunity, Recognition and Response Rely on Shared Traits of Pathogens

-Both invertebrates and vertebrates depend on innate immunity to fight infection

-Vertebrates also develop acquired immune defenses

Innate Immunity of Invertebrates

1. In insects, an exoskeleton made of chitin forms the first barrier to pathogens

2. The digestive system is protected by low pH and lysozyme, an enzyme that digests microbial cell walls

3. Hemocytes circulate within hemolymph and carry out phagocytosis, the ingestion and digestion of foreign substances including bacteria

4. Hemocytes also secrete antimicrobial peptides that disrupt the plasma membranes of Bacteria

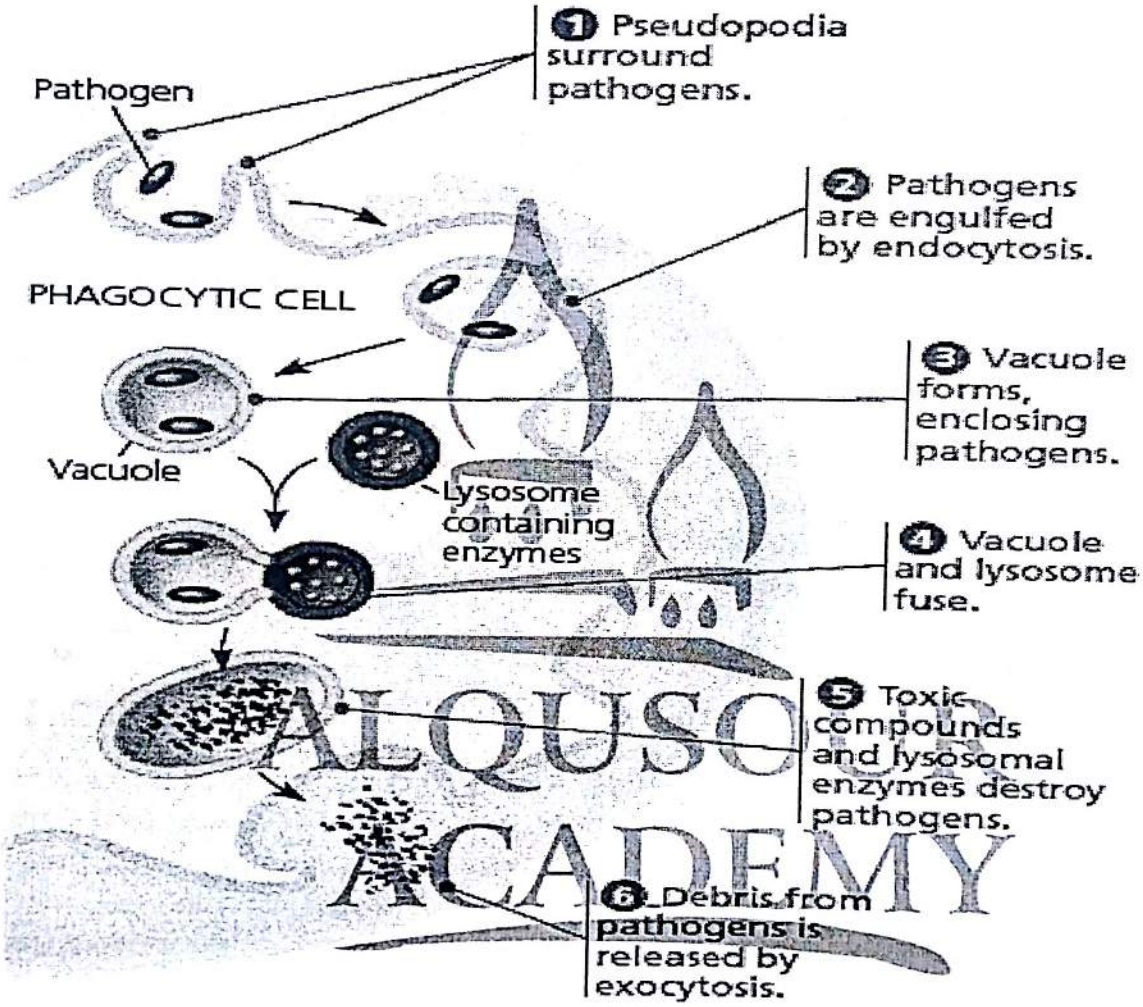
-The immune system recognizes bacteria and fungi by structures on their cell walls

-Innate immune responses are distinct for different classesof pathogens.

-For example, when the fungus *Neurospora crassa* infects a fruit fly, pieces of the fungal cell wall bind toa recognition protein.

-Together, the complex activates theprotein Toll, a receptor on the surface of hemocytes.

-Signal transduction from the Toll receptor to the cell nucleus leads to synthesis of a set of antimicrobial peptides active against fungi.



Innate Immunity of Vertebrates

-The immune system of mammals is the best understood of the vertebrates

-Innate defenses include barrier defenses, phagocytosis, antimicrobial peptides

-Additional defenses are unique to vertebrates: the inflammatory response and natural killer cells

1. Barrier Defenses

-**Intact skin and mucous membranes** form physical barriers that bar the entry of microorganisms and viruses

-**Certain cells of the mucous membranes produce mucus,** a viscous fluid that traps microbes and other particles

-**In the trachea, ciliated epithelial cells** sweep mucus and any entrapped microbes upward, preventing the microbes from entering the lungs

-**Secretions of the skin and mucous membranes** provide an environment that is often hostile to microbes

-**Secretions from the skin** give the skin a pH between 3 and 5, which is acidic enough to prevent colonization of many microbes

-Also include proteins such as lysozyme, an enzyme that digests the cell walls of many bacteria

2. Cellular Innate Defenses

-White blood cells (leukocytes) engulf pathogens in the body

-Groups of pathogens are recognized by TLR(**Toll Like Receptors)** which are a class of proteins that play a key role in the innate immune system

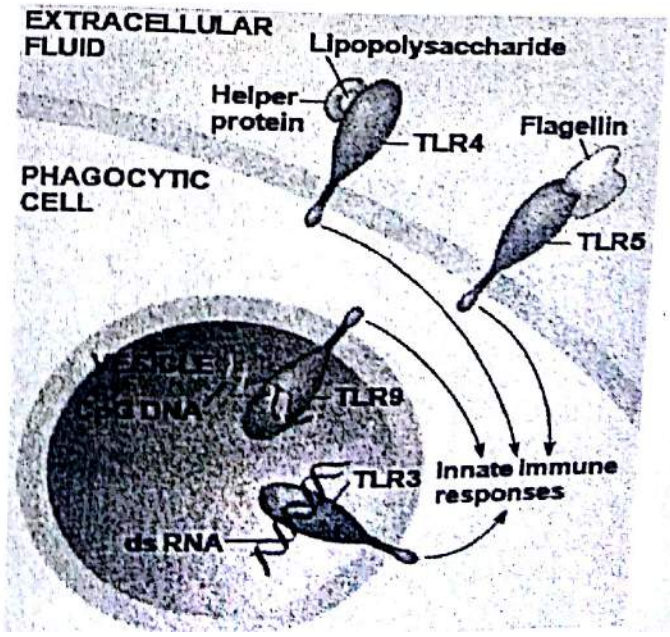
-They are single membrane-spanning non-catalytic receptors that recognize structurally conserved molecules derived from microbes.

-Once these microbes have breached physical barriers such as the skin or intestinal tract mucosa, they are recognized by TLRs which activates immune cell responses

-TLR3, on the inner surface of vesicles formed by endocytosis, binds to double-stranded RNA, a form of nucleic acid characteristic of certain viruses.

-Similarly,TLR4, located on immune cell plasma membranes, recognizes lipopolysaccharide, a type of molecule found on the surface of many bacteria

-TLR5 recognizes flagellin, the main protein of bacterial flagella.



-Four Types of Phagocytic Cells

1. Neutrophils (60-70% of total WBCs): attracted by chemical signals (chemotaxis), they enter infected tissue by amoeboid movement

2. Macrophages: specific type of phagocyte that can be found migrating through the body and can be found in various organs of the lymphatic system and comprise about 5% of WBC

3. Eosinophils: have lower phagocytic activity and are crucial against intracellular parasites such as *schistosoma mansoni* by secreting enzymes damaging the parasite

4. Dendritic cells: can ingest microbes but their major role to stimulate development of acquired immunity

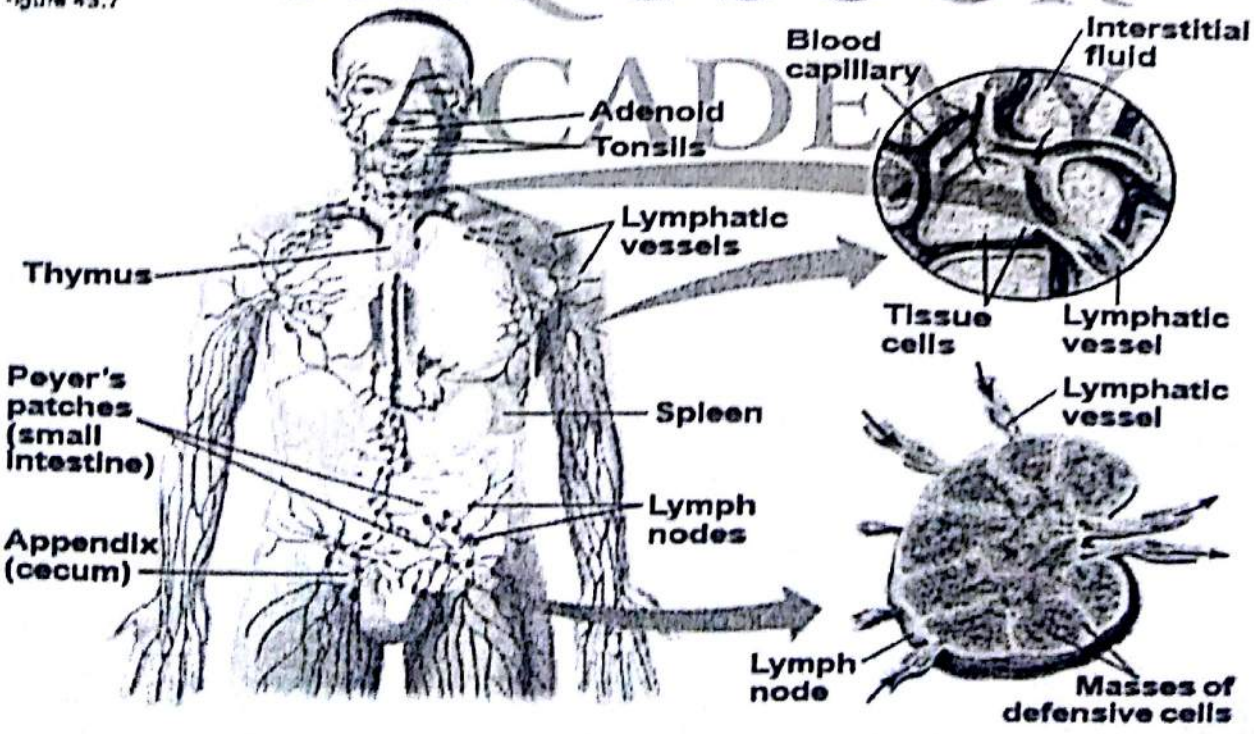
3.Natural killer cells

-These circulate through the body and detect abnormal cells

-They release chemicals leading to cell death, inhibiting the spread of virally infected or cancerous cells

4. The lymphatic system

Plays an active role in defending the body from pathogens



5. Antimicrobial Peptides and Proteins

-Numerous proteins function in innate defense by attacking microbes directly of by impeding their reproduction

-About 30 proteins make up the complement system which can cause lysis of invading cells and help trigger inflammation

-Interferons provide innate defense against viruses and help activate macrophages

6. Inflammatory Response

-One important inflammatory signaling molecule is **histamine**, which is stored in **mast cells**.

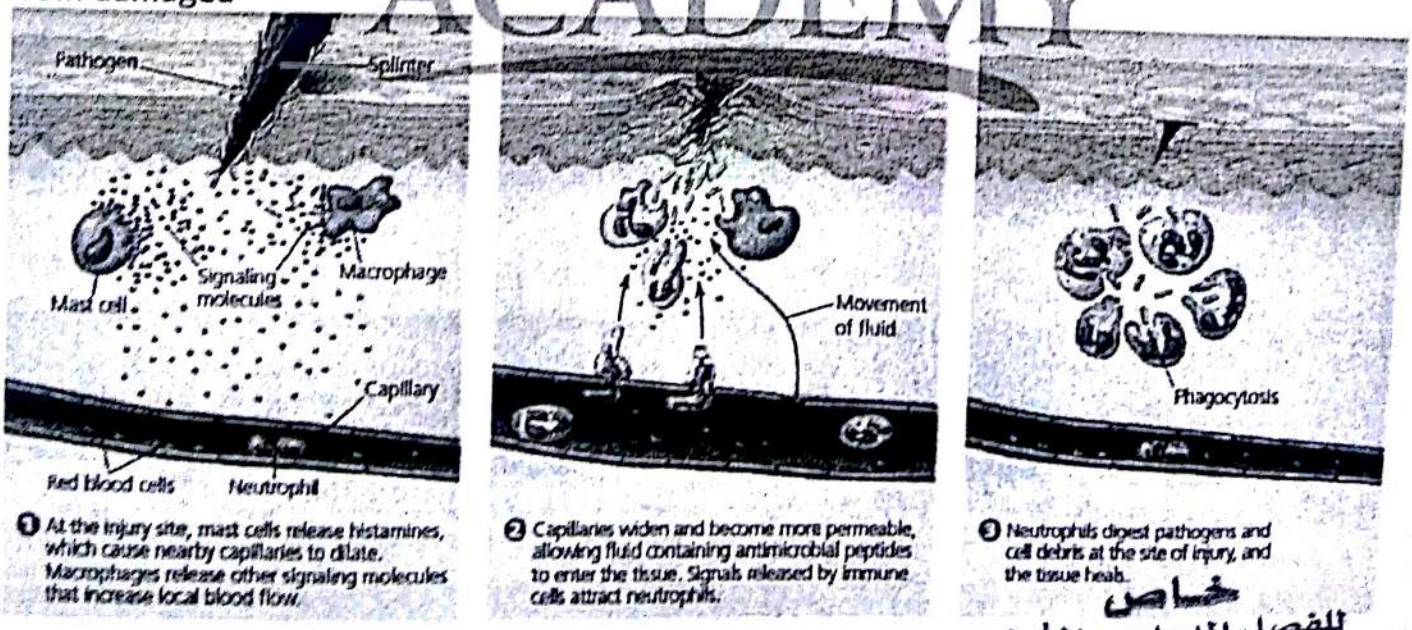
- Histamine released at sites of damage triggers nearby blood vessels to dilate and become more permeable. The dilated capillaries leak fluid into neighboring tissues, causing localized swelling.

-Macrophages and neutrophils also participate in the inflammatory response. Once activated, these cells discharge ***cytokines***

-The released cytokines promote blood flow to the site of injury or infection.

-The increase in local blood supply produces the redness and increased skin temperature typical of the inflammatory response.

-Enhanced blood flow to the site helps deliver antimicrobial peptides result in accumulation of *pus*, a fluid rich in white blood cells, dead pathogens, and cell debris from damaged



1 At the injury site, mast cells release histamines, which cause nearby capillaries to dilate. Macrophages release other signaling molecules that increase local blood flow.

2 Capillaries widen and become more permeable, allowing fluid containing antimicrobial peptides to enter the tissue. Signals released by immune cells attract neutrophils.

3 Neutrophils digest pathogens and cell debris at the site of injury, and the tissue heals.

-A minor injury or infection causes a local inflammatory response, but severe tissue damage or infection may lead to a response that is systemic (throughout the body).

-In sever infections, e.g. meningitis or appendicitis, the bone marrow may be stimulated to release more neutrophils by molecules emitted by injured cells and several fold leukocytes will be produced within hours

-Another systemic inflammatory response is fever. **Fever** may develop in response to toxins released by pathogens, or due to **pyrogens** released by certain leukocytes, which set the body thermostat at higher temperature

-Moderate fever inhibits the growth of some microorganisms and also facilitate phagocytosis and speed up tissue repair. However, sever fever is dangerous

-Certain pathogens can induce an overwhelming immune response causing what is called **septic shock** that is characterized by high fever and low blood pressure and poor blood flow through capillaries.

Evasion of Innate Immunity by Pathogens

-Some pathogens avoid destruction by modifying their surface to prevent recognition or by resisting breakdown following phagocytosis

-Tuberculosis (TB) is one such disease and kills more than a million people a year Which resistant to lysozome

In acquired Immunity, Lymphocytes Receptors Provide Pathogen-Specific Recognition

-Acquired immunity is the body's second major kind of defense, involves the activity of white blood cells called lymphocytes

-Lymphocytes that mature in the thymus above the heart are called **T cells**, and those that mature in bone marrow are called **B cells**

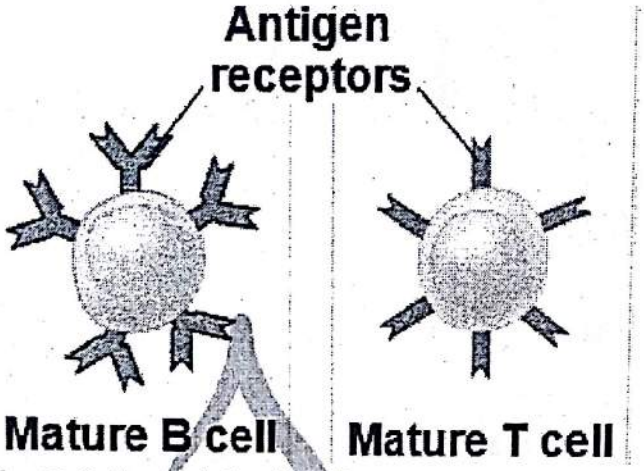
-Lymphocytes contribute to immunological memory, an enhanced response to a foreign molecule encountered previously

-Cytokines are secreted by macrophages and dendritic cells to recruit and activate Lymphocytes

-Antigens are substances that can elicit a response from a B or T cell

-Exposure to the pathogen activates B and T cells with **antigen receptors** specific for parts of that pathogen

-The small accessible part of an antigen that binds to an antigen receptor is called an **epitope** , A single antigen usually has several epitopes each binding a receptor with a different specificity.



Antigen Recognition by B Cells and Antibodies

-Each B cell antigen receptor is a Y-shaped molecule consisting of four polypeptide chains: two identical **heavy chains** and two identical **light chains**, with disulfide bridges linking the chains together

- A transmembrane regionnear one end of each heavy chain anchors the receptor in the cell's plasma membrane.

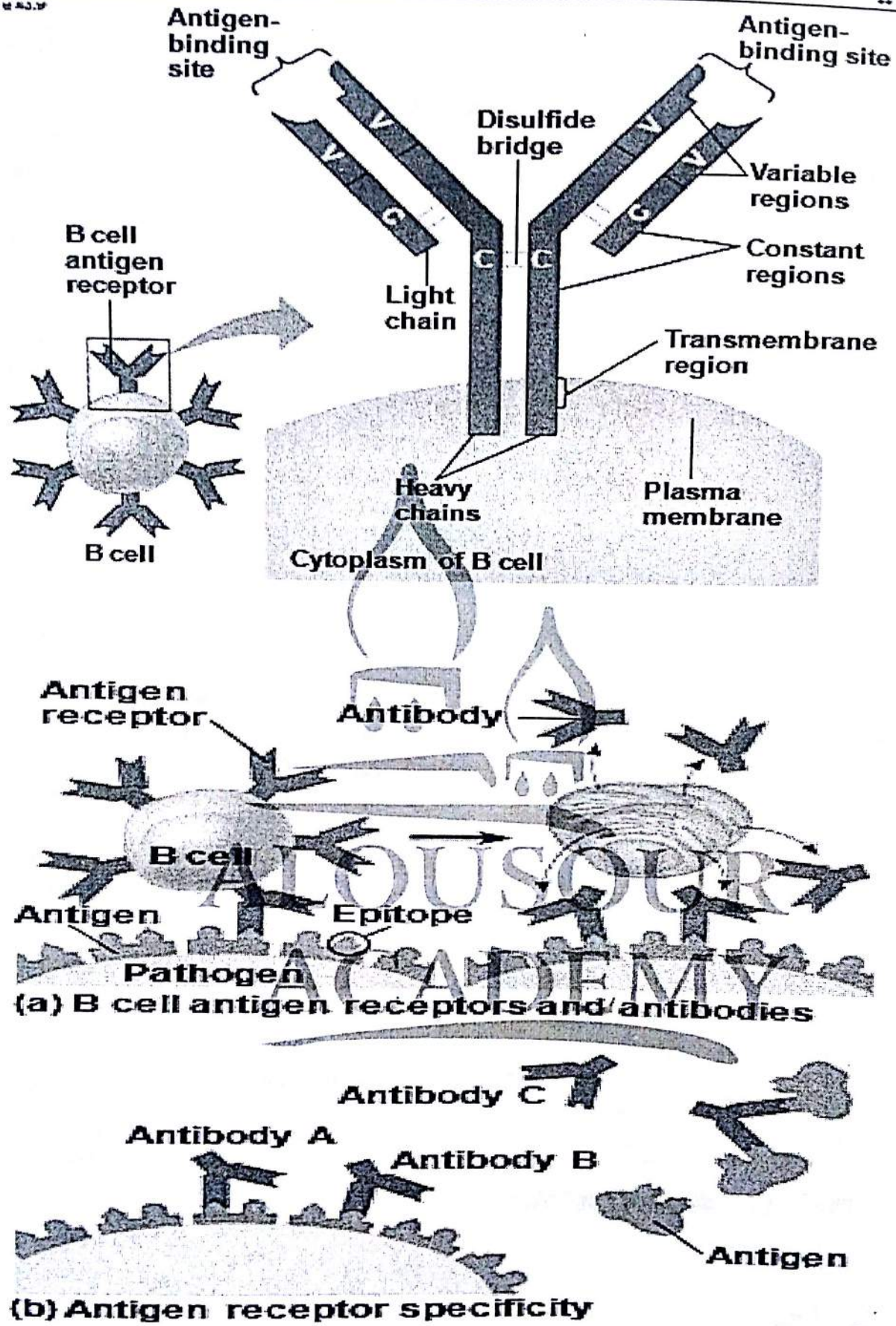
-The light and heavy chains each have a *constant (C)region*, The C region includes the cytoplasmic tail and transmembrane region of the heavy chain and all of the disulfide bridges.

-Within the two tips of the Y shape, each chain has a *variable (V) region*, so named because its amino acid sequence varies extensively from one B cell to another. Together.

-parts of a heavy-chain V region and a light-chain V region form an asymmetric binding site for an antigen. each B cell antigen receptor has two identical antigen-binding sites.

-Binding of a B cell antigen receptor to an antigen is an early step in B cell activation leading to formation of cells that secrete a soluble form of the receptor This secreted protein is called an **antibody**, also known as an **immunoglobulin (Ig)**.

-Secreted antibodies are similar to B cell receptors but lack transmembrane regions that anchor receptors in the plasma membrane



Antigen Recognition by T Cells

-For a T cell, the antigen receptor consists of two different polypeptide chains, an *α chain* and a *6 chain*, linked by a disulfide bridge

At the outer tip of the molecule, the variable (V) regions of the α and β chains together form a single antigen-binding site. The remainder of the molecule is made up of the constant (C) regions.

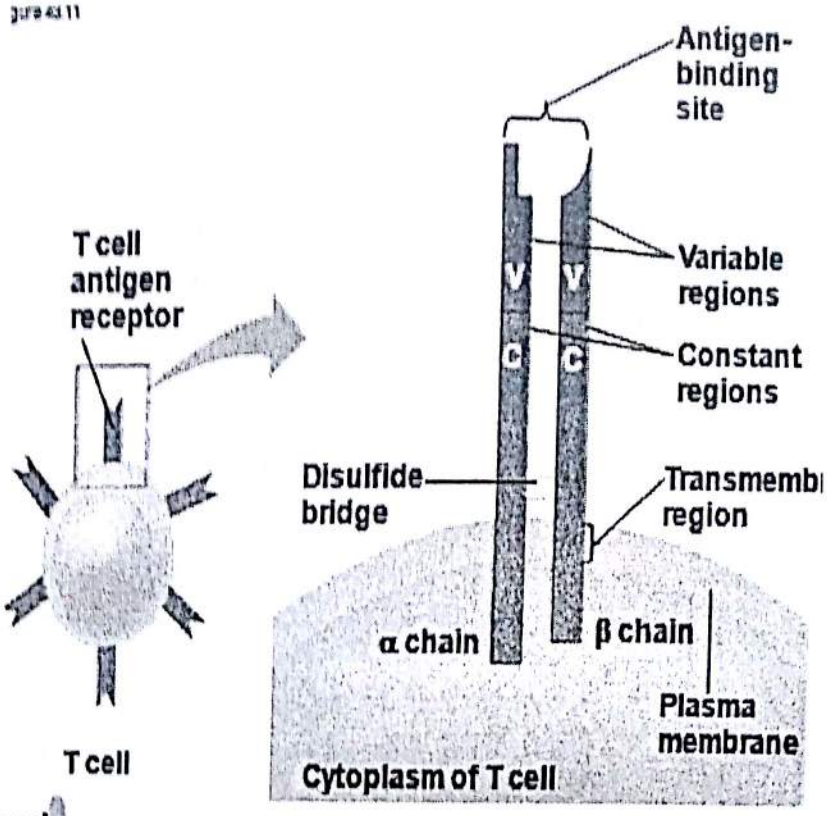
-The antigen receptors of T cells bind only to fragments of antigens that are displayed, or presented, on the surface of host cells.

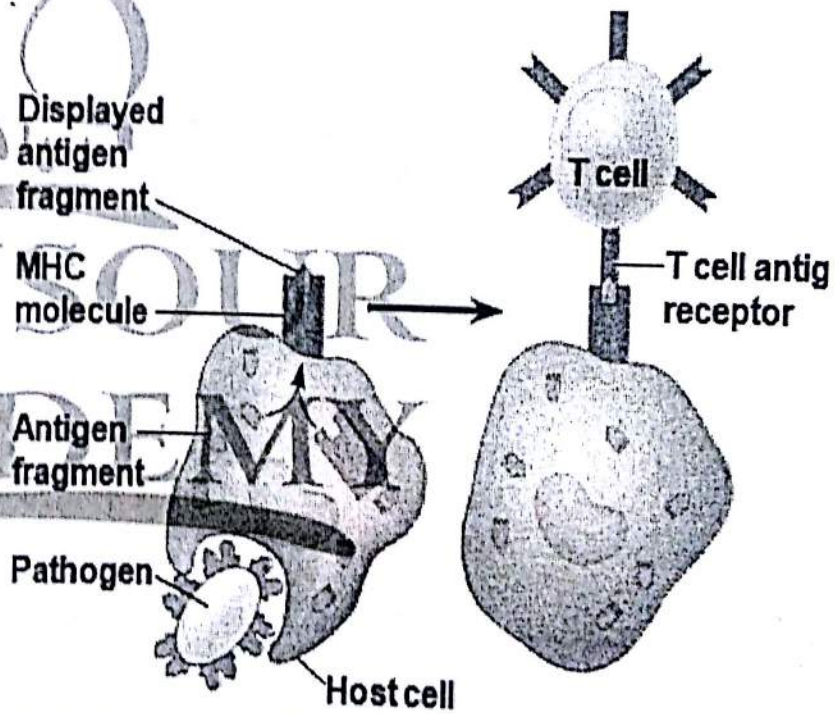
The host protein that displays the antigen fragment on the cell surface is called a **major histocompatibility complex (MHC) molecule.**

-Inside the host cell, enzymes cleave the antigen into smaller peptides. Each peptide, called an *antigen fragment*, then binds to an MHC molecule inside the cell.

-Movement of the MHC molecule and bound antigen fragment up to the cell surface results in **antigen presentation**

-A T cell can then bind both the antigen fragment and the MHC molecule, and this interaction is necessary for the T cell to participate in the adaptive immune response





(a) Antigen recognition by a T cell

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B Cell and T Cell Development

-The adaptive immune system has four major characteristics

1. Diversity of lymphocytes and receptors
2. Self-tolerance; lack of reactivity against an animal's own molecules
3. B and T cells proliferate after activation
4. Immunological memory

Lymphocyte Development

-**Lymphocytes** arise from pluripotent stem cells in the bone marrow

-Newly formed lymphocytes are all alike but they later develop into B cells or T cells, depending on where they continue their maturation

-**There are three events in the life of a lymphocyte:** first 2 events are: Lymphocyte maturation of B or T, and the third event is the lymphocyte encounter with an antigen that leads to its activation, proliferation and differentiation, a process called **clonal selection**

Generation of B Cell and T Cell Diversity

Each person makes more than 1 million different B cell antigen receptors and 10 million different T cell antigen receptors. Yet there are only about 20,000 protein-coding genes in the human genome

-By combining variable elements, the immune system assembles many different receptors from a much smaller collection of parts.

To understand the origin of receptor diversity, we will take the example of immunoglobulin (Ig) gene that encodes its light chain, because all B and T cell antigen receptor genes undergo very similar transformations.

-A receptor light chain is encoded by three gene segments: a variable (*V*) segment, a joining (*J*) segment, and a constant (*C*) segment.

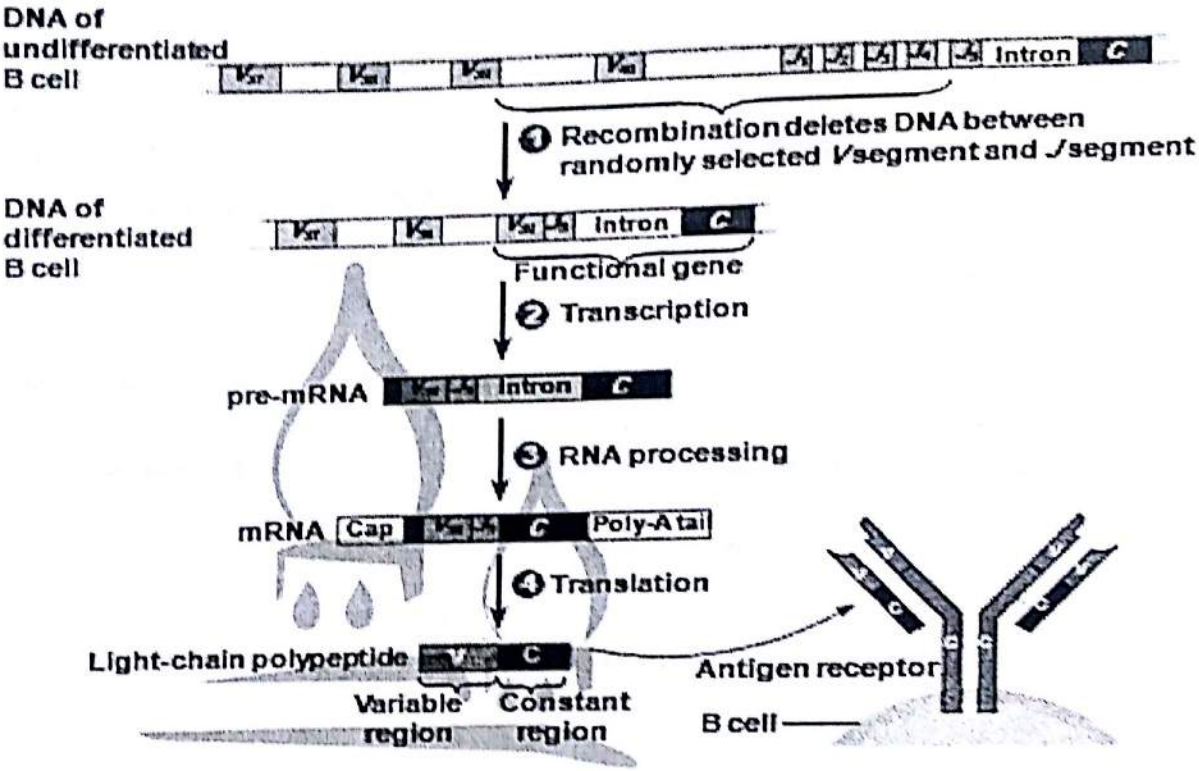
-The *V* and *J* segments together encode the variable region of the receptor chain, while the *C* segment encodes the constant region.

-The light-chain gene contains a single *C* segment, 40 different *V* segments, and 5 different *J* segments. These alternative copies of the *V* and *J* segments are arranged within the gene in a series

-A functional gene is built from one copy of each type of segment, the pieces can be combined in 200 different ways (40 *V* * 5 *J* * 1 *C*).

-Many different chains can be produced from the same gene by rearrangement of the DNA

-Rearranged DNA is transcribed and translated and the antigen receptor formed.



Origin of Self-Tolerance

-Antigen receptors are generated by random rearrangement of DNA

-As lymphocytes mature in bone marrow or the thymus, they are tested for self-reactivity

-Some B and T cells with receptors specific for the body's own molecules are destroyed by apoptosis, or programmed cell death, the remainder are rendered nonfunctional

Proliferation of B Cells and T Cells

-In the body there are few lymphocytes with antigen receptors for any particular epitope

-In the lymph nodes, an antigen is exposed to a steady stream of lymphocytes until a match is made

-This binding of a mature lymphocyte to an antigen initiates events that activate the lymphocyte

-Once activated, a B or T cell undergoes multiple cell divisions

-This proliferation of lymphocytes is called **clonal selection**

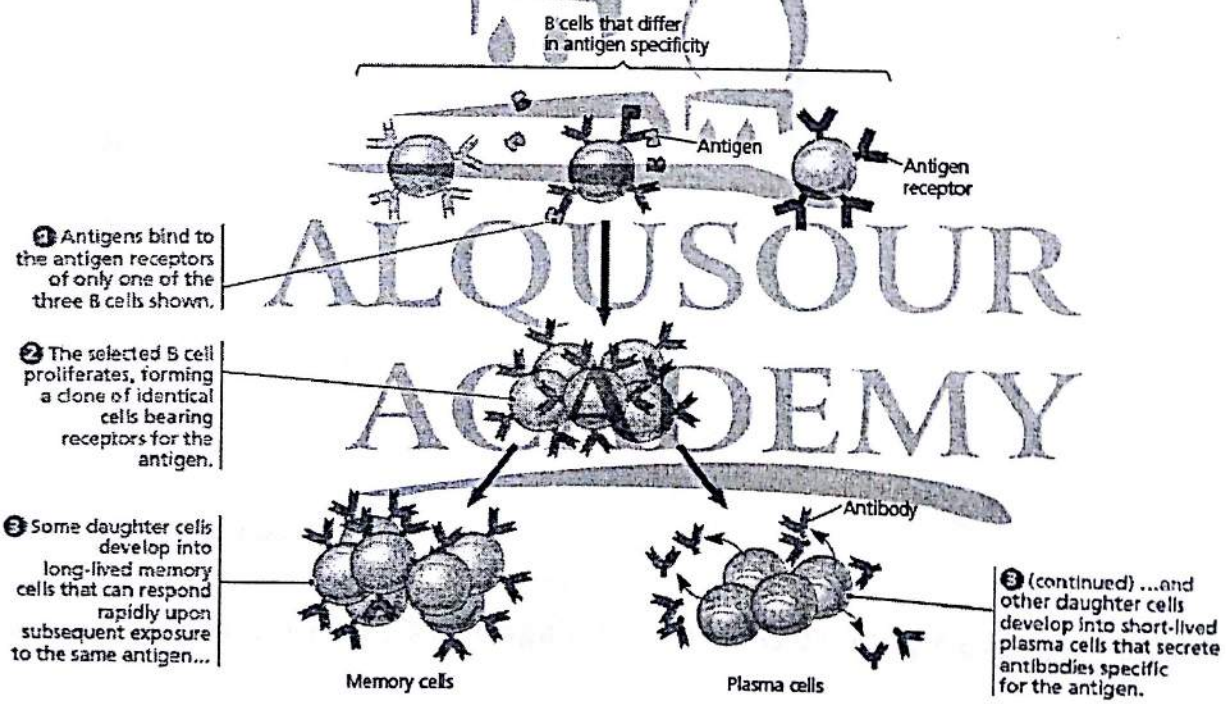
-Two types of clones are produced:

1. Short-lived activated **effector cells** that act immediately against the antigen
2. Long-lived **memory cells** that can give rise to effector cells if the same antigen is encountered again

-clonal selection is called so because an encounter with an antigen *selects* which lymphocyte will divide to produce a *clonal* population of thousands of cells specific for a particular epitope.

-The effector forms of B cells are **plasma cells**, which secrete antibodies

-The effector forms of T cells are helper T cells andcytotoxic T cells.



Primary Immune Response

-Is the proliferation of lymphocytes to form effecter cells specific to an antigen during the body's first exposure to the antigen

-There is 10-17 days lag period between initial exposure and maximum production of effecter cells mainly IgM

-The lymphocytes selected by the antigen are differentiated into B and T cells during the lag period

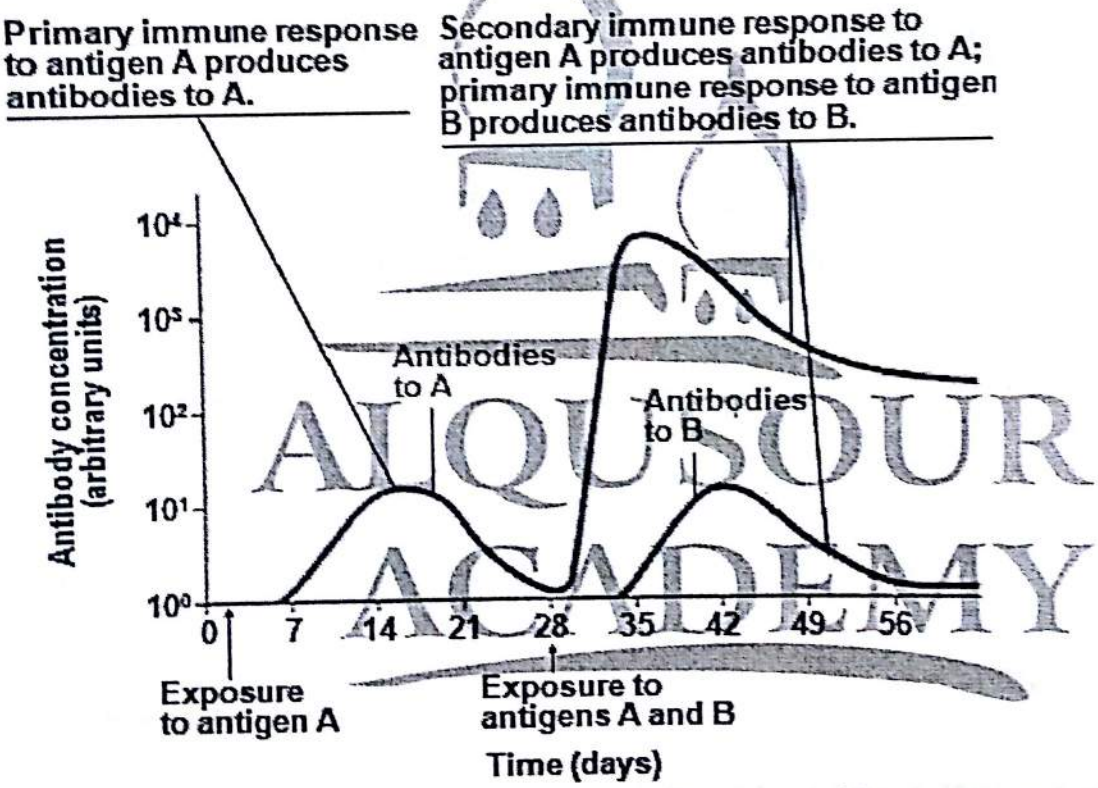
-Activated B cells give rise to effecter cells called *plasma cells* which secrete antibodies (humoral response)

Secondary Immune Response

-Memory cells facilitate a faster, more efficient response that takes 2-7 days, IgG Mainly

-Secondary response leads to the production of very high amount of antibodies that have more affinity than the antibodies produced in the primary response

-The immunes system capacity to generate secondary immune response is called **Immmunological memory**

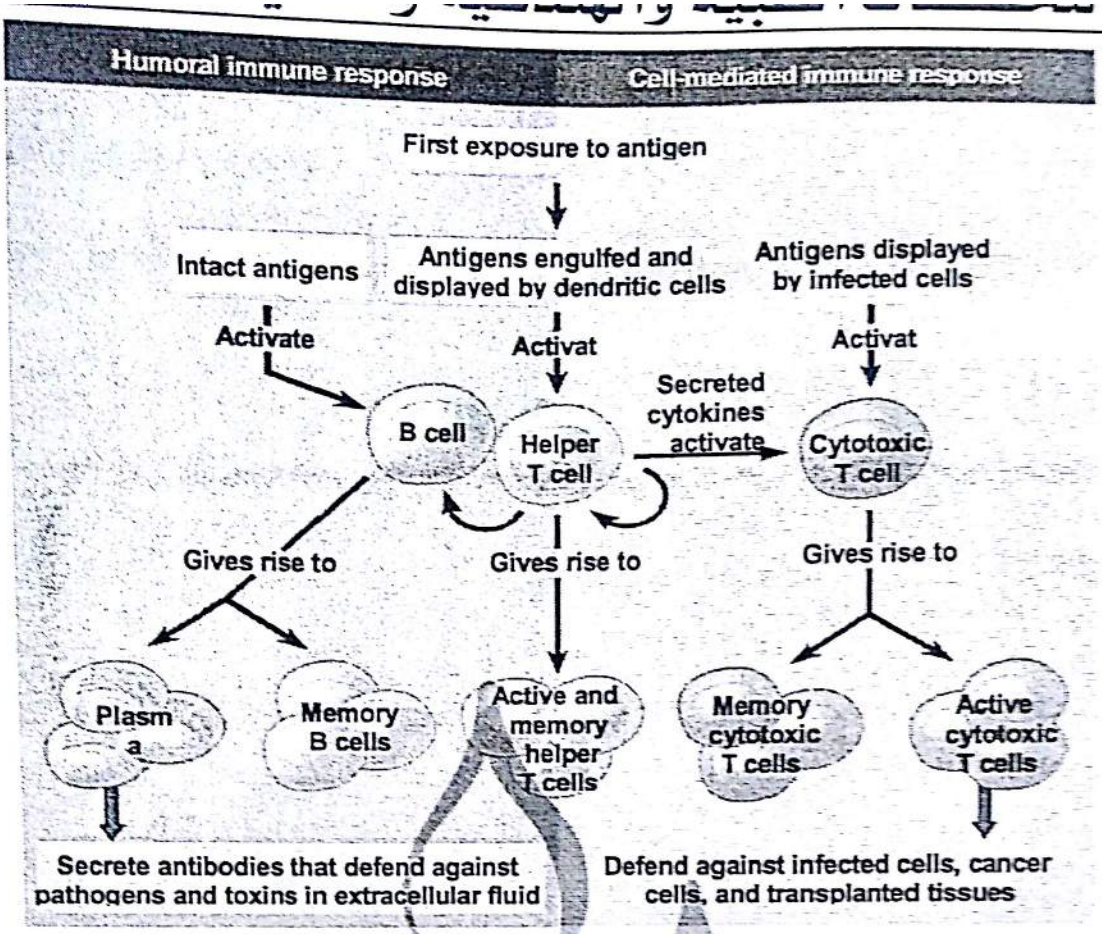


Adaptive immunity defends against infection of body fluids and body cells

-Acquired immunity includes two branches:

1. The humoral immune response involves the activation and clonal selection of B cells, resulting in the production of secreted antibodies

2. In the cell-mediated immune response specialized T cells destroy affected host cells



Helper T Cells: A Response to Nearly All Antigens

-A type of T cell called a **helper t** cell triggers both the humoral and cell-mediated immune responses

-Signals from helper T cells initiate production of antibodies that neutralize pathogens and activate T cells that kill infected cells

-Two requirements must be met for a helper T cell to activate adaptive immune responses:

First: a foreign molecule must be present that can bind specifically to the antigen receptor of the T cell.

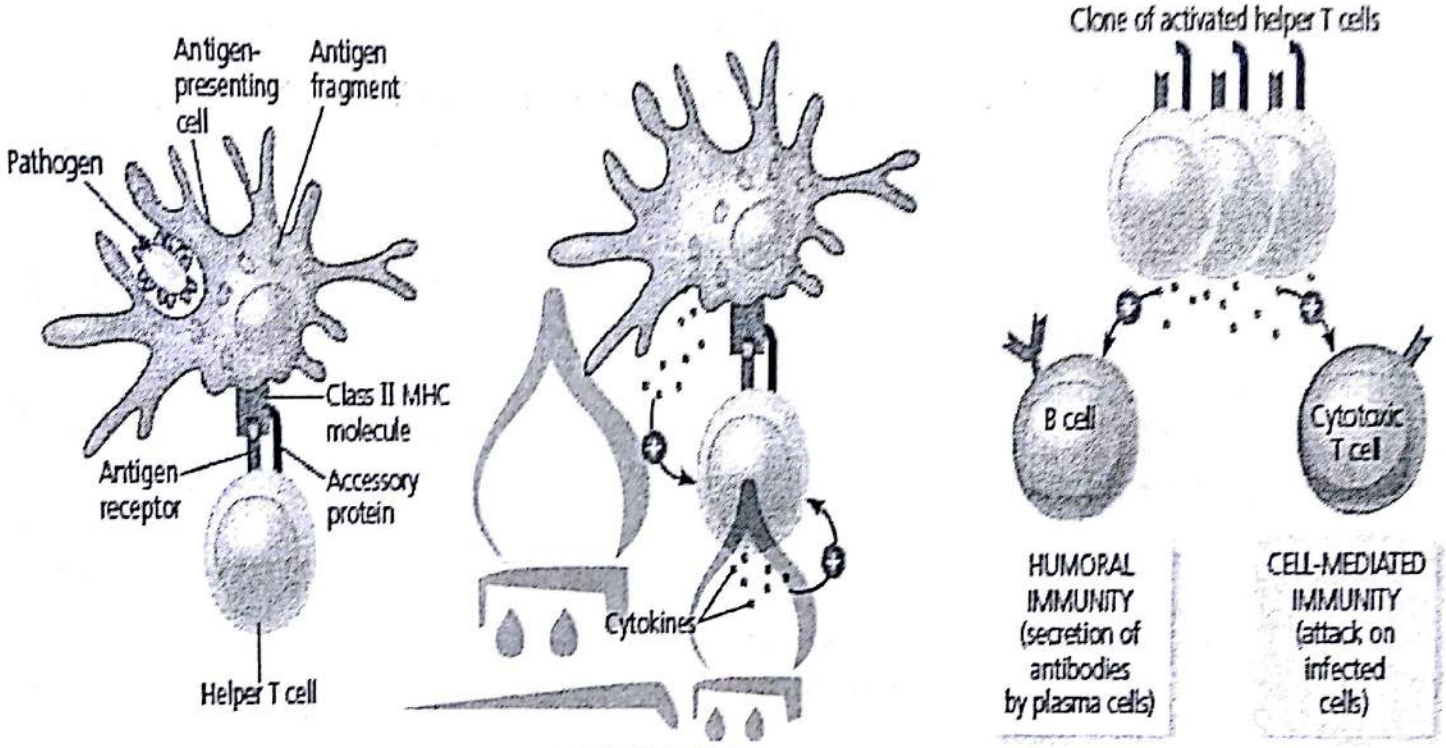
Second: this antigen must be displayed on the surface of an **antigen-presenting cell,** The antigen presenting cell can be a dendritic cell, macrophage, or B cell.

-There 2 types of MHC, Most body cells have only the class I MHC molecules, but antigen-presenting cells have class I and class II MHC molecules.

-Class II molecules provide a molecular signature by which an antigen-presenting cell is recognized.

- T cells produce CD4, a surface protein that enhances their binding to class II MHC molecule–antigen complexes on antigen-presenting cells, then signals are exchanged between the two cells

-The helper T cell is activated, proliferates, and forms a clone of helper T cells, which then activate the appropriate B cells



1. An antigen-presenting cell engulfs a pathogen, degrades it, and displays antigen fragments complexed with class II MHC molecules on the cell surface. A specific helper T cell binds to this complex via its antigen receptor and an accessory protein (called CD4).
2. Binding of the helper T cell promotes secretion of cytokines by the antigen-presenting cell. These cytokines, along with cytokines from the helper T cell itself, activate the helper T cell and stimulate its proliferation.
3. Cell proliferation produces a clone of activated helper T cells. All cells in the clone have receptors for the same antigen fragment complex with the same antigen specificity. These cells secrete other cytokines, which help activate B cells and cytotoxic T cells.

Cytotoxic T Cells: A Response to Infected Cells

-Cytotoxic T cells make CD8, a surface protein that greatly enhances the interaction between a target cell and a cytotoxic T cell

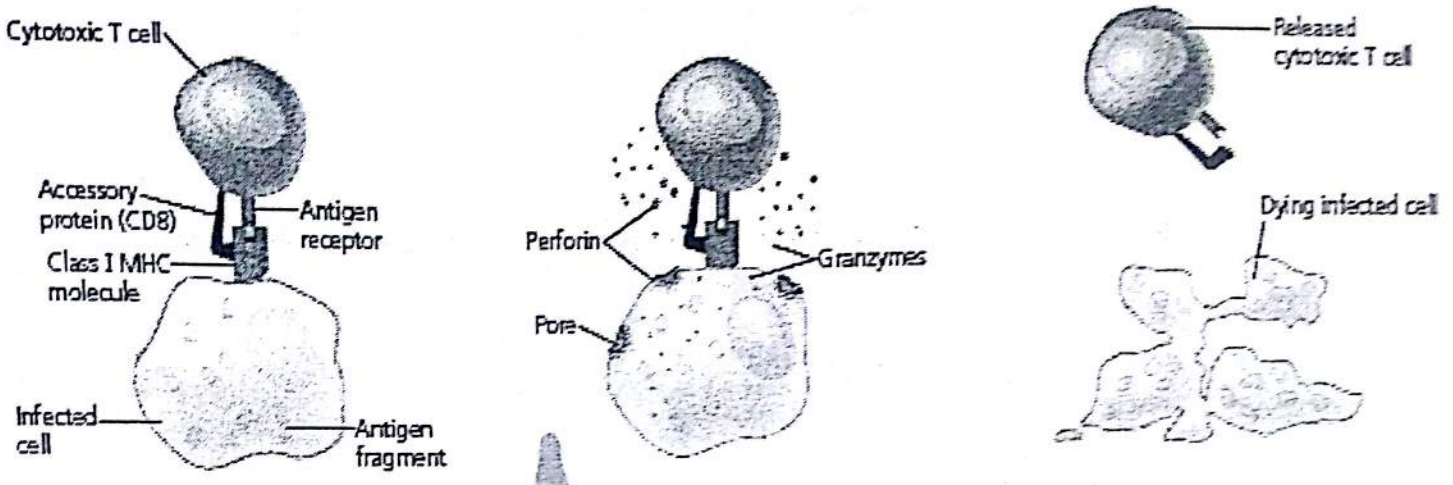
-The role of class I MHC molecules and the CD8 is similar to that for class II MHC and CD4

-Cytotoxic T cells bind to viral infected cells , cancer cells, and transplanted tissues

-Binding to a class I MHC complex on an infected body cell activates a cytotoxic T cell and differentiates it into an active killer

-Nearby helper T cells secrete cytokines that promote this activation

-The activated cytotoxic T cell secretes proteins that destroy the infected target cell and present its fragments to circulating antibodies for long immunity



1. An activated cytotoxic T cell binds to a class I MHC–antigen fragment complex on an infected cell via its antigen receptor and an accessory protein (called CD8).
2. The T cell releases perforin molecules, which form pores in the infected cell membrane, and granzymes, enzymes that break down proteins. Granzymes enter the infected cell by endocytosis.
3. The granzymes initiate apoptosis within the infected cell, leading to fragmentation of the nucleus and cytoplasm and eventual cell death. The released cytotoxic T cell can attack other infected cells.

B Cells: A Response to Extracellular Pathogens

-Antigens that elicit a humoral response are typically proteins and polysaccharides present on surface of bacteria or from pollens or transplanted tissues

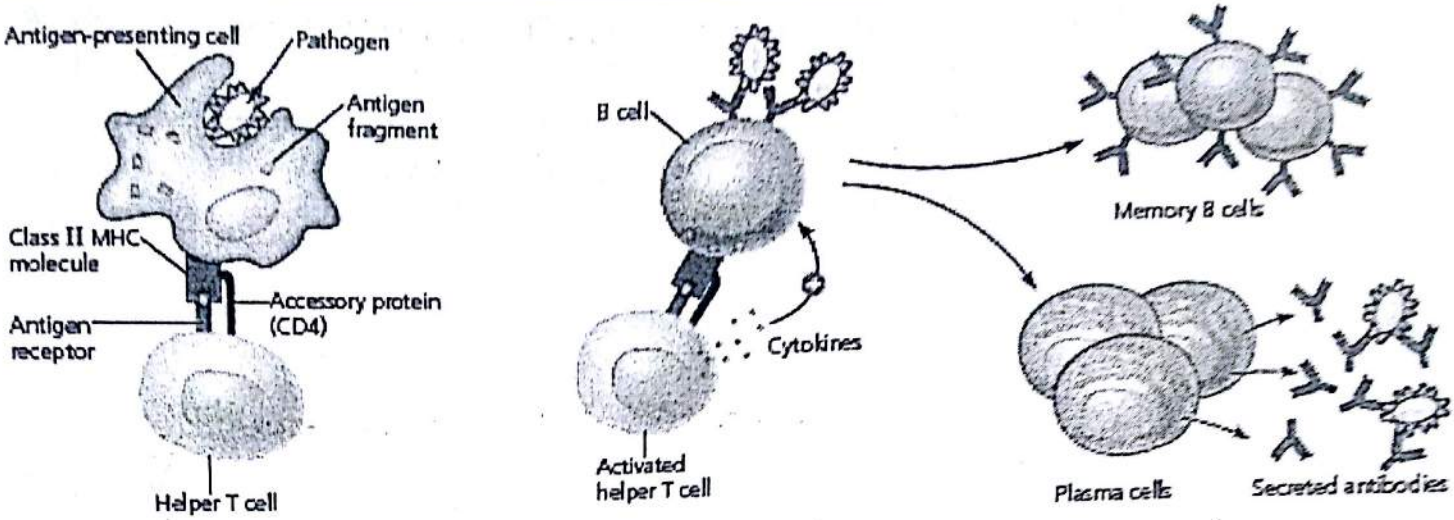
-Activation of B cells is aided by cytokines and antigen binding to helper T cells

-Upon stimulation, active B cells proliferate and differentiate into a clone of antibody secreting plasma cells and a clone of memory cells

-This is called the clonal selection of B-cells

-When an antigen binds to a receptor on surface of B cells, cells takes in a few molecules from the fragmented molecule by endocytosis

-Cell presents these antigen fragments to HT which will guarantee a direct binding between HT and the B-cell which is necessary for their activation



1 After an antigen-presenting cell engulfs and degrades a pathogen, it displays an antigen fragment complexed with a class II MHC molecule. A helper T cell that recognizes the complex is activated with the aid of cytokines secreted from the antigen-presenting cell.

2 When a B cell with receptors for the same epitope internalizes the antigen, it displays an antigen fragment on the cell surface in a complex with a class II MHC molecule. An activated helper T cell bearing receptors specific for the displayed fragment binds to and activates the B cell.

3 The activated B cell proliferates and differentiates into memory B cells and antibody-secreting plasma cells. The secreted antibodies are specific for the same antigen that initiated the response.

Antibody function

-Antibodies do not kill pathogens; instead they mark pathogens for destruction

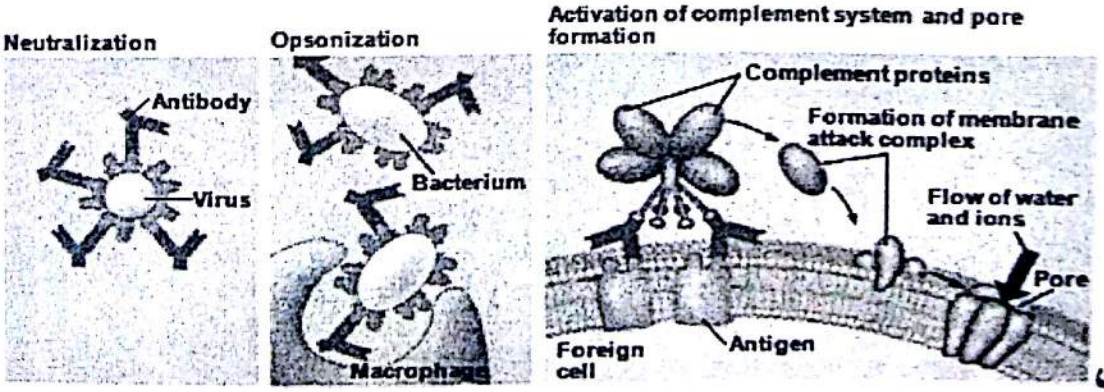
-In neutralization, antibodies bind to viral surface proteins preventing infection of a host cell

-Antibodies may also bind to toxins in body fluids and prevent them from entering body cells

-In opsonization, antibodies bind to antigens on bacteria creating a target for macrophages or neutrophils, triggering phagocytosis

-Antigen-antibody complexes may bind to a complement protein—which triggers a cascade of complement protein activation

-Ultimately a membrane attack complex forms a pore in the membrane of the foreign cell, leading to its lysis



-B cells can express five different forms (or classes) of immunoglobulin (Ig) with similar antigen-binding specificity but different heavy chain C regions

1. IgD: Membrane bound
2. IgM: First soluble class produced
3. IgG: Second soluble class; most abundant
4. IgA and IgE: Remaining soluble classes

Active and Passive Immunization

1. Active immunity: develops naturally in response to an infection and also develop following immunization, often called **vaccination**

-In immunization a nonpathogenic form of a microbe or part of a microbe elicits an immune response to an immunological memory for that microbe

2. Passive immunity: which provides immediate, short-term protection is conferred naturally when IgG crosses the placenta from mother to fetus or when IgA passes from mother to infant in breast milk

-Can be conferred artificially by injecting antibodies into a nonimmune person

Antibodies as Tools

-Antibody specificity and antigen-antibody binding has been harnessed in research, diagnosis, and therapy

-Polyclonal antibodies, produced following exposure to a microbial antigen, are products of many different clones of plasma cells, each specific for a different epitope

-**Monoclonal antibodies** are prepared from a single clone of B cells grown in culture

Immune Rejection

-Cells transferred from one person to another can be attacked by immune defenses
-This complicates blood transfusions or the transplant of tissues or organs

Glossary

A:

Acquired immunity مناعة مكتسبة
Antigen presentation عرض مولد الضد

B:

Barrier Defenses دفاعات حاجزة

C:

Memory cells خلايا ذاكره
Clonal selection اختيار النسخة

F:

Fever حمى

I:

Immune system جهاز المناعة
Innate immunity مناعة فطرية
Invertebrates لافقاريات
Inflammatory Response استجابة التهابية
Immune rejection رفض مناعي
Infection عدوى

L:

Lymphatic system الجهاز الليمفاوي

M:

Mucus مخاط
Meningitis التهاب السحايا

P:

Pathogens مسببات المرض
Proliferation تكاثر