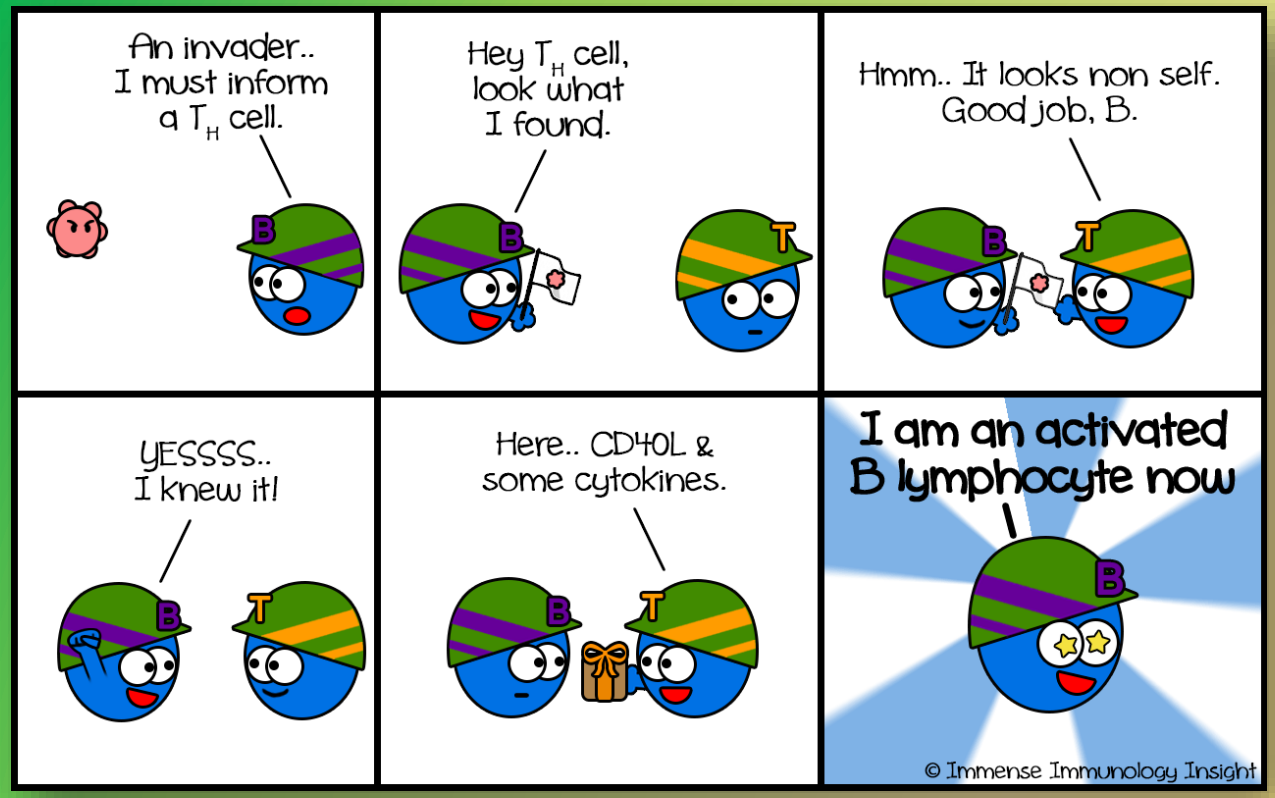
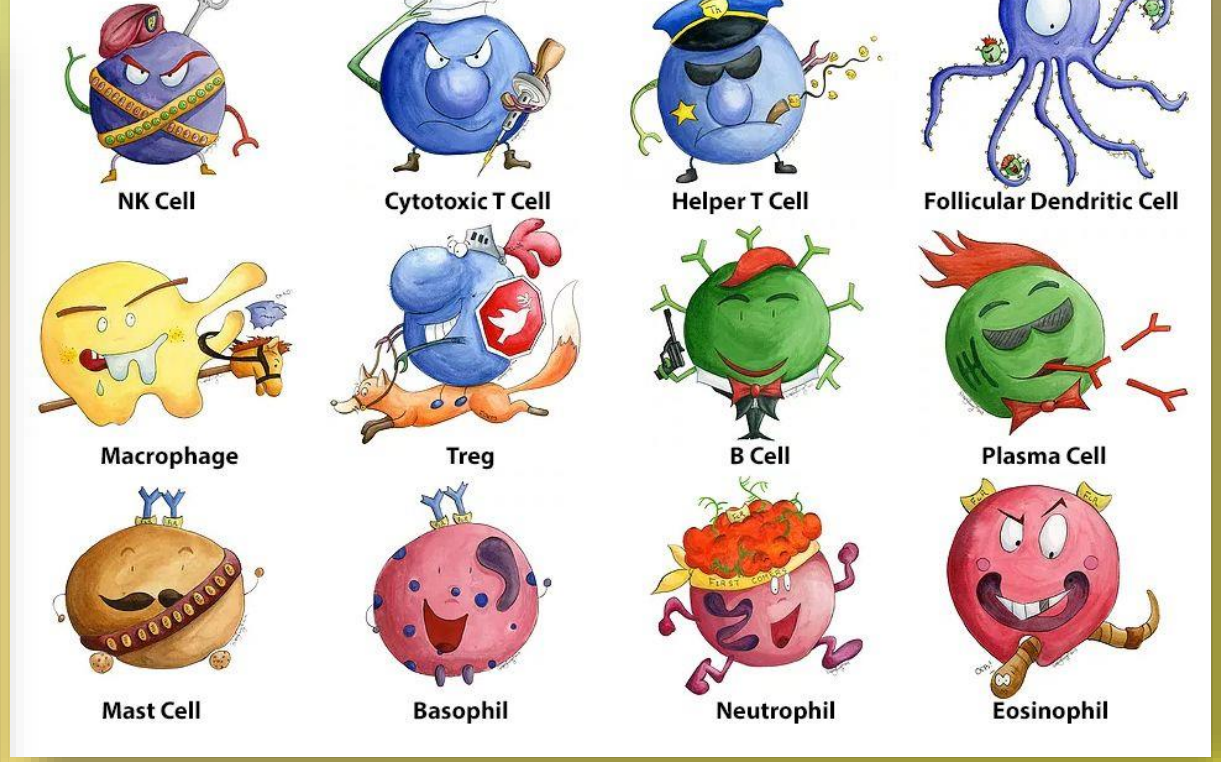




# The Immune System

- Humans are susceptible to a multitude of disease-causing bacteria, viruses, parasitic worms, fungi, and protists.

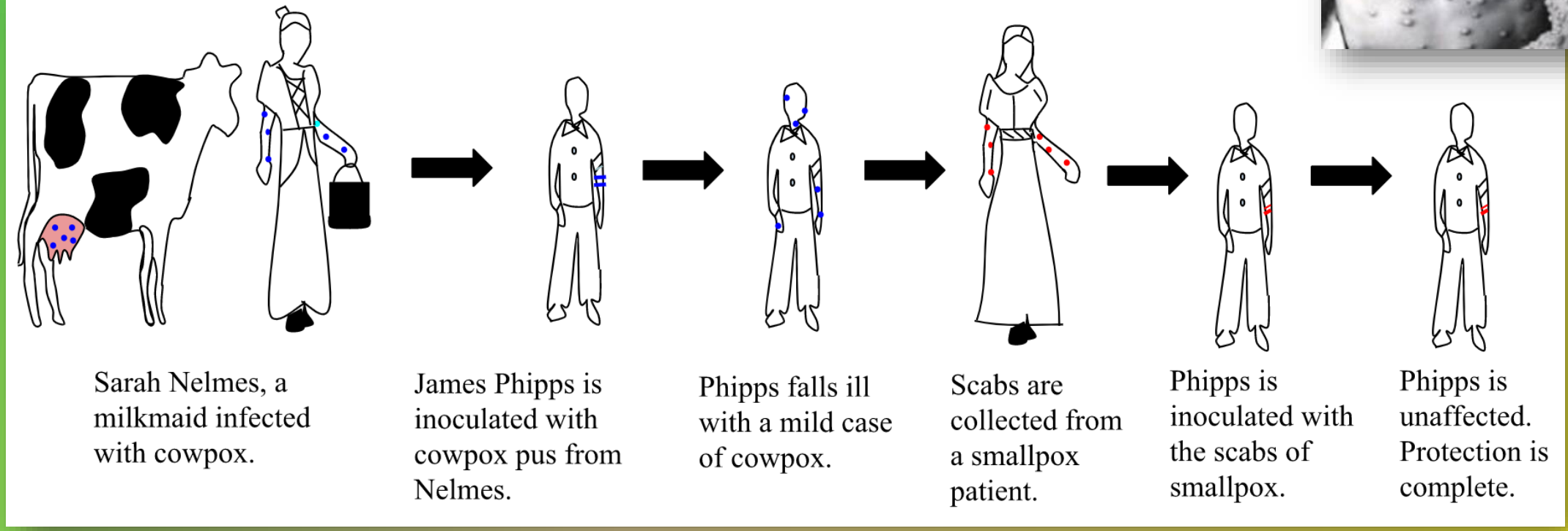
- To understand how animals stay healthy for most of their lives, biologists have investigated three observations:

1. Wounds usually heal, even if they become infected.
2. Most people who contract a bacterial or viral illness eventually recover without medication.
3. People who acquire bacterial or viral infections and recover frequently do not contract the same disease again.

- **Immunity** is a resistance to or protection against disease-causing pathogens that prevents individuals from contracting a disease more than once.

- **Immunization** is the conferring of immunity to a particular disease.
  - **Vaccination** is the introduction of a weakened or altered pathogen to prime the body's immune system, so it fights later infections effectively.

- In the late 1700s, Edward Jenner had a key insight about why milkmaids often avoided smallpox infections.
- Because cows suffered from a smallpox-like disease called cowpox, Jenner reasoned that milkmaids were immune to smallpox because they had been exposed to cowpox.
- To test his hypothesis, he inoculated a boy with cowpox pathogens and then with smallpox pathogens. As predicted, the boy did not contract smallpox.



# Layers of Immunity:

## 1. Barrier Immunity

SKIN

LUNGS

GI TRACT

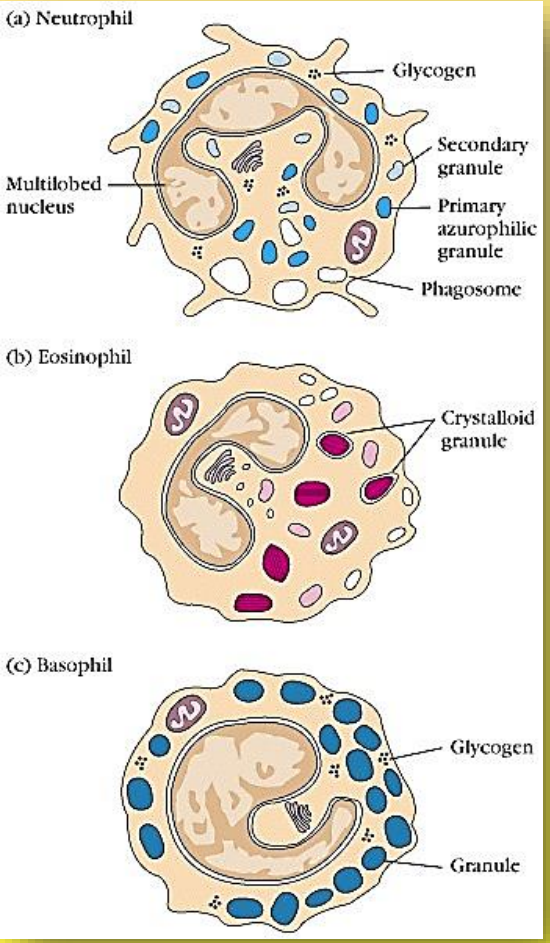
EYES

What if a foreign invader gets past our barrier immunity?

2. Innate immunity responds (2nd line of defense)

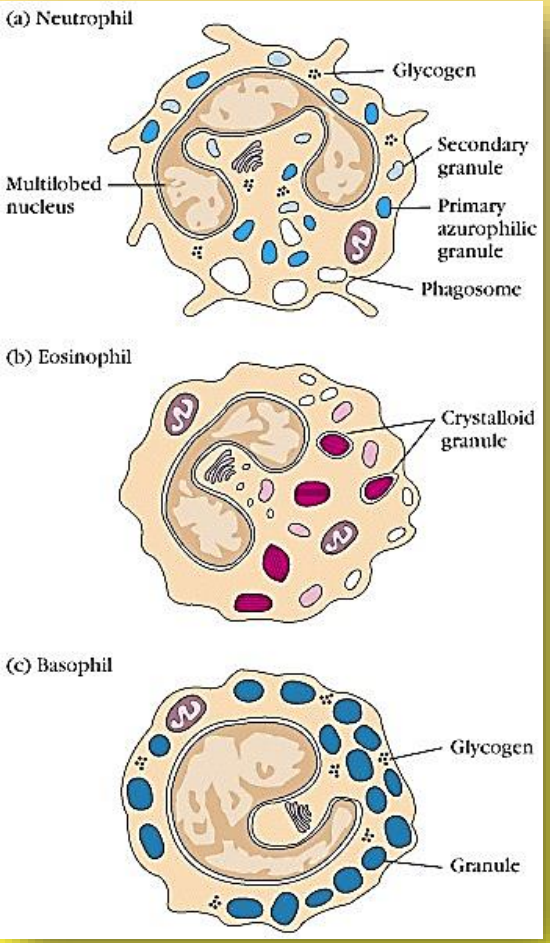
# Cells of the Innate Immunity Response

## 1. Neutrophils -

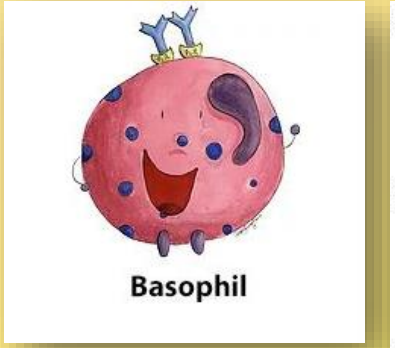
# Cells of the Innate Immunity Response

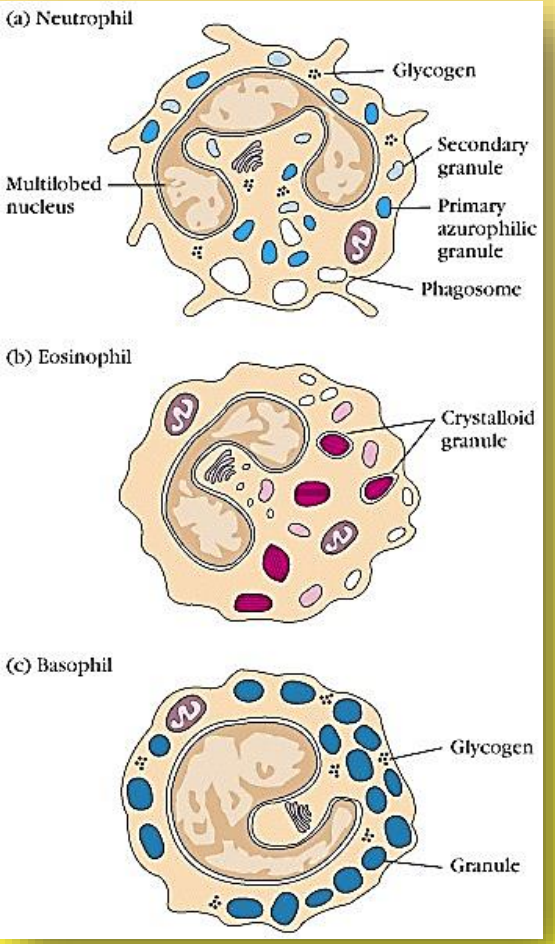
## 2. Eosinophils -

# Cells of the Innate Immunity Response

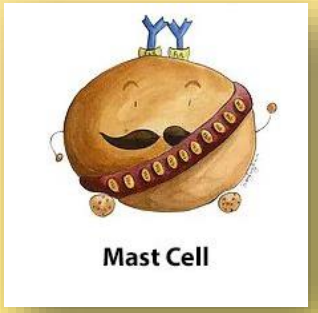
## 3. Basophils -

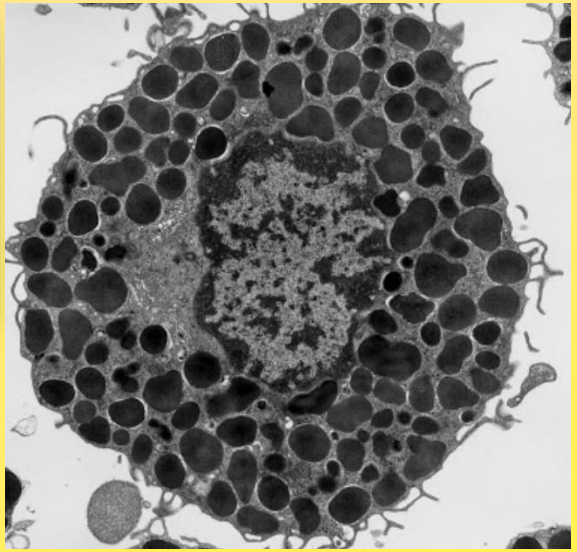


# Cells of the Innate Immunity Response

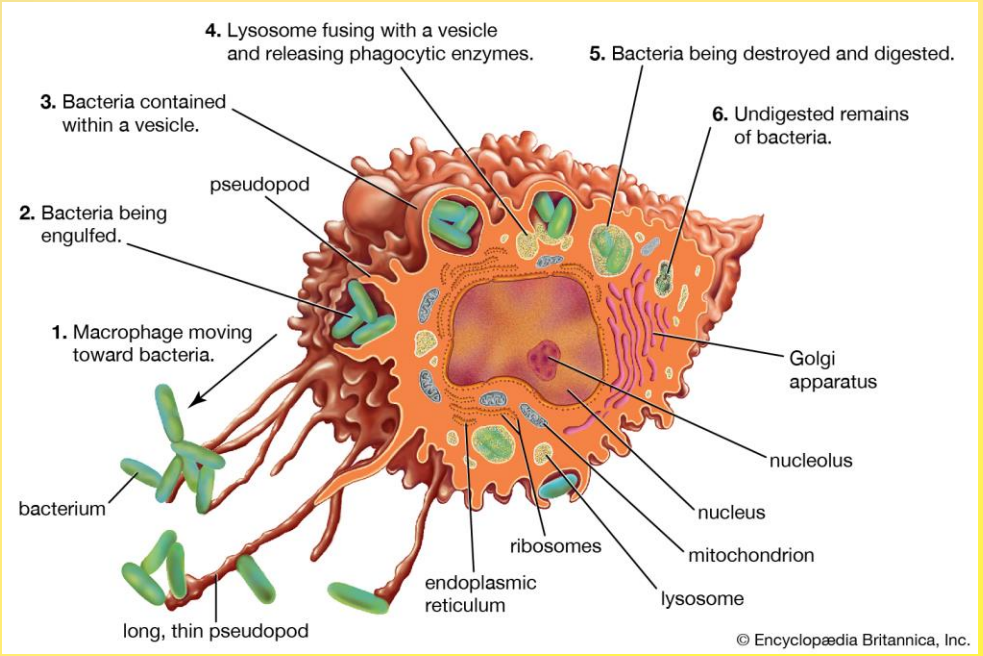
## 4. Mast Cells -

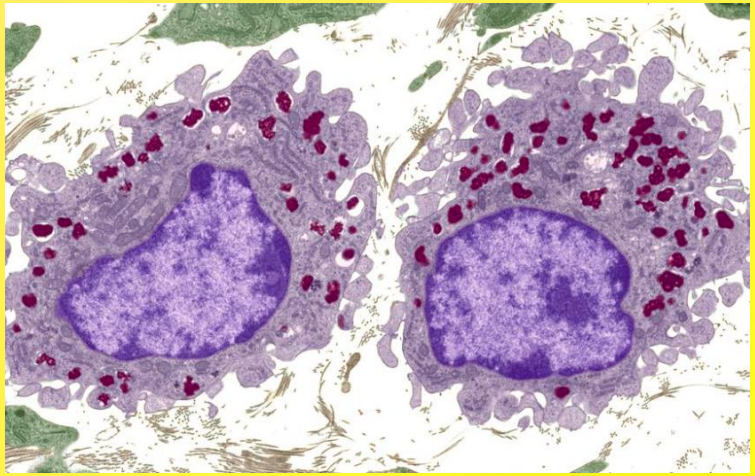


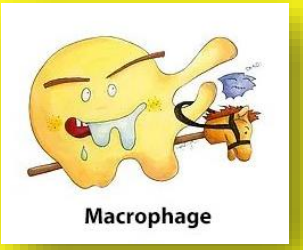



# Cells of the Innate Immunity Response

## 5. Macrophages -

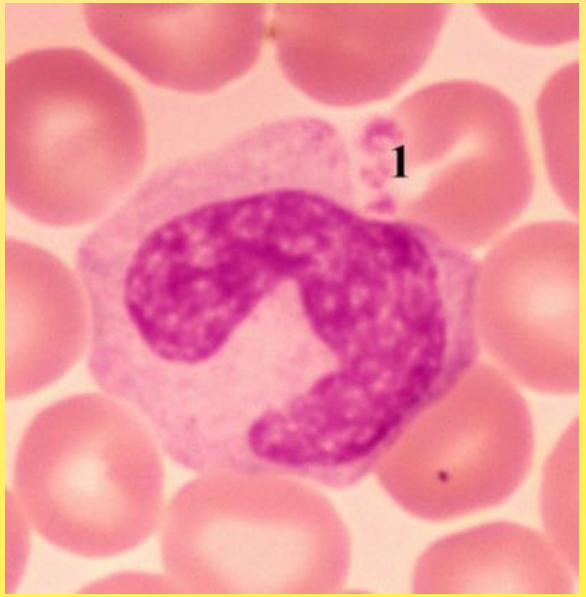




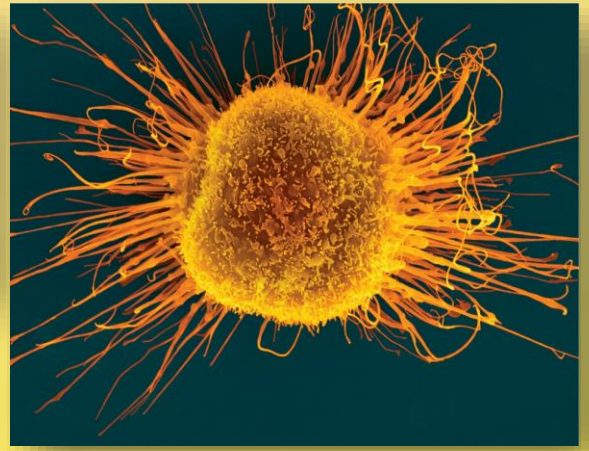
# Cells of the Innate Immunity Response

## 6. Monocytes -



# Cells of the Innate Immunity Response

## 7. Dendritic Cells -

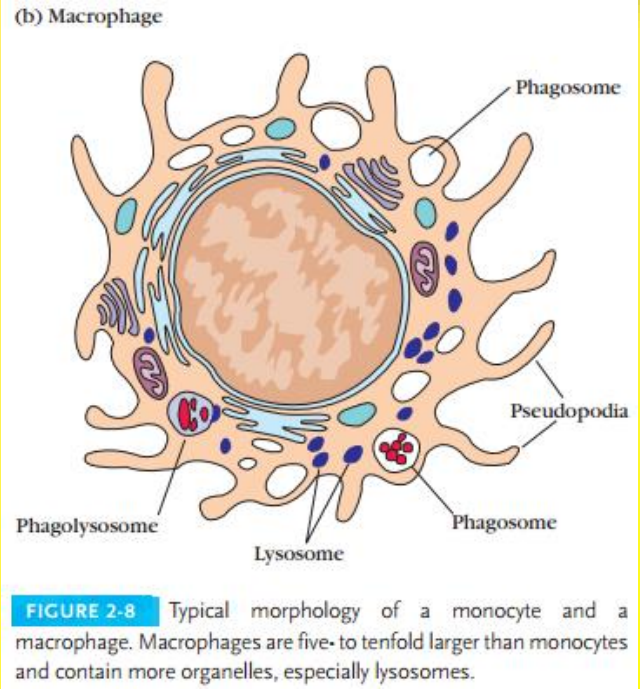
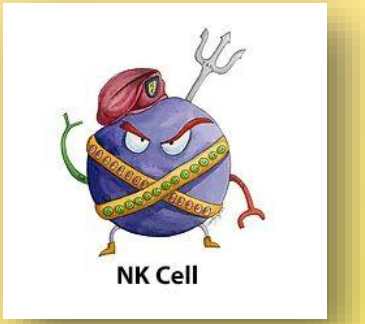
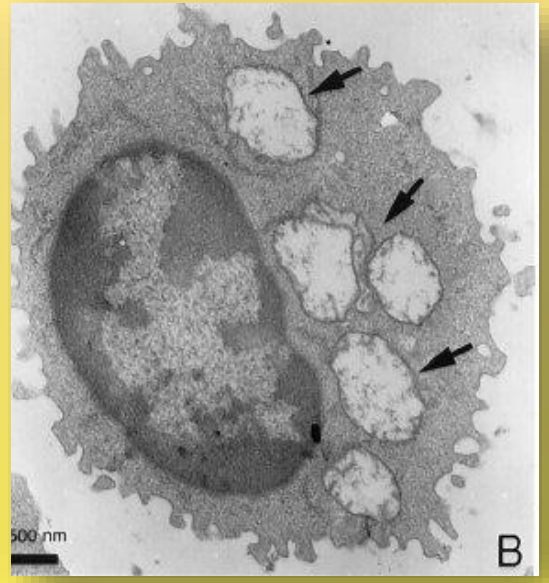


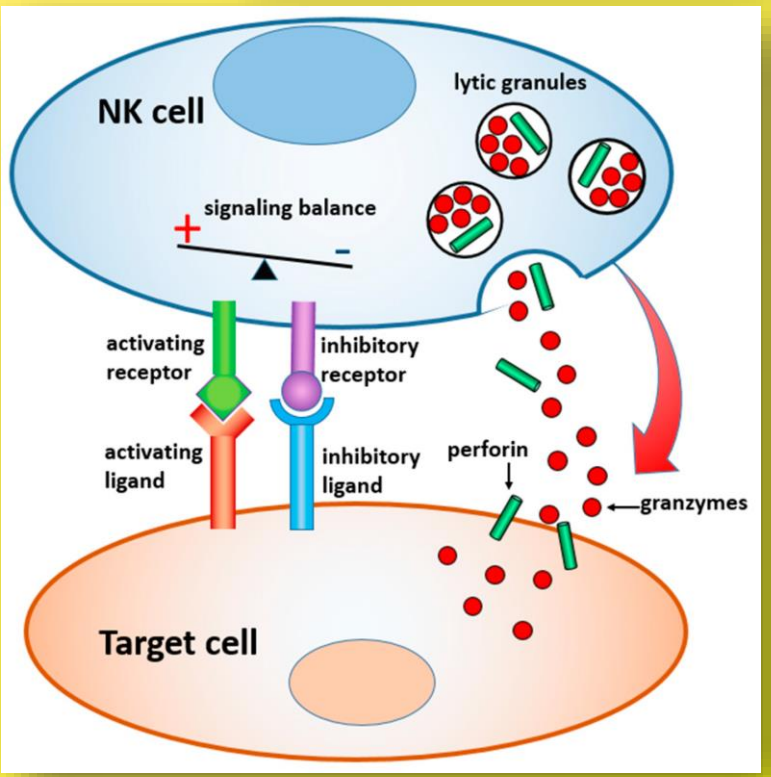

FIGURE 2-8 Typical morphology of a monocyte and a macrophage. Macrophages are five- to tenfold larger than monocytes and contain more organelles, especially lysosomes.

# Cells of the Innate Immunity Response

## 8. Natural Killer Cells (NKCs) -



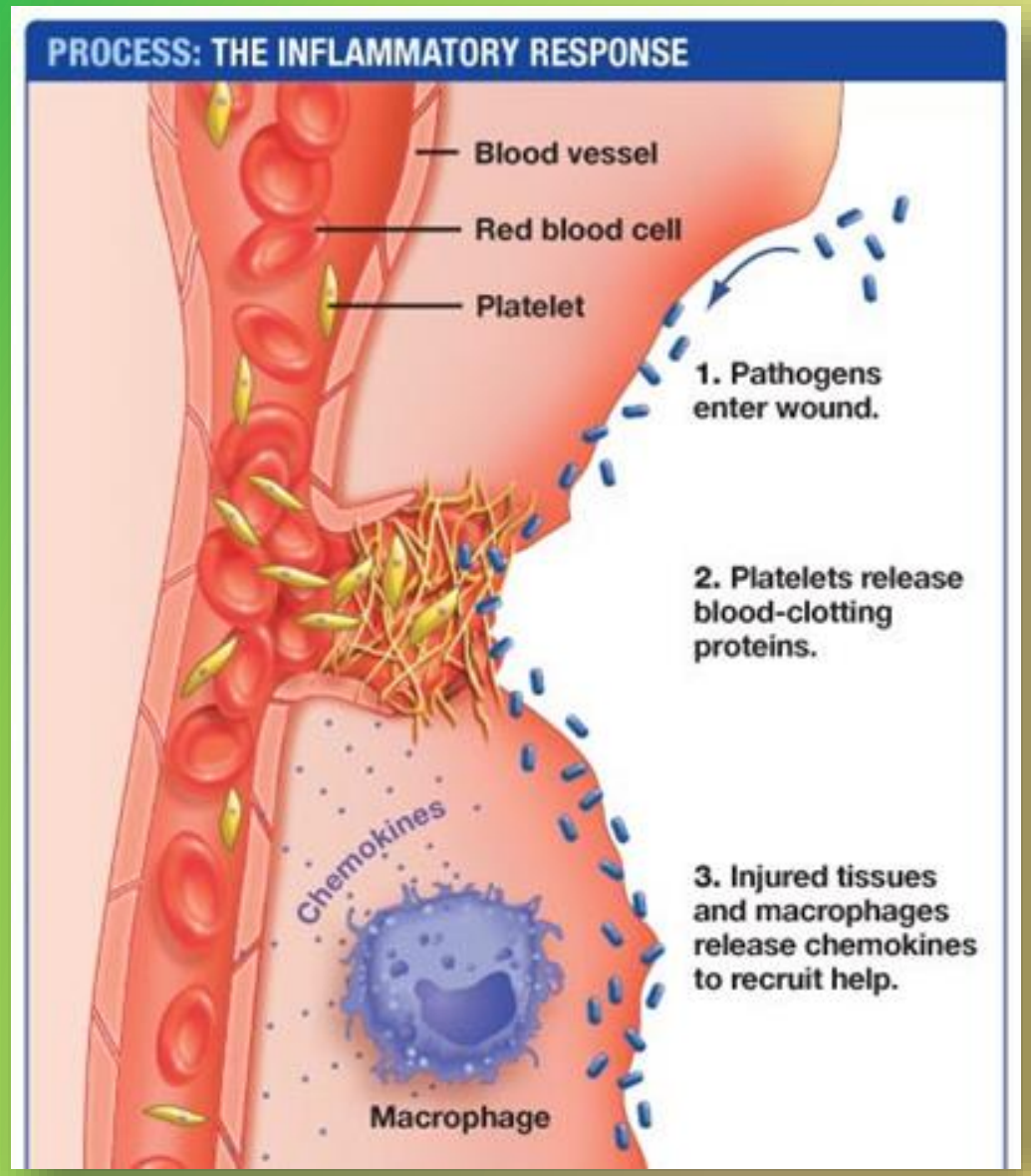



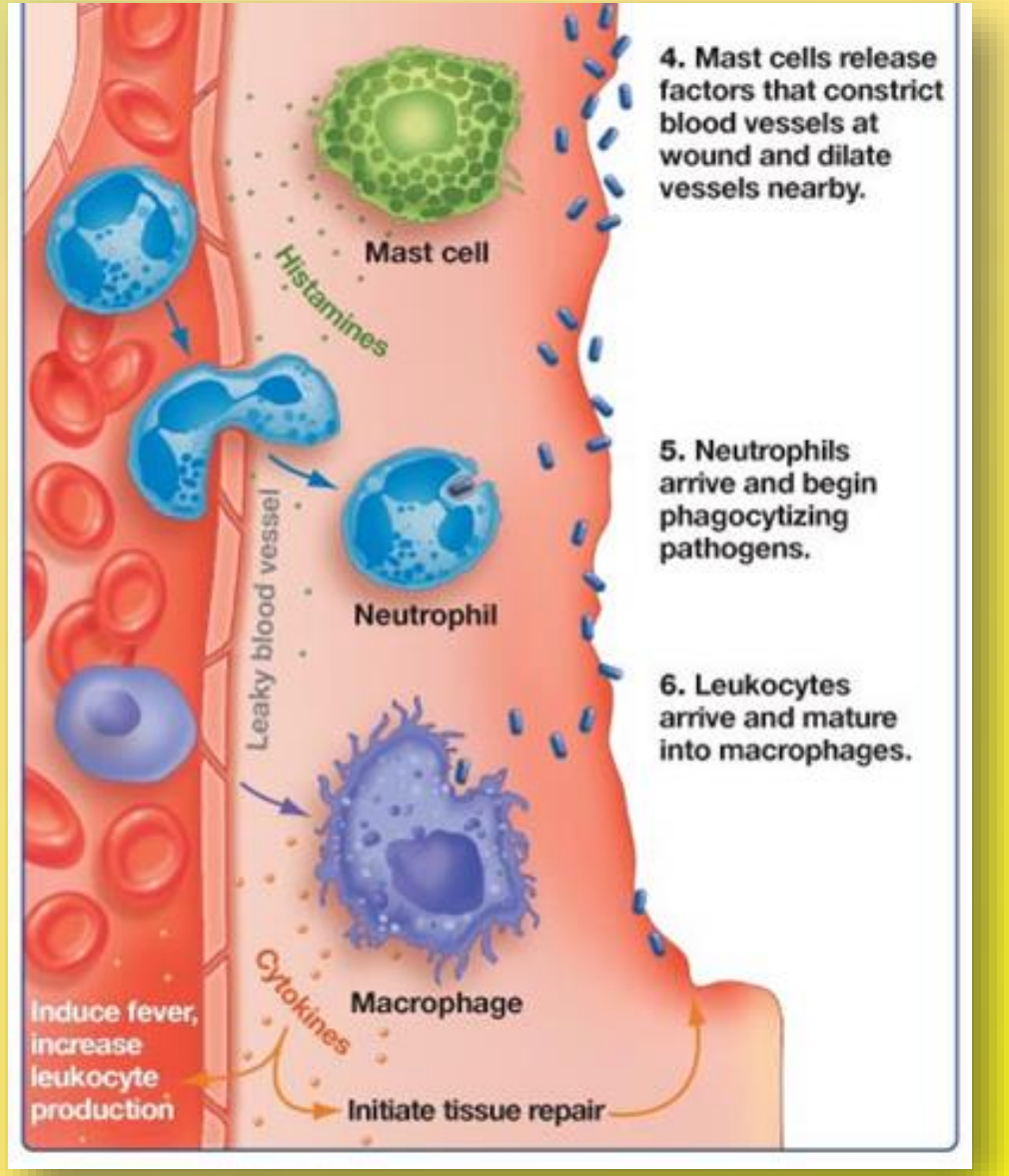
- The **innate immune response** —the body's nonspecific response to pathogens—involves **leukocytes** (white blood cells) such as **mast cells**, **macrophages**, and **neutrophils**.

- Innate immune response leukocytes are alerted to the presence of foreign invaders by antigens that are found on the surfaces of pathogens, but not on host cells.

- Some innate system cells have membrane proteins, known as **pattern-recognition receptors**, that bind to—and are activated by—pathogen-specific compounds.
  - These proteins serve as "on" switches by initiating a cell response.

- The **inflammatory response**, a **multi-step innate immune response** in mammals, occurs at the **site of an injury**. The steps of this process are as follows:
  1. When skin breaks, pathogens enter a wound.
  2. **Platelets** release blood-clotting proteins at the wound site.
  3. Wounded tissues and macrophages at the wound site secrete **chemokines**, signaling molecules that recruit immune cells by forming a gradient to mark the path to the site.
  4. **Mast cells** release chemical messengers that constrict blood vessels near the wound—reducing blood flow and thus blood loss. Mast cells also secrete **histamine** and other signaling molecules, which dilate blood vessels slightly farther away from the wound, making them more permeable.
  5. **Neutrophils** and **macrophages** remove pathogens by **phagocytosis -** the engulfing and digesting of foreign particles.
  6. **Macrophages** secrete **cytokines**, chemicals that attract other immune system cells to the site and activate cells involved in tissue repair. They also induce **fever**—elevated body temperature that aids in healing.




- The inflammatory response continues until the foreign material is eliminated and the wound is repaired.

## SUMMARY TABLE 49.1 The Innate Immune System

### (a) Key Cells

| Name | Primary Function |
|---|---|
| Mast cells | Release signals that increase blood flow to wound site |
| Neutrophils | Kill invading cells via phagocytosis |
| Macrophages | Release cytokines that recruit other cells to wound site; kill invading cells via phagocytosis |

### (b) Key Signaling Molecules

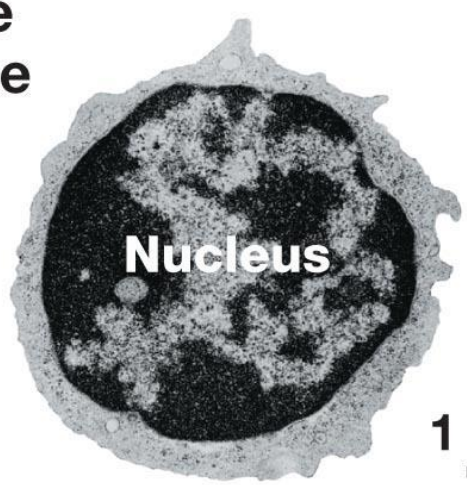
| Name | Produced By | Received By | Message/Function |
|---|---|---|---|
| Histamine | Mast cells | Blood vessels | High concentration next to wound constricts blood vessels; low concentration farther from wound dilates blood vessels |
| Chemokines* | Injured tissues and macrophages in tissues | Neutrophils and macrophages | Mark path to wound; promote dilation and increased permeability of blood vessels |
| Cytokines other than chemokines | Macrophages | Leukocytes | Mark path to wound |
| | | Bone marrow | Increase production of macrophages and neutrophils |
| | | CNS | Induce fever by increasing set point for control of body temperature |
| | | Local tissues | Stimulate cells involved in wound repair |

*Note that chemokines are a subset of cytokines.

# Cells of the Adaptive (aka Acquired) Immunity Response

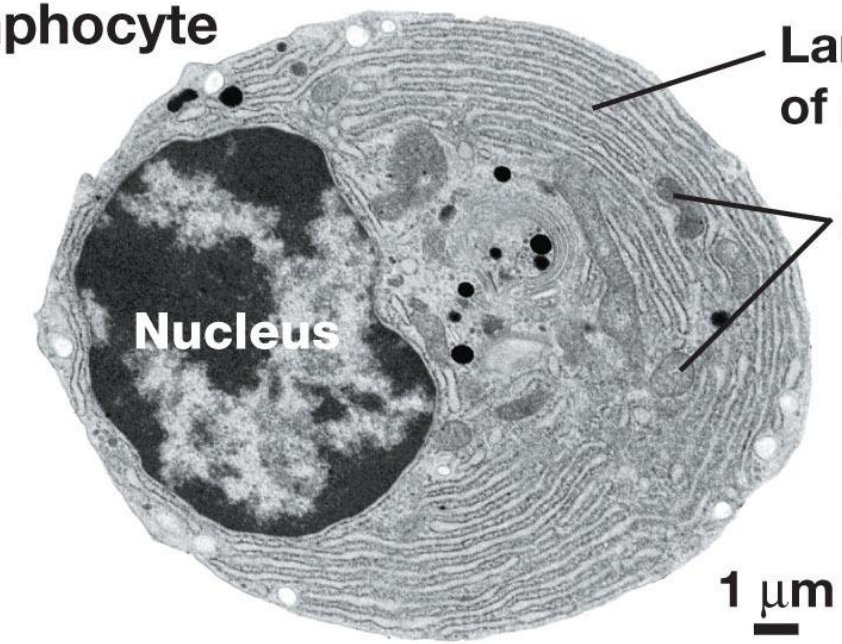
1. B-lymphocytes
2. T-lymphocytes
   - $T_H$
   - $T_C$

(a) Inactive lymphocyte




1 μm

(b) Activated lymphocyte



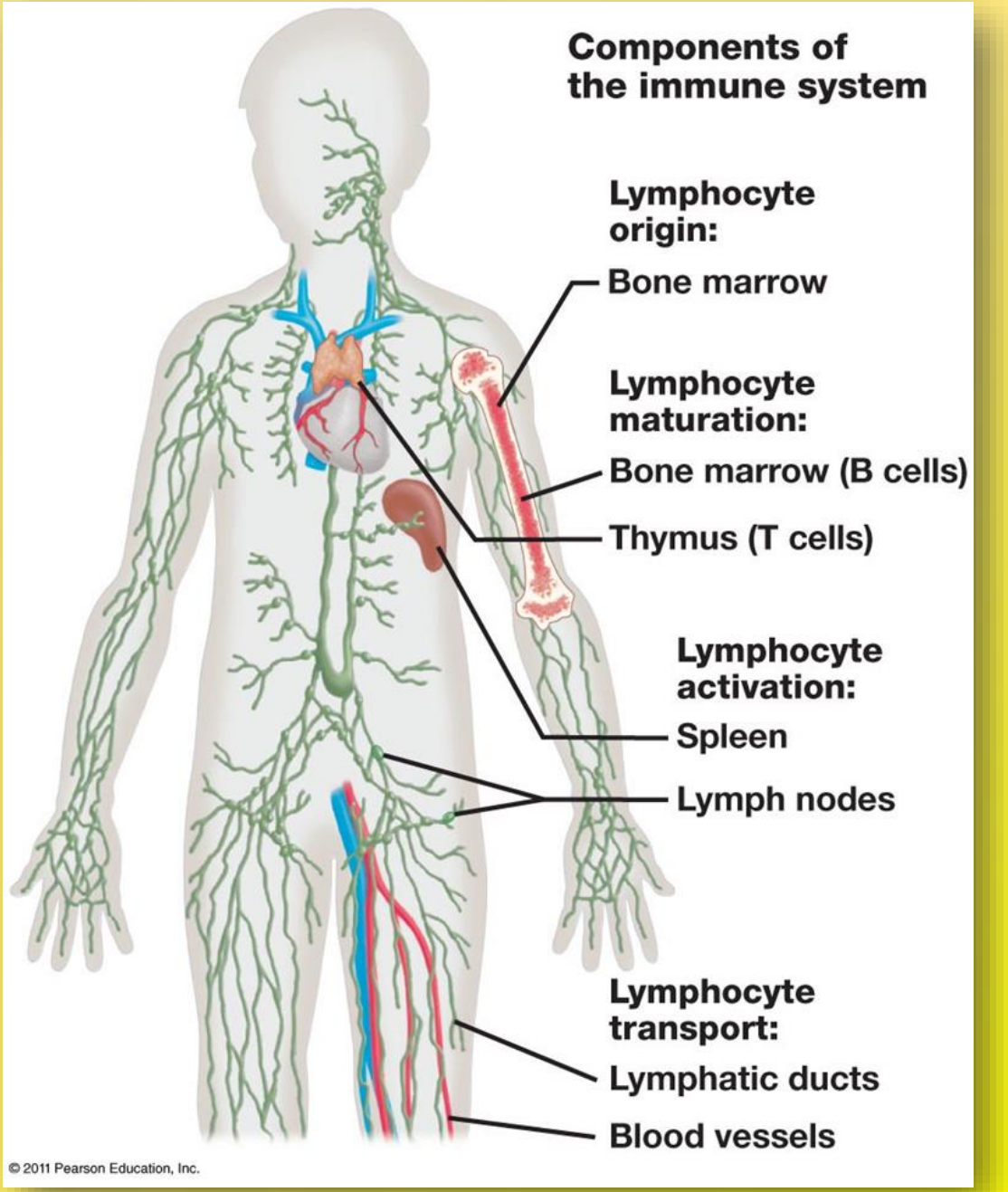

Large amount of rough ER

Mitochondria

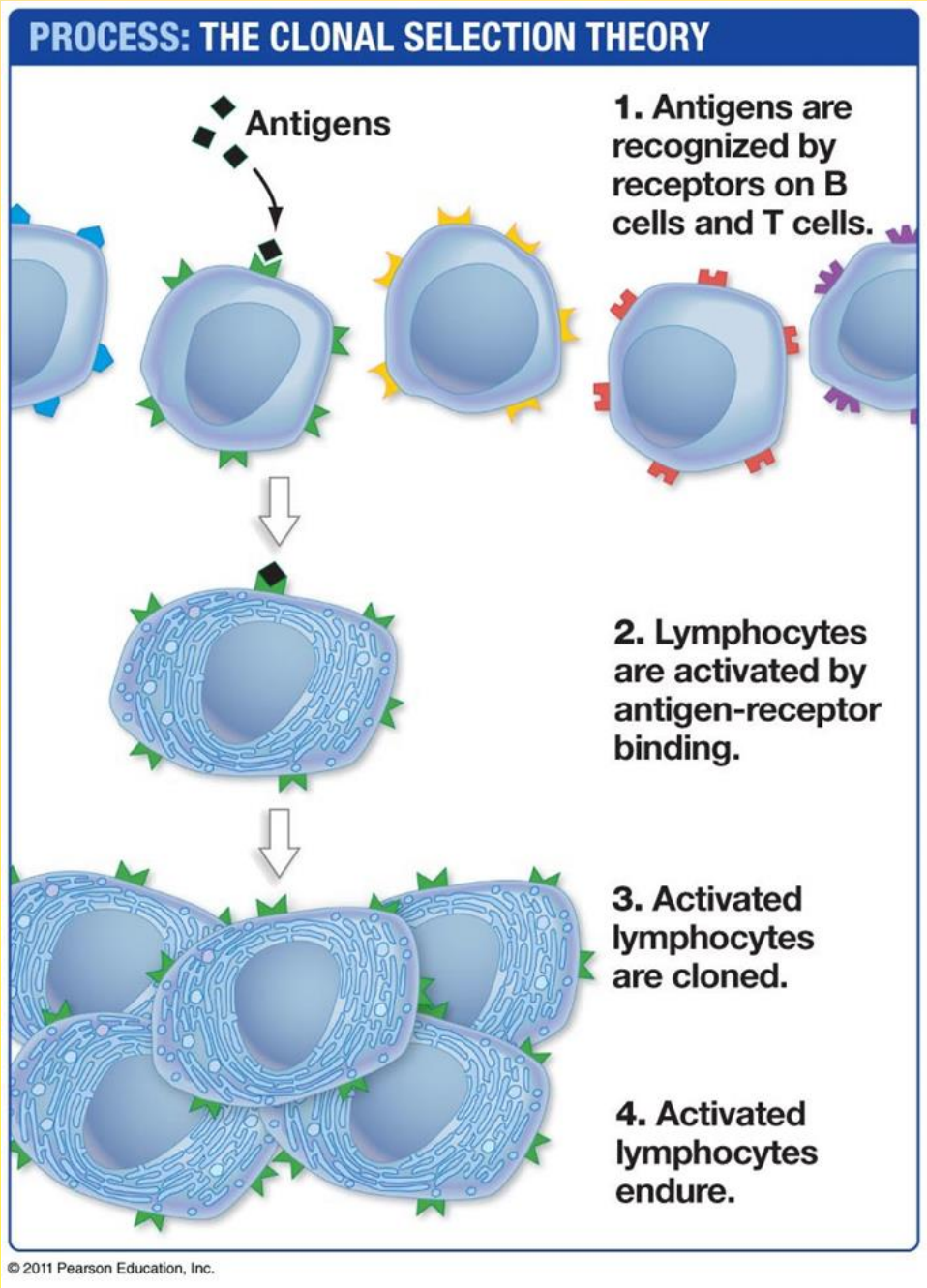
1 μm



Components of the immune system

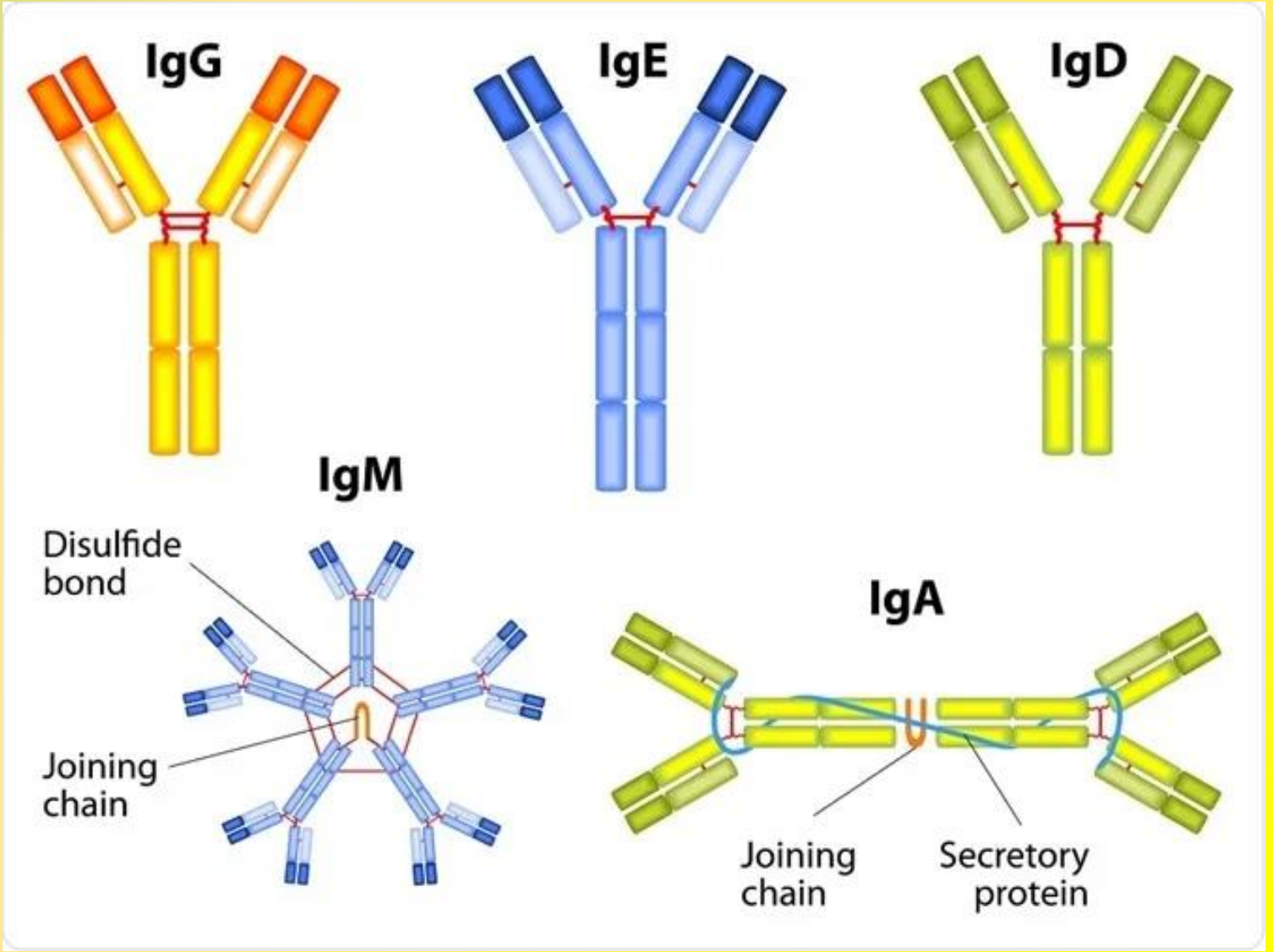


- The **clonal-selection theory** makes **four central claims**:
  1. Each lymphocyte has thousands of copies of a unique receptor on its surface. The receptor, a membrane protein, recognizes only one antigen.
  2. The lymphocyte is activated when it binds to its specific antigen.
  3. An activated lymphocyte divides and makes many identical copies of itself. In this way, specific cells are selected and cloned in response to an infection.
  4. Some of the cloned cells descended from an activated lymphocyte persist after the pathogen is eliminated and allow a rapid response if the infection recurs.



# Cells of the Adaptive (aka Acquired) Immunity Response

## 3. Antibodies (immunoglobulins)



- The **B-cell receptor (BCR)** is the protein on the **surface of B cells that binds to antigens**. Research has found that this protein has the same structure as the antibodies produced by B cells.

- The B-cell receptor has **three components**:

  1. Two identical **light chains**.
  2. Two identical **heavy chains** that are about twice the size of the light chains.
  3. A transmembrane domain within each heavy chain that anchors the protein in the plasma membrane of the B cell.

TABLE 49.2 **Five Classes of Immunoglobulins**

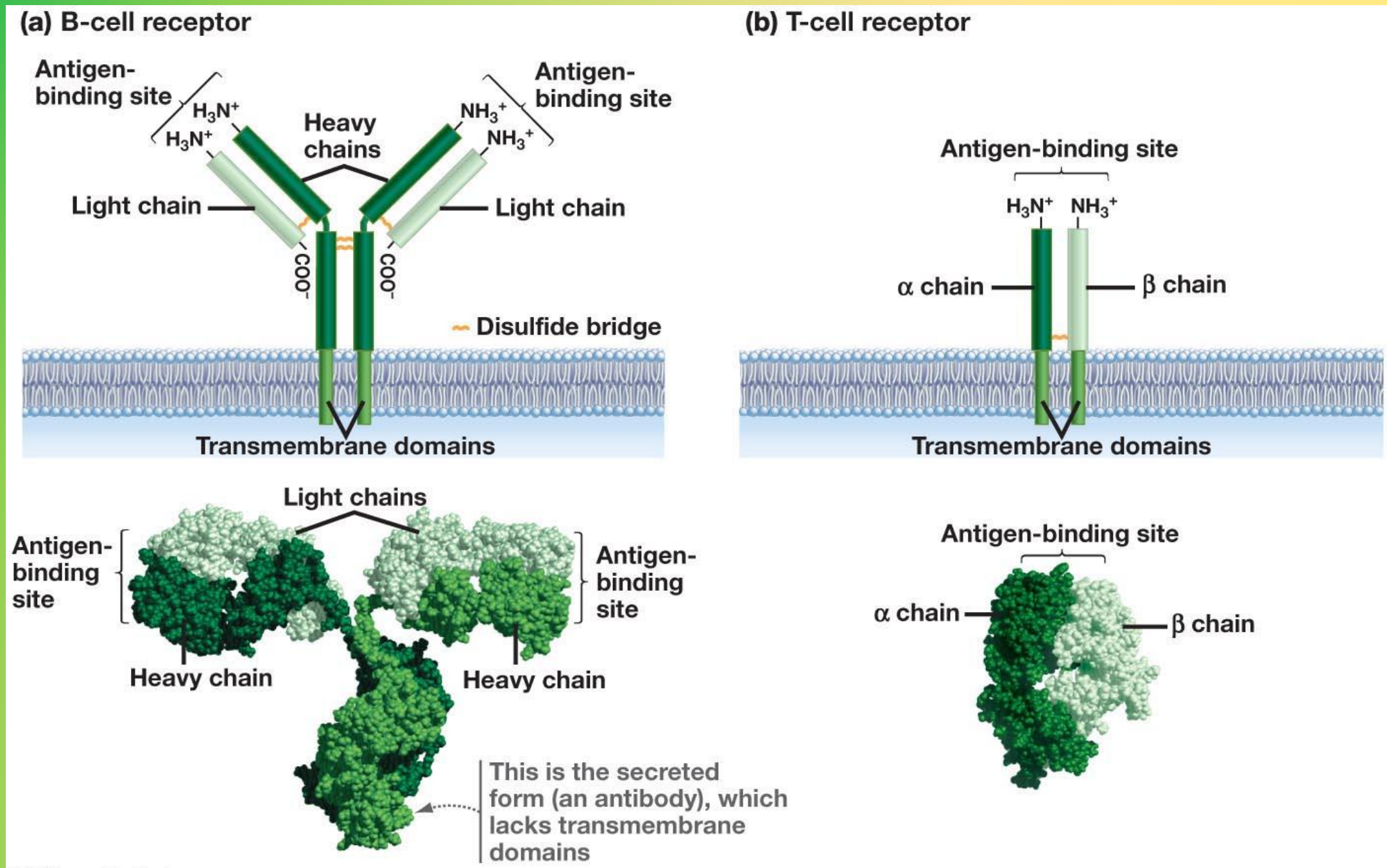
| Name | Structure (secreted form) | Function |
|---|---|---|
| IgG | Monomer  | The most abundant type of secreted antibody. Circulates in blood and interstitial fluid. Protects against bacteria, viruses, and toxins |
| IgD | Monomer  | Present on membranes of immature B cells; rarely secreted. Serves as BCR. |
| IgE | Monomer  | Secreted in minute amounts. Involved in response to parasitic worms. Also responsible for hypersensitive reaction that produces allergies. |
| IgA | Dimer  | Most common antibody in breast milk, tears, saliva, and the mucus lining the respiratory and digestive tracts. Prevents bacteria and viruses from attaching to mucous membranes; helps immunize breastfed newborns |
| IgM | Pentamer  | First type of secreted antibody to appear during an infection. Binds many antigens at once; effective at clumping viruses and bacteria so that they can be killed. |

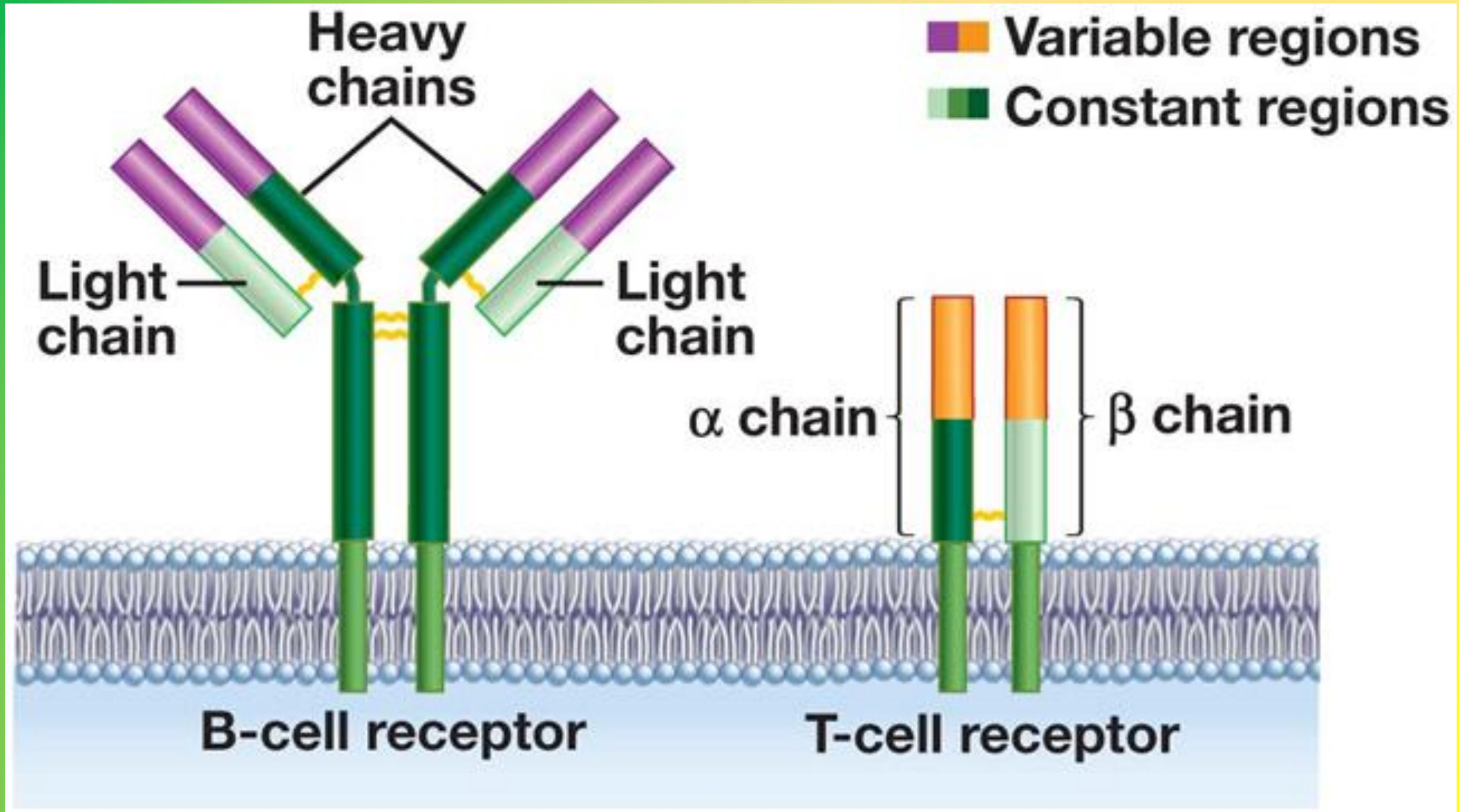
- **T-cell receptors** (**TCRs**) are proteins on the surface of T cells that binds to antigens that:

    1. Have been processed by other immune system cells.
    2. Are displayed on the plasma membranes of these other cells, a process called **antigen presentation**.

- Thus, **B cells bind to antigens directly**; **T cells bind only to antigens that are displayed by other cells**.

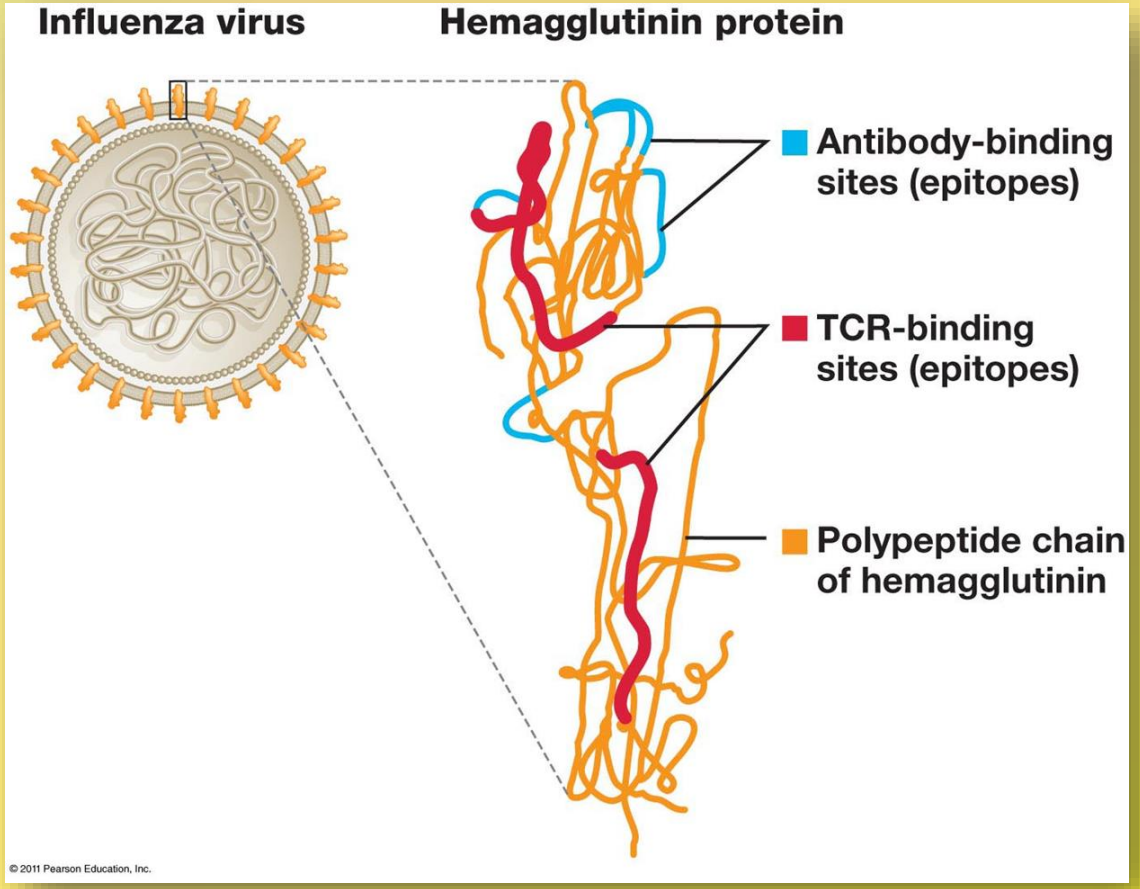
- The TCR is composed of two protein chains—an alpha (α) chain and a beta (β) chain—and has a shape similar to the BCR "arm."




Heavy chains
Variable regions
Constant regions
Light chain
Light chain
α chain
β chain
B-cell receptor
T-cell receptor

- Antibodies, BCRs, and TCRs do not bind to the entire antigen. Instead, they **bind to a selected region** of the antigen called an **epitope**.

- Each epitope is recognized by a particular antibody, BCR, or TCR. It is not unusual for an antigen to have between 10 and 100 different epitopes.



# The Immune System Distinguishes Self from Nonself

- Examples of autoimmunity include:

- **Multiple sclerosis (MS)** → production of anti-self **T cells that attack the myelin sheath** of nerve fibers. Causes muscular and coordination problems.

- **Rheumatoid arthritis (RA)** develops when **T cells and antibodies alter the lining of joints**, causing painful inflammation.

- **Type 1 diabetes mellitus** occurs when **T cells attack and kill insulin-secreting cells in the pancreas**, causing an inability to regulate blood glucose.

- **Human Immunodeficiency Virus (HIV)** & **Autoimmune Immune Deficiency Syndrome (AIDS)** - HIV attacks CD4 cells (helper Ts), it uses the cells to make more virus. HIV destroys CD4 cells by using their replication machinery to create new copies of the virus, causing the CD4 cells to lyse.

**When the virus has destroyed a certain number of CD4 cells and the CD4 count drops below 200, a person will have progressed to AIDS.

# Adaptive (acquired) Immunity

- The **adaptive immune response**, also known as the **acquired immune response**, is based on interactions between specific immune system cells and a specific antigen.

- **Antibodies** are proteins that are produced and secreted by certain lymphocytes and that bind only to a specific part of a specific antigen.

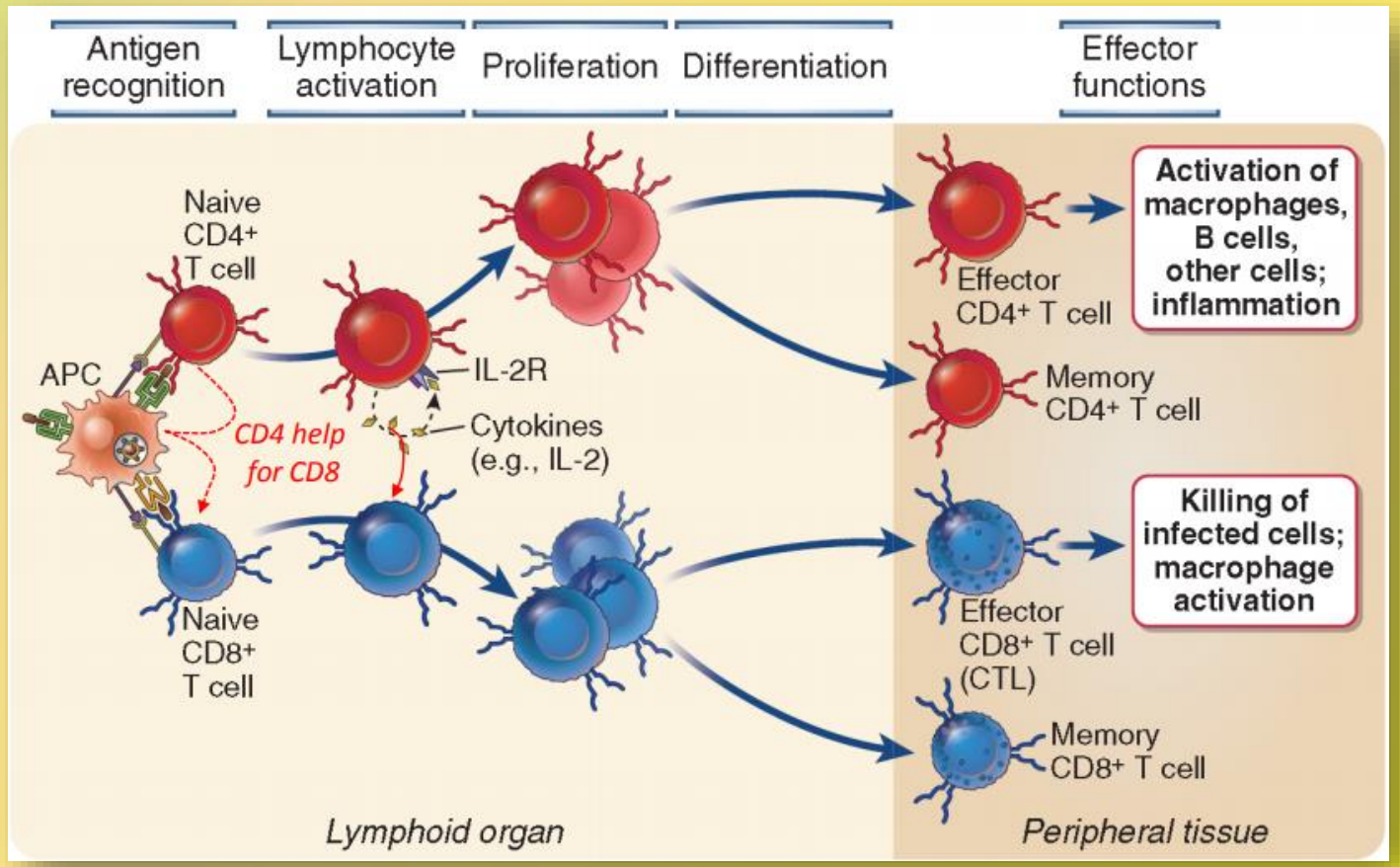
- The four key characteristics of the adaptive immune response are:

1. ***Specificity***—antibodies and other components of the adaptive immune system **bind only to specific sites on specific antigens**.
2. ***Diversity***—the adaptive response recognizes an almost **limitless array of antigens**.
3. ***Memory***—the adaptive response can be **reactivated quickly** if it **recognizes antigens** from a previous infection.
4. ***Self vs. non-self recognition***—molecules that are produced by an individual do not act as antigens, so the adaptive immune system **can distinguish between self and non-self**.

# T-Cell Activation

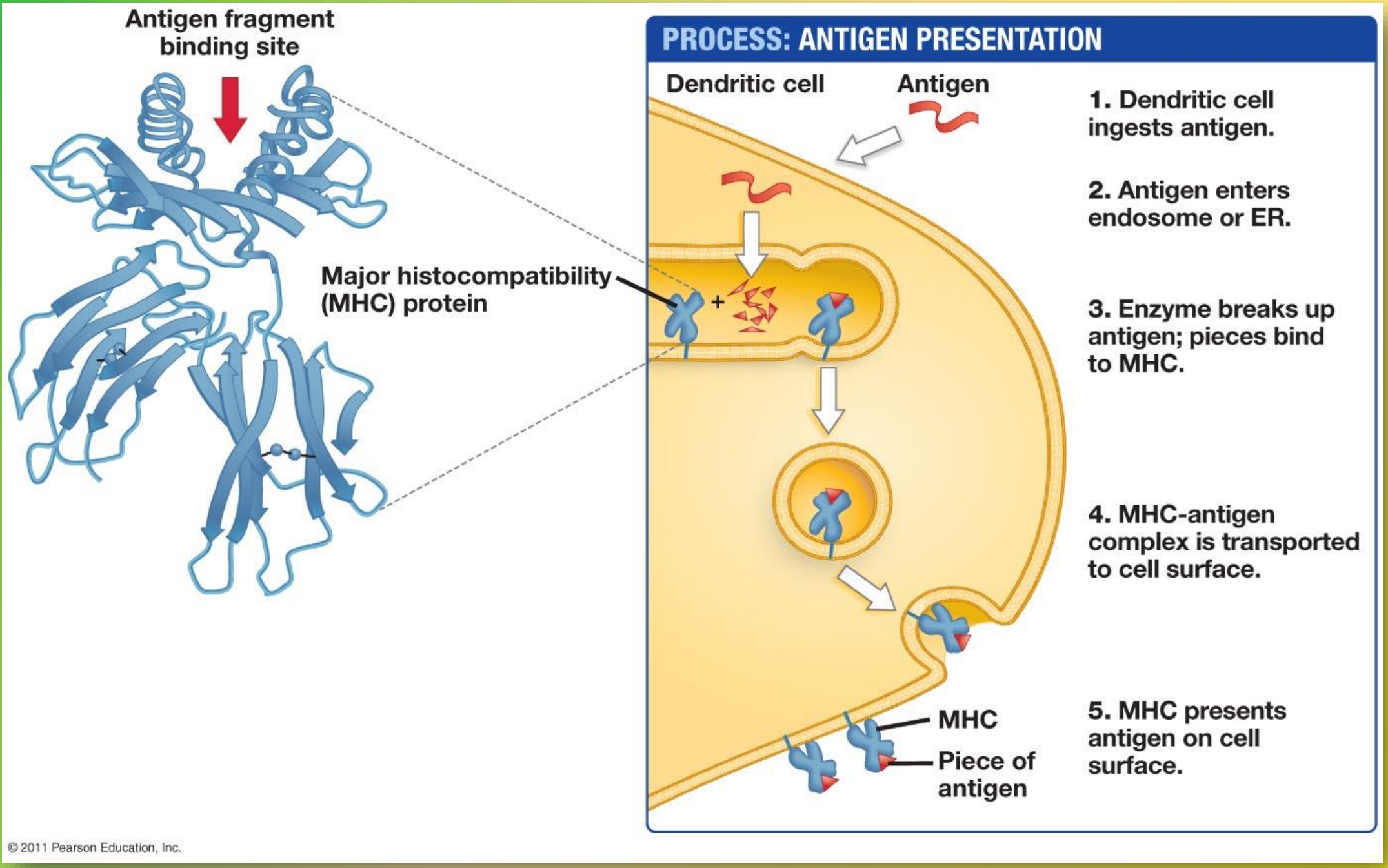
- T lymphocyte activation begins when **antigens are taken up by a specific type of leukocyte or an infected cell**, cut into pieces, packaged with specific cell proteins, and transferred to the cell surface.
  - **T cells then bind to the antigens** via the TCR and begin the activation process.

- Antigen-presenting cells (APCs) interact with T lymphocytes called $CD8^+$ T cells.
  - T cells are classified as $CD4^+$ or $CD8^+$, based on the presence of CD4 or CD8 proteins on their plasma membranes.



# Antigen Presentation by MHC Proteins

- The activation of T cells begins when leukocytes called **dendritic cells** are recruited to the site of infection.
- The dendritic cells contain proteins called **MHC (major histocompatibility) proteins**, antigen-presenting proteins that have a groove where small peptide fragments, typically 8 to 20 amino acids in length, bind.
- There are two MHC classes:
- **Class I (MHC-I), which are found in every nucleated cell of the body,** present normal **self-antigens** as well as abnormal or non-self pathogens to the effector T cells involved in cellular immunity
- **Class II (MHC-II),** only found on **macrophages**, **dendritic cells**, and **B cells**; they present abnormal or non-self pathogen antigens for the initial activation of T cells.

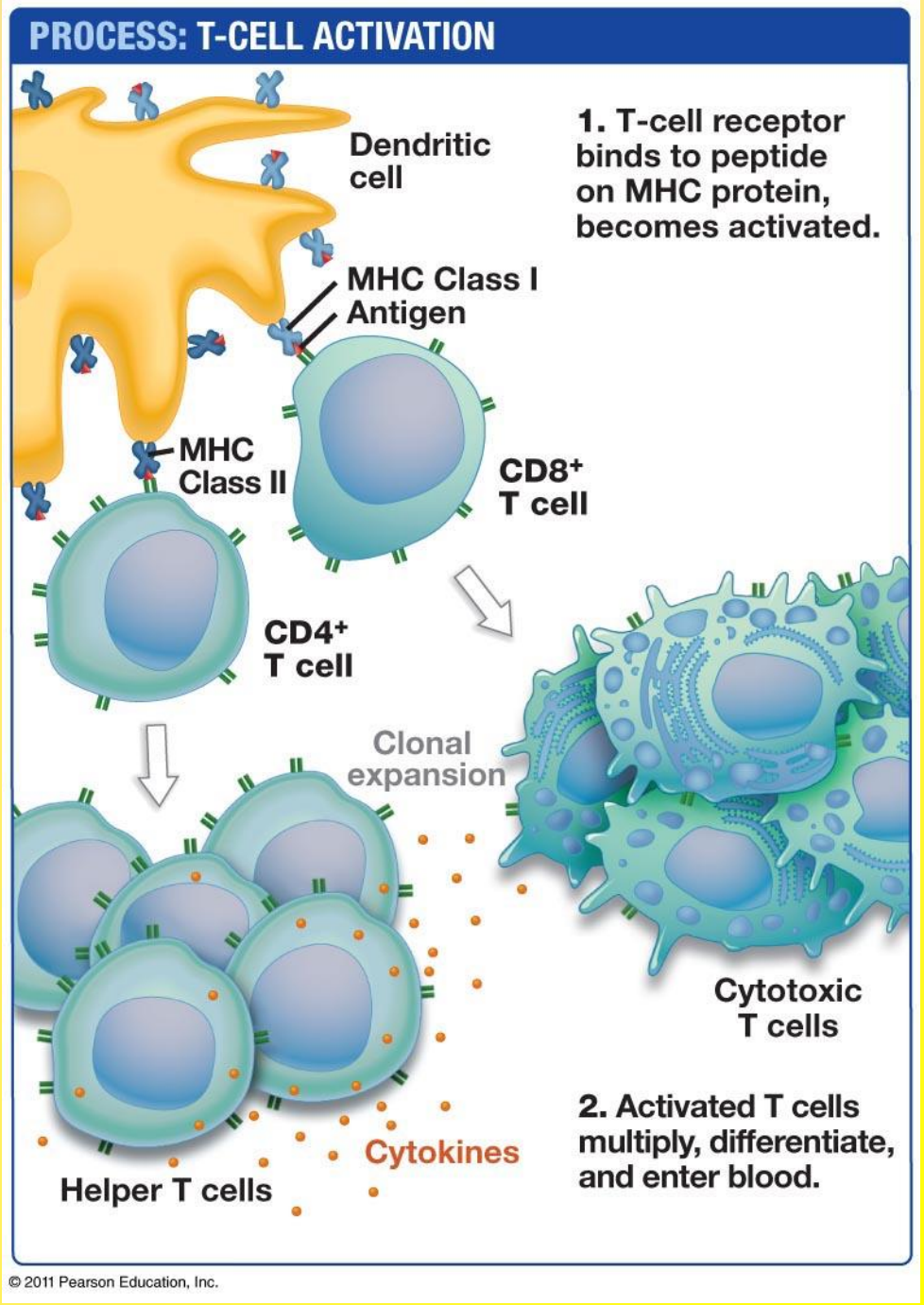


## $T_C$ (aka killer T-cell → CD8+) activation

- When activated $CD8^+$ T cells undergo clonal expansion, the daughter cells develop into **cytotoxic T cells**, or **killer T cells**.
- Cytotoxic T cells interact only with host cells that display antigens presented on Class I MHC proteins (APCs), which signals that the cell is infected and should be sacrificed.
- When a cell displays an antigen bound to a class I MHC protein, it sends a simple message to cytotoxic T cells: "Kill me."

## $T_H$ (aka helper T-cell → CD4+) activation

- The daughter cells of activated $CD4^+$ T cells differentiate into **helper** or **effector T cells** that help to activate other lymphocytes.
- Helper T cells interact only with lymphocytes that display antigens presented on Class II MHC proteins, which signals they should be activated.
- If a leukocyte displays an antigen on a class II MHC protein, the message to helper T cells is "Activate now."



# B-Cell Activation and Antibody Secretion

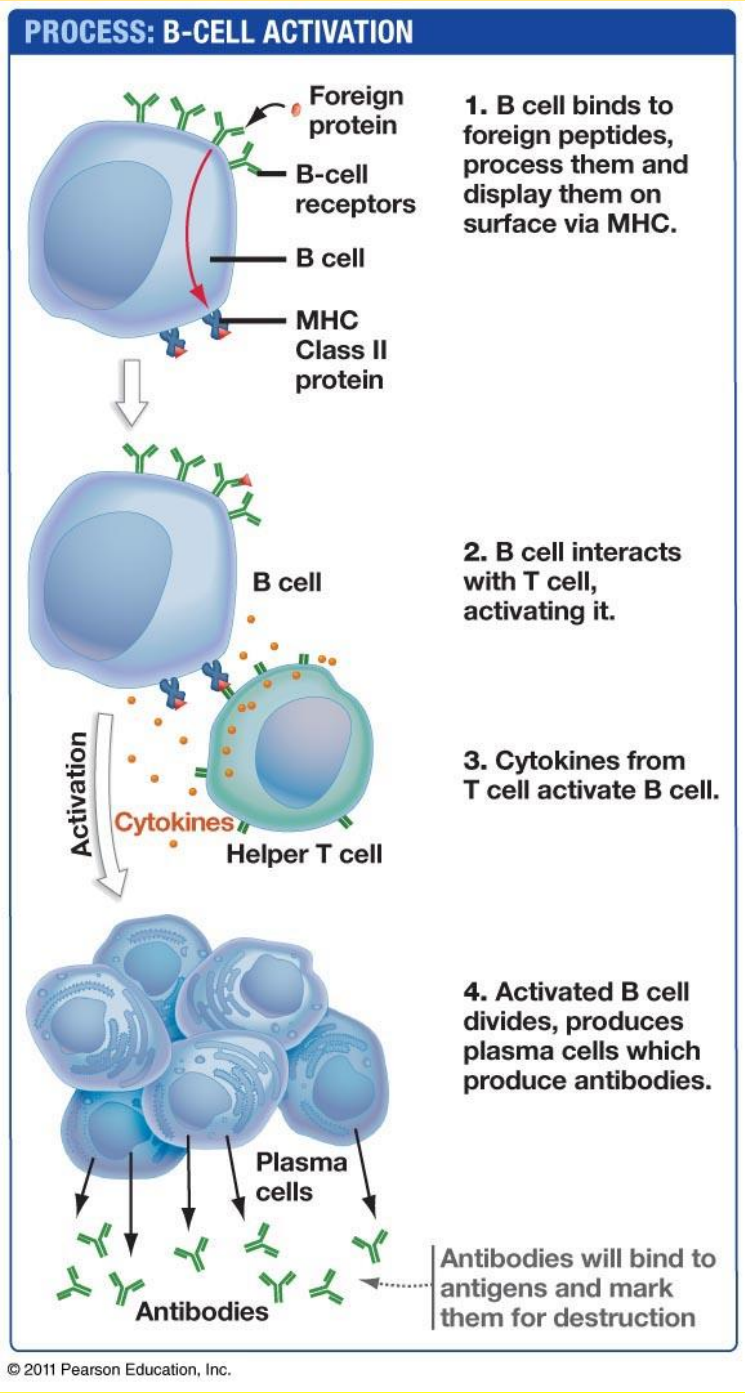
- $CD8^+$ and $CD4^+$ lymphocytes are activated by interactions with antigen-presenting leukocytes.
- B-cell activation involves four steps:

1. A **B cell encounters and binds to a foreign protein in a lymph node or the spleen**. The B cell internalizes and processes the molecule, and **presents it on the cell surface** by an MHC Class II protein.

2. The B cell **activates the helper T cell** when the antigen complex interacts with receptors on the helper T cell. The activated **helper T cell releases cytokines, which activate the B cell**.

3. The **activated B cell begins to divide**. Some daughter cells differentiate into **plasma cells**, which produce large quantities of antibodies.

4. Antibodies specific to the pathogen will circulate in the blood, and will bind to those antigens and mark them for destruction.



SUMMARY TABLE 49.3 **Activation and Function of Adaptive Immune System Cells**

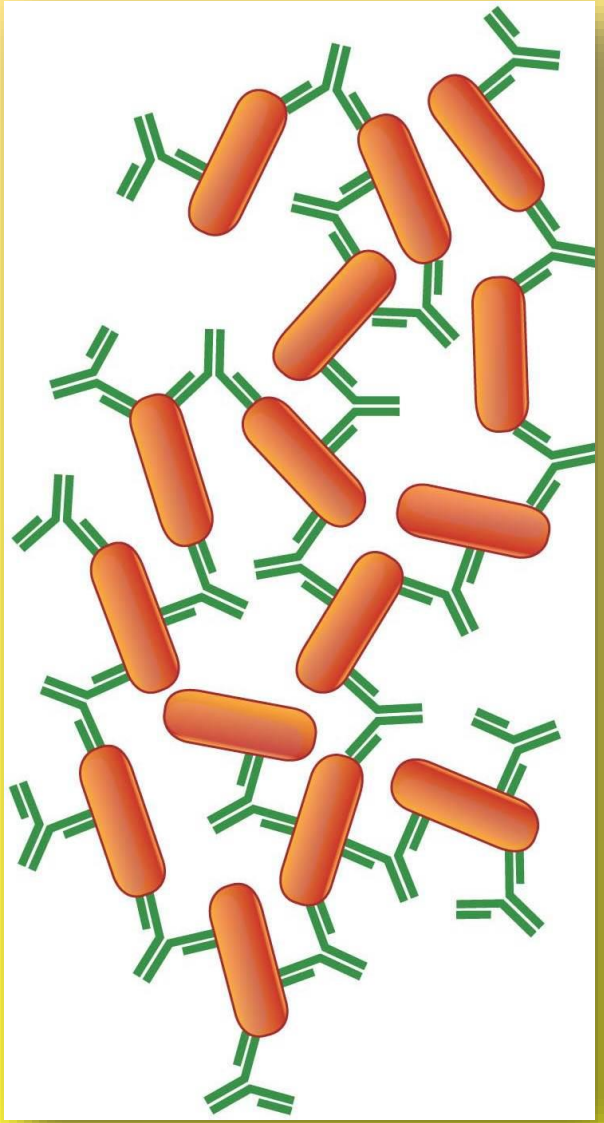
| Type of Lymphocyte | Method of Activation | Cells That Result from Activation and Clonal Expansion | Function of Resulting Cells |
|---|---|---|---|
| B cell | Receptor binds to free antigen, then interacts with $T_H2$ cell | Plasma cells | Secrete antibodies |
| | | Memory B cells | Participate in secondary response (secrete antibodies) |
| $CD4^+$ T cell | Receptor binds to antigen-MHC class II protein complex on dendritic cell or other antigen-presenting cell | $T_H1$ helper T cells | Activate cytotoxic T cells, regulate inflammatory response |
| | | $T_H2$ helper T cells | Activate B cells |
| | | Memory T cells | Participate in secondary response |
| $CD8^+$ T cell | Receptor binds to antigen-MHC class I protein complex on infected cell; may also interact with $T_H1$ cells | Cytotoxic T cells | Kill infected host cells |
| | | Memory T cells | Participate in secondary response |

# How Are Bacteria and Other Foreign Cells Killed?

- When antibodies coat foreign cells, it causes **agglutination** (clumping of bacteria). Cells that are agglutinated are readily phagocytized by macrophages.

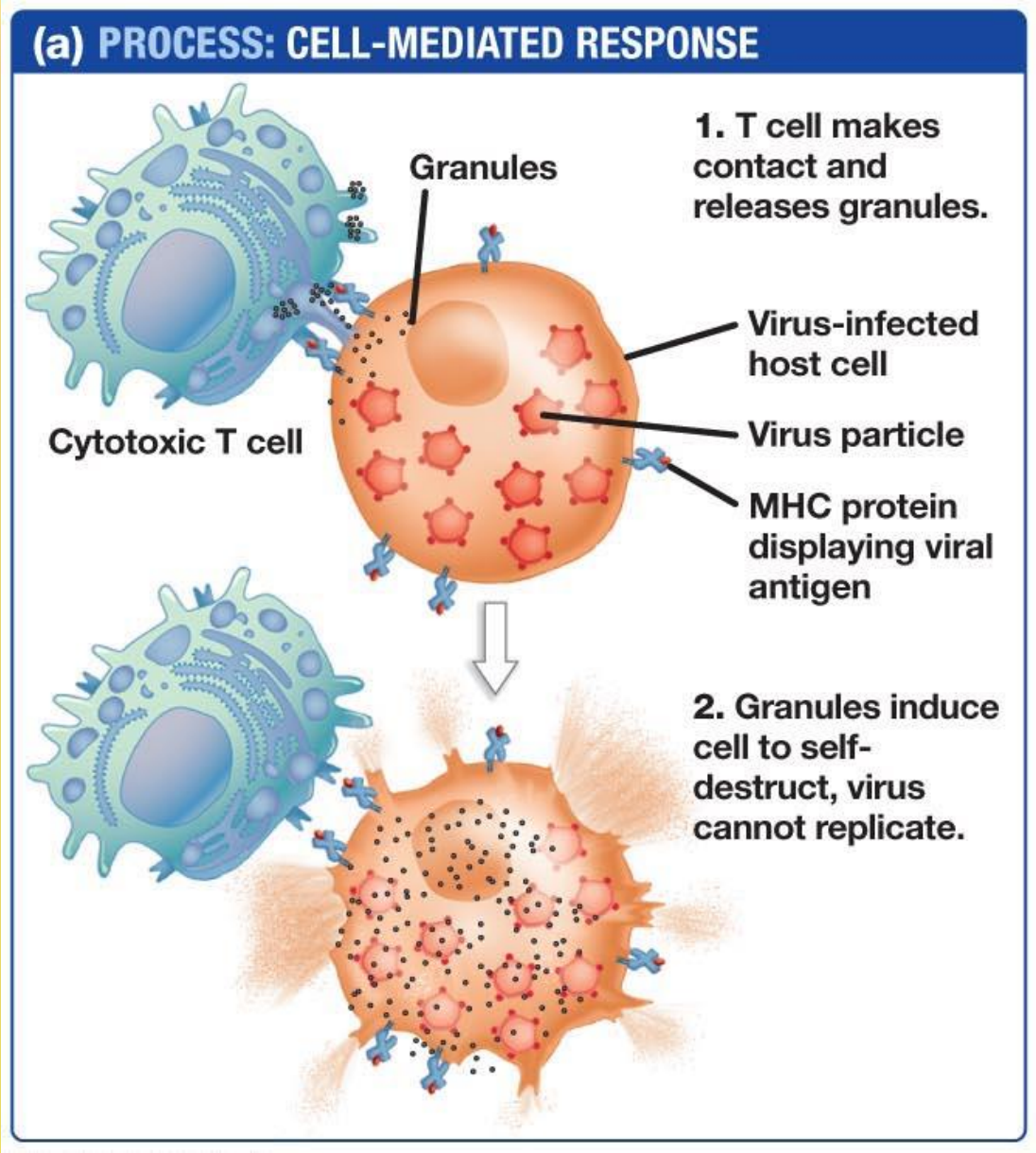
- Clumped and single cells that are tagged with antibodies are readily destroyed by macrophages via phagocytosis. Antibodies that are bound to antigens also stimulate a lethal group of proteins called the **complement system**.

- A combination of the innate and adaptive immune responses usually eliminates all invading bacteria within a few days.



# The Cell-Mediated Response

- In the **cell-mediated response**, cells that display viral antigens bound to class I MHC molecules are recognized by activated $CD8^+$ cells.
- These cytotoxic T cells bind to the virus-infected cell, produce pores in the membrane, and activate a self-destruct response.
- Because viruses can reproduce only inside host cells, the cell-mediated response limits the spread of infection by preventing new generations of virus particles from maturing.

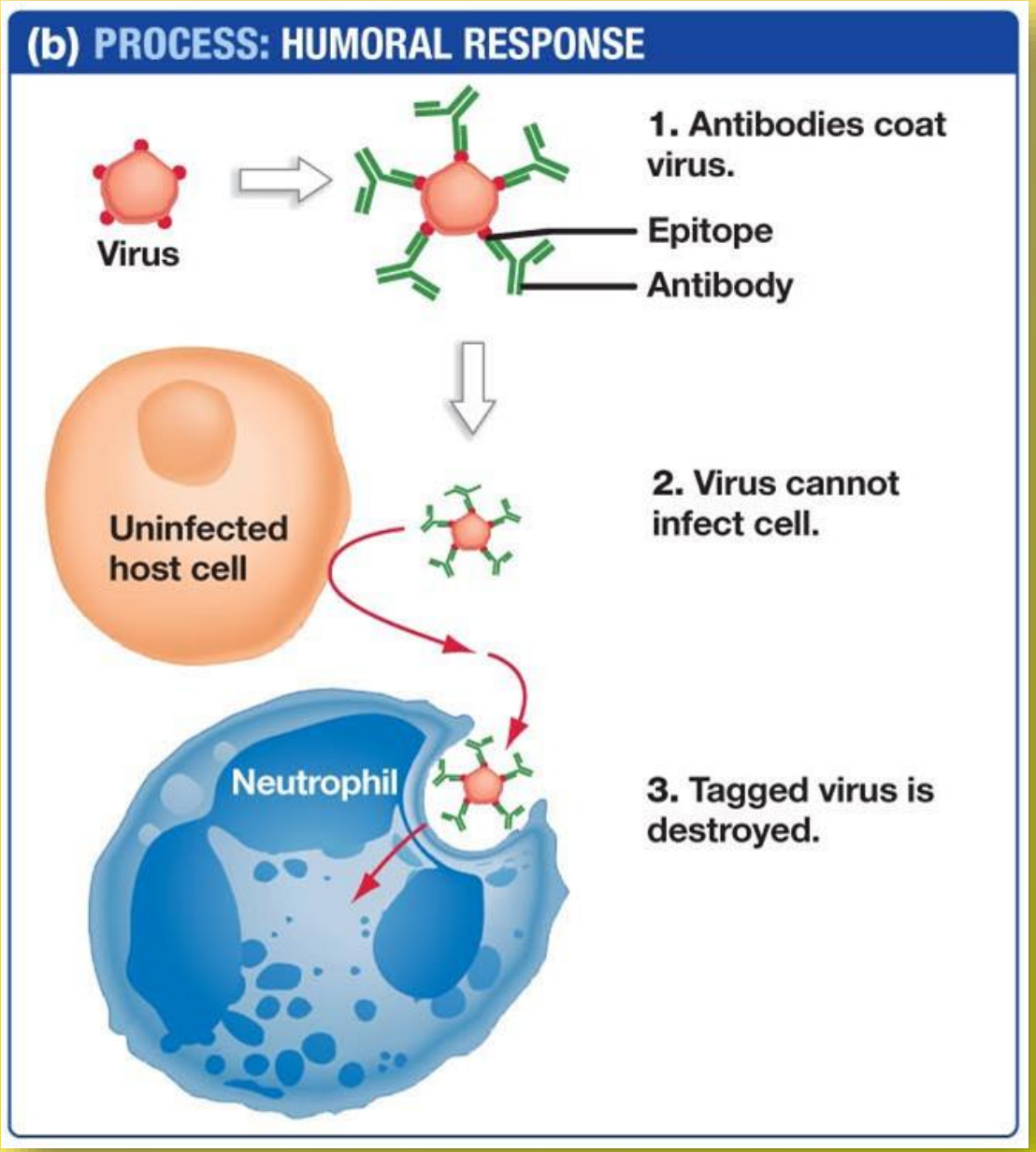


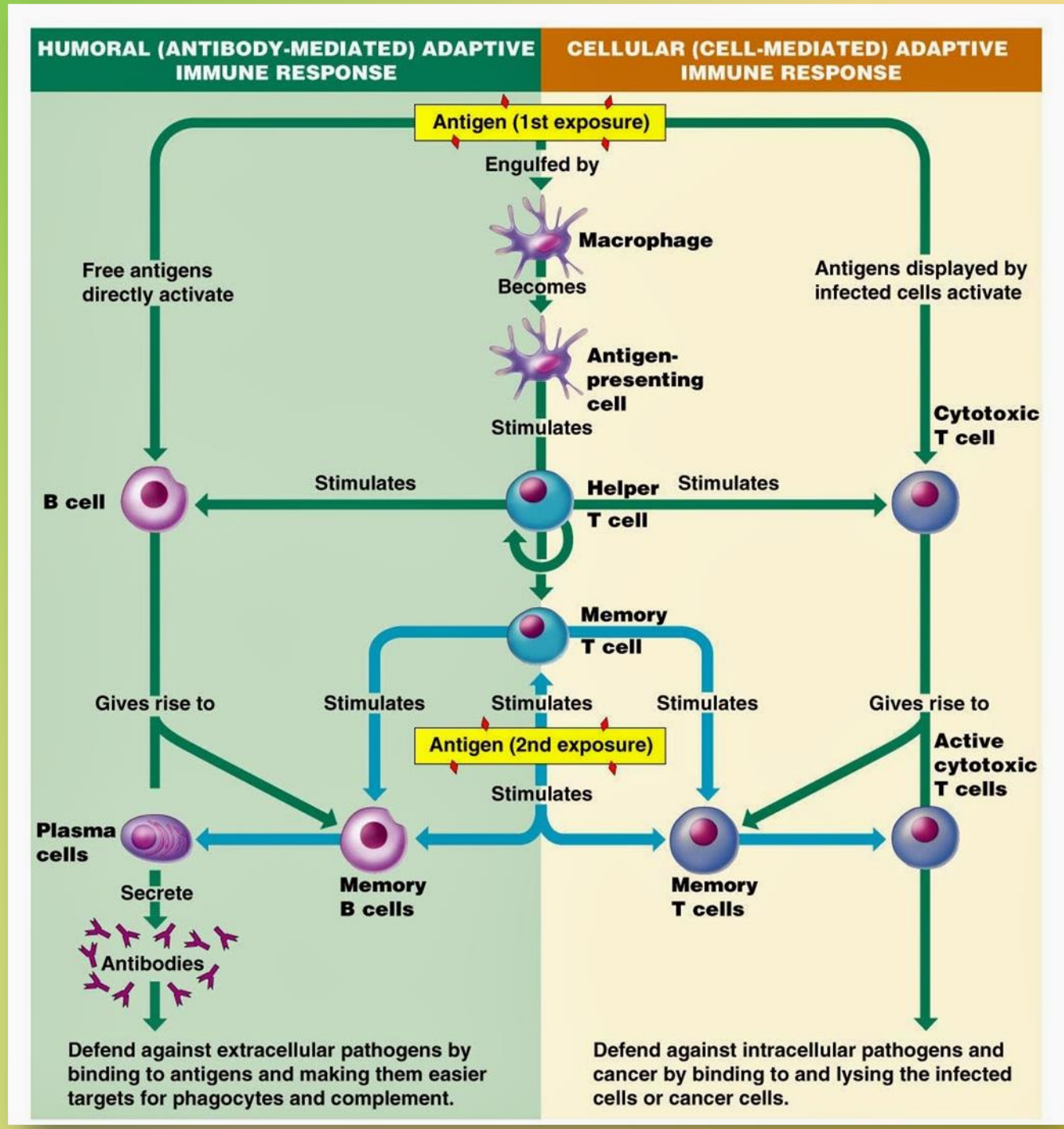
# The Humoral Response

- In the **humoral response**, antibodies coat free virus particles so that they cannot infect cells.
- Two things happen once antibodies bind to the outside of a virus:

    1. The virus is blocked from infecting host cells.
    2. Macrophages and other phagocytic cells recognize the antibody-coated particles and phagocytize them.

- Eventually, the virus population is reduced to zero.




HUMORAL (ANTIBODY-MEDIATED) ADAPTIVE IMMUNE RESPONSE
CELLULAR (CELL-MEDIATED) ADAPTIVE IMMUNE RESPONSE
Antigen (1st exposure)
Engulfed by
Macrophage
Becomes
Free antigens directly activate
Antigens displayed by infected cells activate
Antigen-presenting cell
Stimulates
Cytotoxic T cell
B cell
Stimulates
Helper T cell
Stimulates
Memory T cell
Gives rise to
Stimulates
Stimulates
Stimulates
Gives rise to
Antigen (2nd exposure)
Active cytotoxic T cells
Stimulates
Plasma cells
Memory B cells
Memory T cells
Secrete
Antibodies
Defend against extracellular pathogens by binding to antigens and making them easier targets for phagocytes and complement.
Defend against intracellular pathogens and cancer by binding to and lysing the infected cells or cancer cells.

# The Immune System Rejects Foreign Tissues and Organs

- Transplanted tissues and organs contain antigens that are recognized as foreign, and an immune response is mounted, leading to rejection of the organ and the possible death of the patient.

- To prevent strong immune reactions, physicians do two things:

1. Obtain the organ to be transplanted from a sibling or other donor whose MHC proteins are extremely similar to those of the recipient.
2. Treat the recipient with drugs that suppress the immune response.

# Responding to Future Infections: Immunological Memory

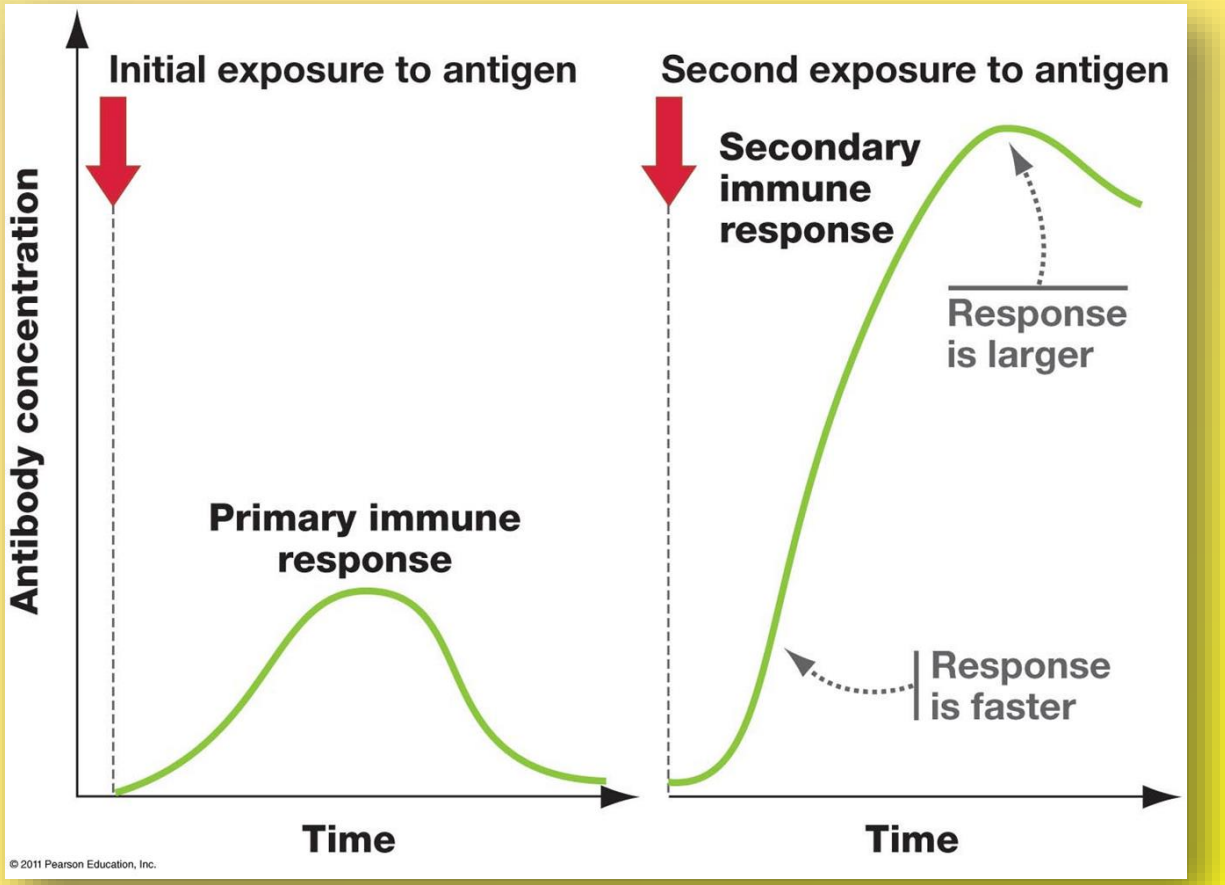
- Activated B cells and T cells produce specialized daughter cells called **memory cells** that do not participate in the **primary immune response**.

- They instead provide for a **secondary immune response** if the same antigen enters the body again.

- Circulating memory T and B cells increase the likelihood that lymphocytes with the correct antigen-specific receptors will find the antigen and activate quickly.
  - Therefore, the secondary response is faster and more efficient than the primary response.

# The Secondary Response Is Strong and Fast

- The ability of memory B cell receptors to bind to the antigen's epitope results in a process called **somatic hypermutation**, which fine-tunes the immune response.
    - Memory B cells with receptors that bind best to the antigen's epitope live and produce daughter cells; those that bind to the antigen less effectively die.
- The antibodies that result from somatic hypermutation are better-fitting than the antibodies produced by plasma cells during the primary immune response.



# Why Does Vaccination Work?

- A **vaccine** contains antigens from a pathogen or a killed or weakened version of the pathogen itself. There are three types of vaccines:

1. **Subunit vaccines**, such as those for hepatitis B and influenza, consist of isolated viral proteins.
2. **Inactivated viruses**, used in hepatitis A and polio, have been damaged by chemical treatments or exposure to ultraviolet light. They do not cause infections, but are antigenic.
3. **Attenuated**, or "**live**" **viruses** consist of complete virus particles that have lost the ability to grow rapidly in their normal host cells. The smallpox, polio, and measles vaccines consist of attenuated viruses.

- After **vaccination** (inoculation with a vaccine), the body mounts a primary immune response that produces memory cells. If a second infection occurs later, these memory cells respond quickly and eliminate the threat before illness appears.

- Viruses such as influenza and the human immunodeficiency virus (HIV) mutate so rapidly that they present the immune system with a constantly changing array of epitopes.

- Memory cells that were effective during a previous infection by these viruses are unlikely to bind to the changed epitopes and trigger a response to a later infection. As a result, it is extremely difficult to design an effective vaccine against these agents.

- Individuals with badly impaired adaptive immune systems suffer debilitating illness from infections. The immune system can fail by not reacting or by overreacting to a particular antigen.

# Immunodeficiency Diseases

- People infected with the **human immunodeficiency virus (HIV)** suffer a progressive loss of $CD4^+$ T cells because HIV kills $CD4^+$ T cells and macrophages.
  - Eventually, HIV-infected people develop **AIDS—acquired immune deficiency syndrome**.

# Allergies

- An **allergy**, or **allergic reaction**, is an abnormal over-reactive response to an antigen.
- Certain people produce IgE antibodies—which are normally only produced in response to infection by worms—in response to specific molecules found in cat dander, nuts, plant pollen, or other products.
  - Molecules that trigger this response are called **allergens** instead of antigens
- The presence of IgE antibodies in an allergic response triggers a series of events known as the **hypersensitive reaction**.
- When a person is first exposed to an allergen, receptors on certain leukocytes bind to the IgE antibodies that are produced.
- Once this binding event occurs, the cells (and the person) are said to be **sensitized**.
- Subsequent exposure to the allergen results in the onset of allergy symptoms.

# Allergies

- Later exposure causes the sensitized cells to produce large quantities of histamine, cytokines, chemokines, and other substances that all result in dilation and increased permeability of blood vessels, contraction of smooth muscles, and secretion by mucus-producing cells.

- A potentially lethal reaction called anaphylactic shock can occur if the immune response is very severe.