

The Immune System

Innate immunity

Acquired immunity

Antibody Classes

Examples of immune system disorders

Overview

- An animal must defend itself from the many dangerous pathogens it may encounter in the environment.
- Two major kinds of defense have evolved that counter these threats:
 - **Innate immunity**
 - **Acquired immunity**, also called *adaptive immunity*

What are the differences?

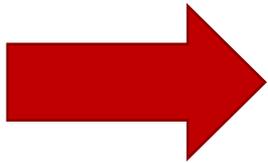
Innate immunity

- Present before any exposure to pathogens
- Effective from the time of birth
- Involves nonspecific responses to pathogens
- Provides broad defenses against infection

Acquired immunity

- Develops only after exposure to inducing agents such as microbes, toxins, or other foreign substances
- Involves a very specific response to pathogens

**Pathogens
(microorganisms
and viruses)**



INNATE IMMUNITY

- Recognition of traits shared by broad ranges of pathogens, using a small set of receptors
- Rapid (ready) response

Barrier defenses:

Skin
Mucous membranes
Secretions

Internal defenses:

Phagocytic cells
Antimicrobial proteins
Inflammatory response
Natural killer cells

ACQUIRED IMMUNITY

- Recognition of traits specific to particular pathogens, using a vast array of receptors
- Slower (unready) response

Humoral response:

Antibodies defend against infection in body fluids.

Cell-mediated response:

Cytotoxic lymphocytes defend against infection in body cells.

Innate immunity

Barrier Defenses

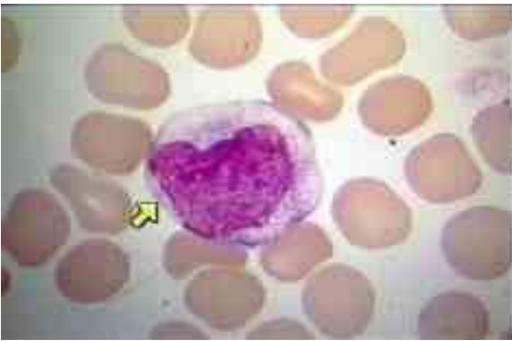
- Barrier defenses include **skin and mucous membranes** of the respiratory, urinary, and reproductive tracts
 - Mucus traps and allows removal of microbes
- Many **body fluids** including saliva, mucus, and tears are hostile to microbes
- The **low pH** of skin and the digestive system prevents growth of microbes

Innate immunity

Internal defenses

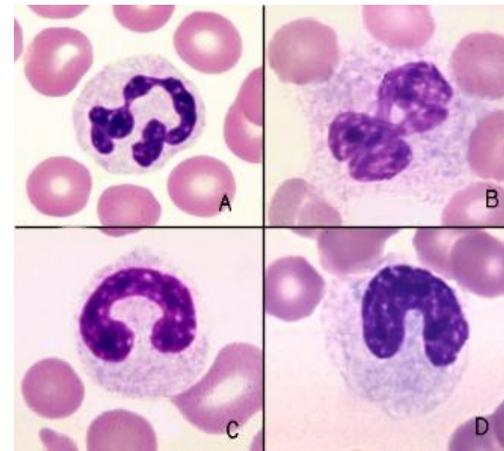
Cells of the Immune System: White Blood Cells

- **Lymphocytes**
 - Produce antibodies
- **Phagocytes**
 - Internal cellular defenses depend mainly on phagocytosis
 - ***Neutrophils & Macrophages*** are two types of WBC do phagocytosis
 - They Produced throughout life by the bone marrow.
 - They work as Scavengers – remove dead cells and microorganisms



Macrophages

- Larger than neutrophils.
- Found in the organs, not the blood.
- Made in bone marrow as monocytes, called macrophages once they reach organs.
- Long lived
- **Initiate** immune responses as they display antigens from the pathogens to the



Neutrophils

- 60% of WBCs
- ‘Patrol tissues’ as they squeeze out of the capillaries.
- Large numbers are released during infections
- Short lived – die after digesting bacteria
- Dead neutrophils make up a large proportion of

Phagocytes and Their Relatives

There are different types of **phagocytic cells**:

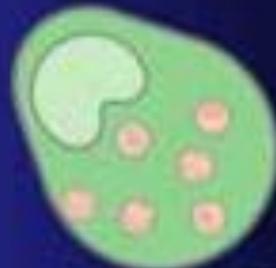
- **Neutrophils** engulf and destroy microbes
- **Macrophages** are part of the lymphatic system and are found throughout the body
- **Eosinophils** discharge destructive enzymes
- **Dendritic cells** stimulate development of acquired immunity



Monocyte



Eosinophil



Mast cell



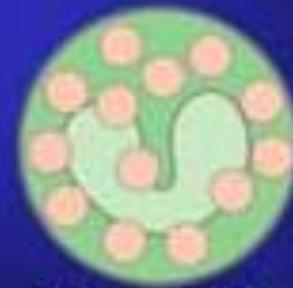
Macrophage



Dendritic cell



Neutrophil

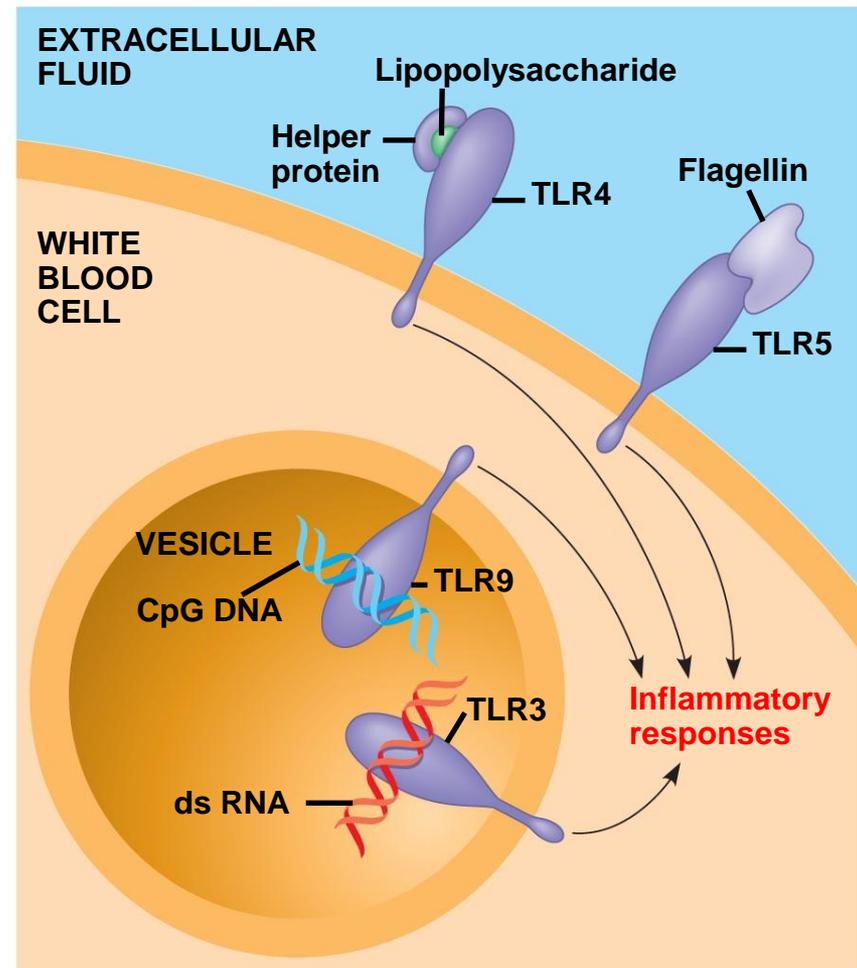


Basophil

Phagocytic cells - White blood cells

- A white blood cell engulfs a microbe, then fuses with a lysosome to destroy the microbe
 - attach to their prey via **surface receptors** and engulf them, forming a vacuole that fuses with a lysosome
 - Initiate the **inflammatory response**

Groups of pathogens are recognized by **TLR** [Toll-like receptors]



Phagocytosis

- If cells are under attack they release **histamine**.
- Histamine plus chemicals from pathogens mean **neutrophils** are attracted to the site of attack.
- Pathogens are attached to antibodies and neutrophils have **antibody receptors**.
- Endocytosis of neutrophil membrane → phagocytic vacuole → Lysosomes attach to phagocytic vacuole → pathogen digested by proteases

Antimicrobial Peptides and Proteins

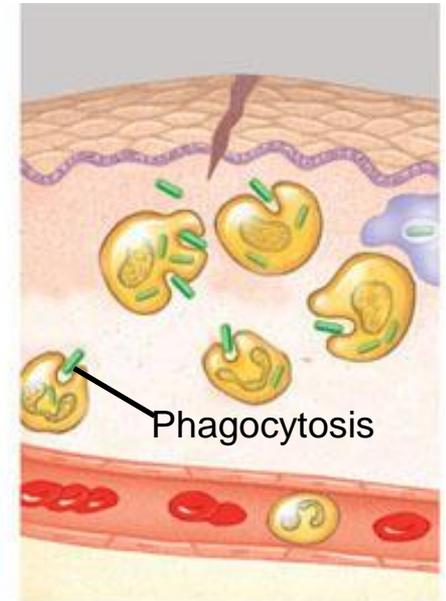
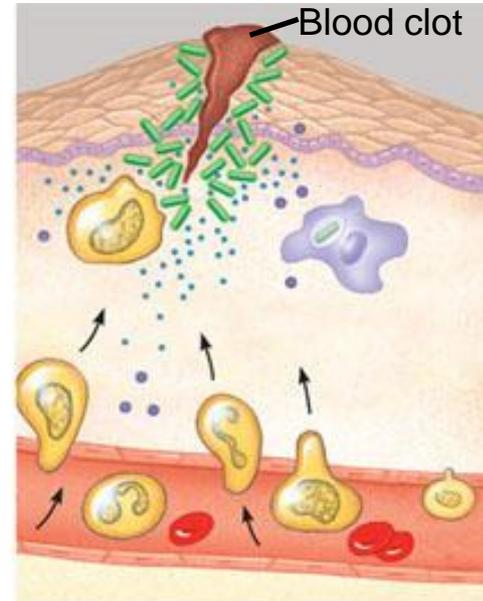
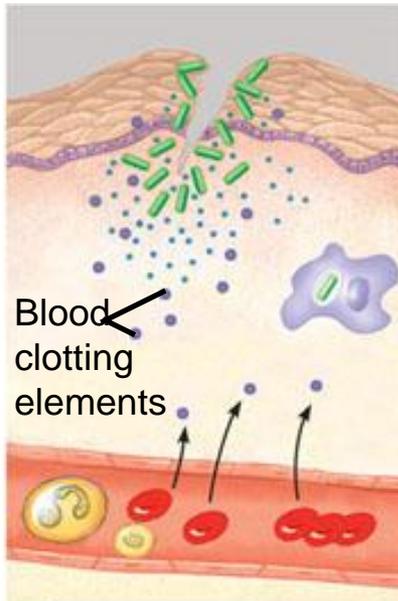
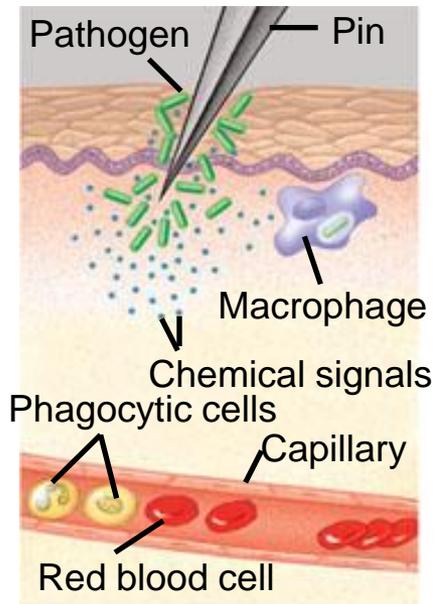
- Numerous proteins function in innate defense by attacking microbes directly by impeding their reproduction
- About 30 proteins make up the complement system which can cause lysis of invading cells and help trigger inflammation
- ***Interferons (IFN)*** provide innate defense against viruses and help activate macrophages
 - Among the molecules with important biological functions induced by IFN is the double-stranded RNA (dsRNA)-dependent protein kinase (**PKR**), an enzyme with multiple effects in cells, which plays a critical role

Internal defenses

Inflammatory Responses

- Following an injury, **mast cells** release **histamine**, which promotes changes in blood vessels; this is part of **inflammatory response**
- **Inflammatory responses** are these changes which increase local blood supply and allow more phagocytes and antimicrobial proteins to enter tissues
 - ***Pus***, a fluid rich in white blood cells, dead microbes, and cell debris, accumulates at the site of inflammation
- **Inflammation** can be either local or systemic (throughout the body)
 - **Fever** is a systemic inflammatory response triggered by ***pyrogens*** released by macrophages, and ***toxins*** from pathogens
 - **Septic shock** is a life-threatening condition caused by an overwhelming

Major events in the local inflammatory response



1 Chemical signals released by activated macrophages and mast cells at the injury site cause nearby capillaries to widen and become more permeable.

2 Fluid, antimicrobial proteins, and clotting elements move from the blood to the site. Clotting begins.

3 Chemokines released by various kinds of cells attract more phagocytic cells from the blood to the injury site.

4 Neutrophils and macrophages phagocytose pathogens and cell debris at the site, and the tissue heals.

Internal defenses

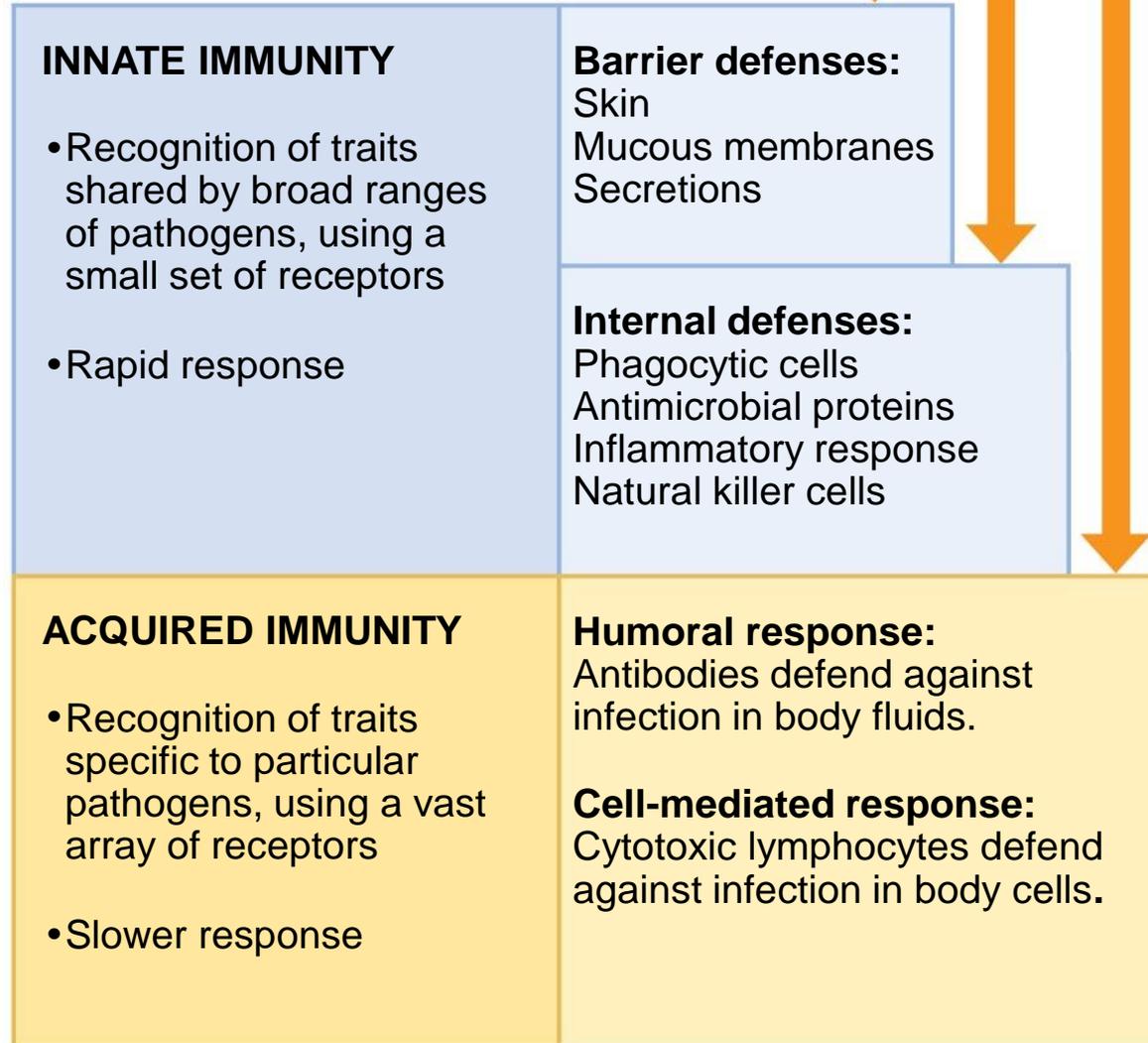
Natural Killer Cells

- Natural killer (NK) cells
 - Patrol the body and attack virus-infected body cells and cancer cells
 - Trigger apoptosis in the cells they attack
- How do Natural killer (NK) cells work?
 - All cells in the body (except red blood cells) have a class-I of **MHC** (**M**ajor **H**istocompatibility **C**omplex) protein on their surface
 - Cancerous or infected cells no longer express this protein; causing **natural killer (NK) cells** attack these damaged cells

Innate Immune System Evasion by Pathogens

- Some pathogens avoid destruction by modifying their surface to prevent recognition or by resisting breakdown following phagocytosis
- Mycobacterium Tuberculosis (TB) السل is one such disease that kills more than a million of people a year

**Pathogens
(microorganisms
and viruses)**

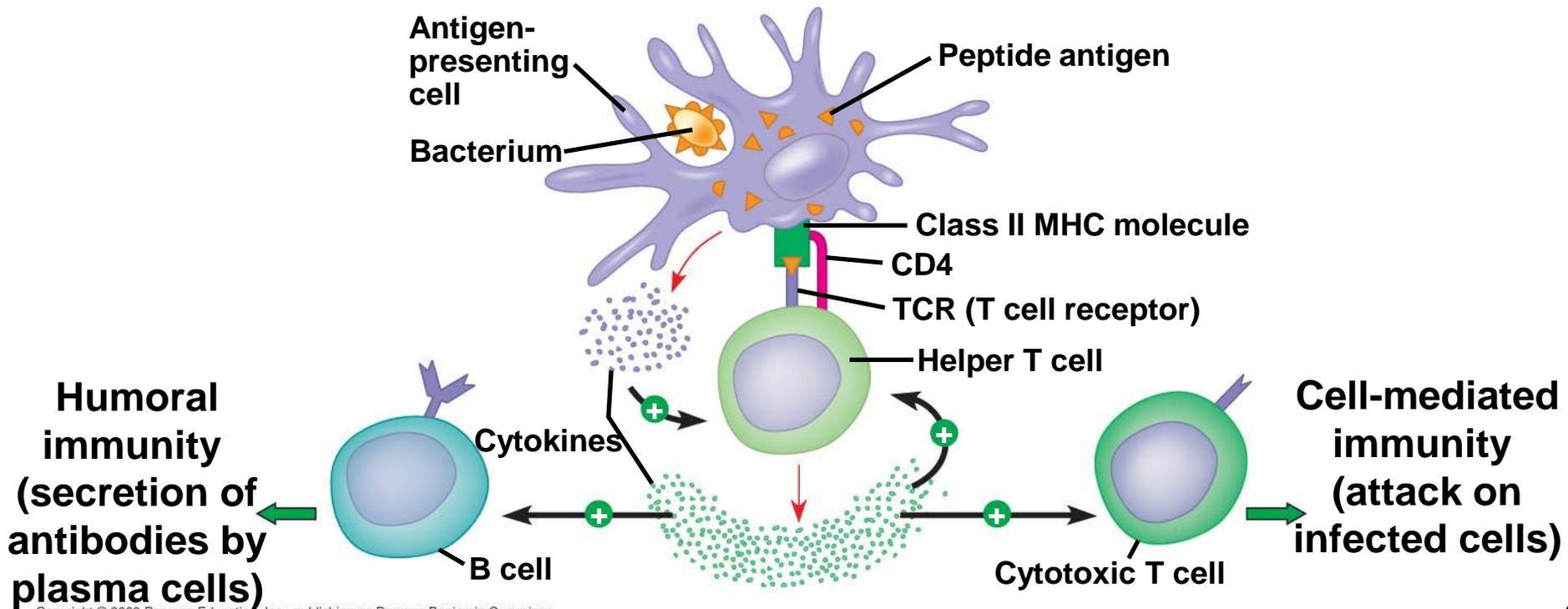


Acquired immunity

- **Lymphocytes** the white blood cells recognize and respond to antigens, foreign molecules
- Lymphocytes contribute to immunological memory, an enhanced response to a foreign molecule encountered previously
- Two types of lymphocytic cells:
 - **T cells**, mature in *Thymus*
 - **B cells**, mature in *Bone marrow* then concentrate in lymph nodes and spleen

Acquired immunity

- Acquired immunity has two responses where **Helper T cells** aid both:
 - Humoral immune response** involves activation and clonal selection of B cells, resulting in production of secreted antibodies
 - Cell-mediated immune response** involves activation



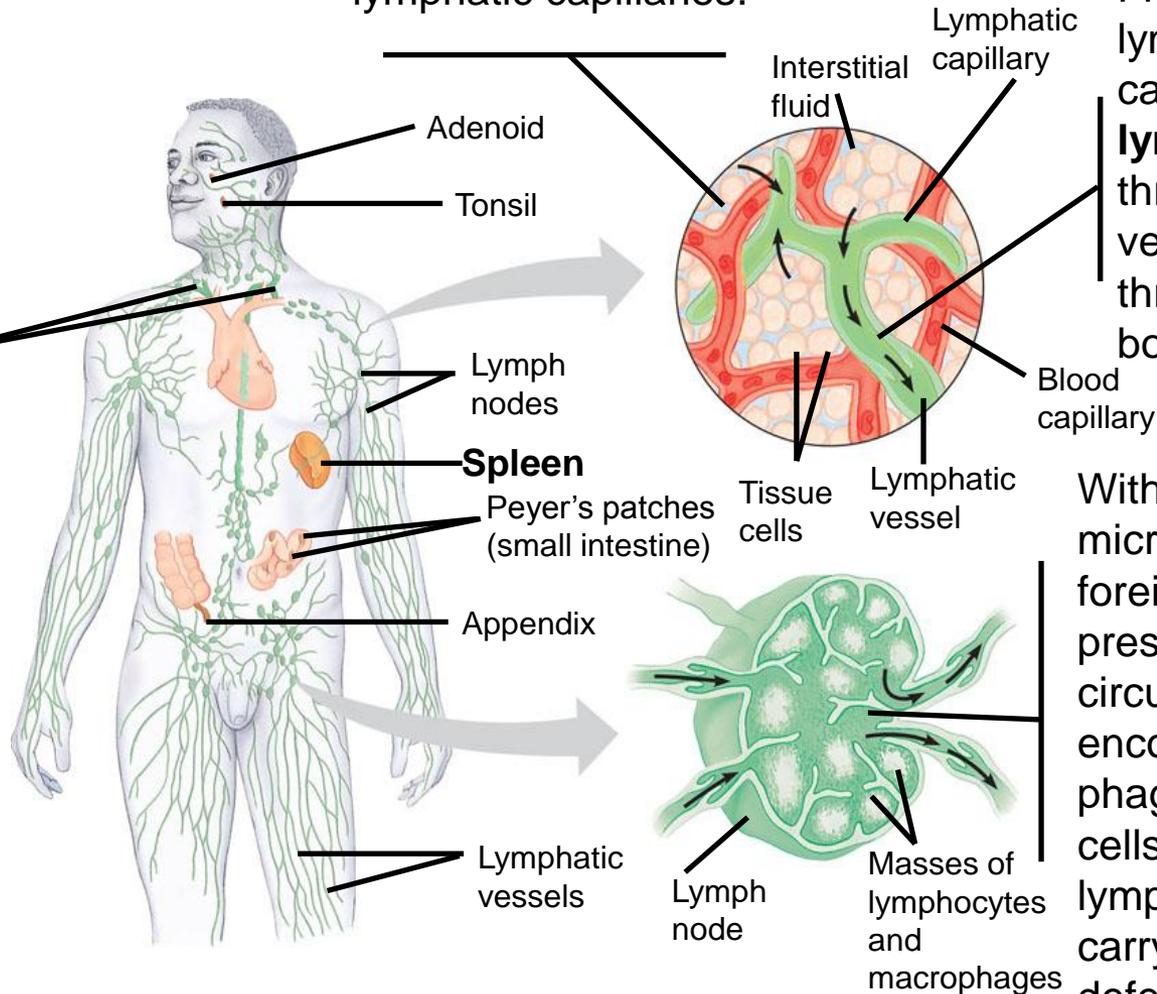
The lymphatic system plays an active role in defending the body from pathogens

1 Interstitial fluid bathing the tissues, along with the white blood cells in it, continually enters lymphatic capillaries.

2 Fluid inside the lymphatic capillaries, called **lymph**, flows through lymphatic vessels throughout the body.

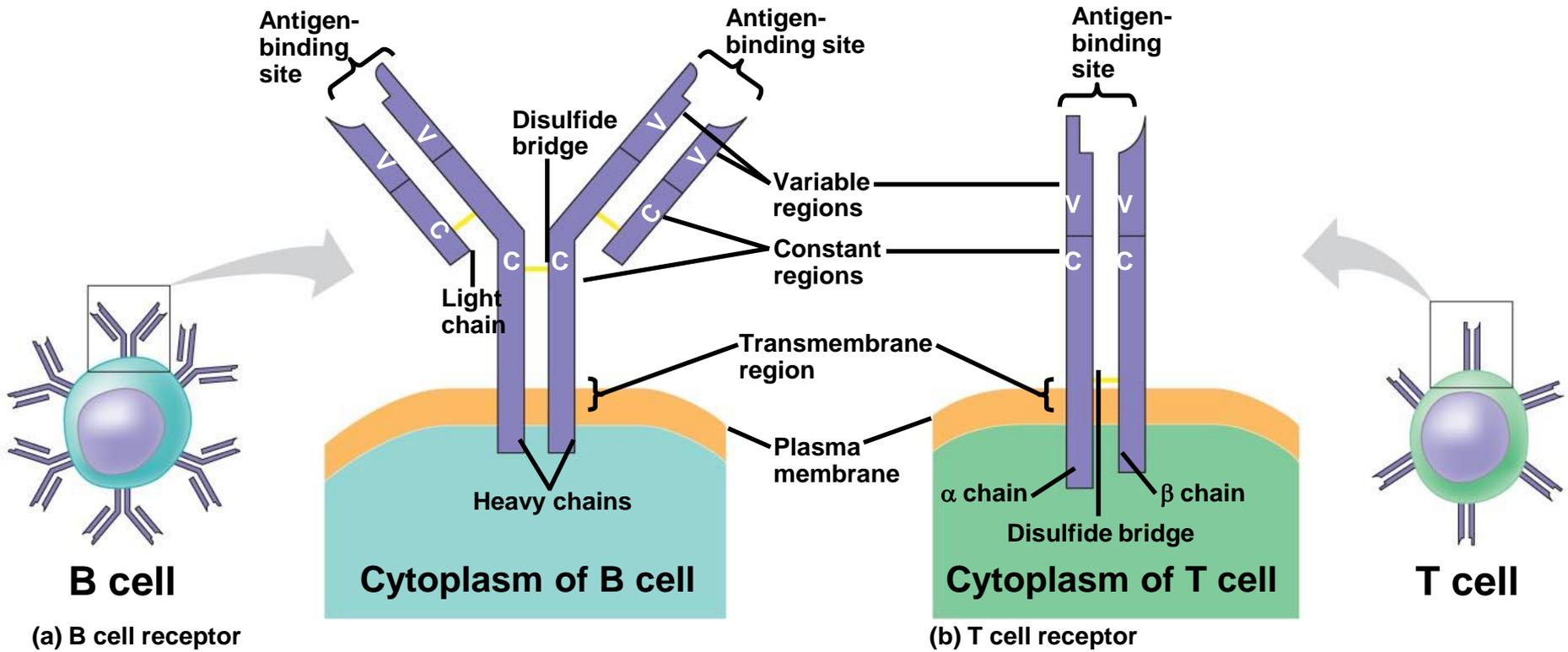
3 Within lymph nodes, microbes and foreign particles present in the circulating lymph encounter macrophages, dendritic cells, and lymphocytes, which carry out various defensive actions.

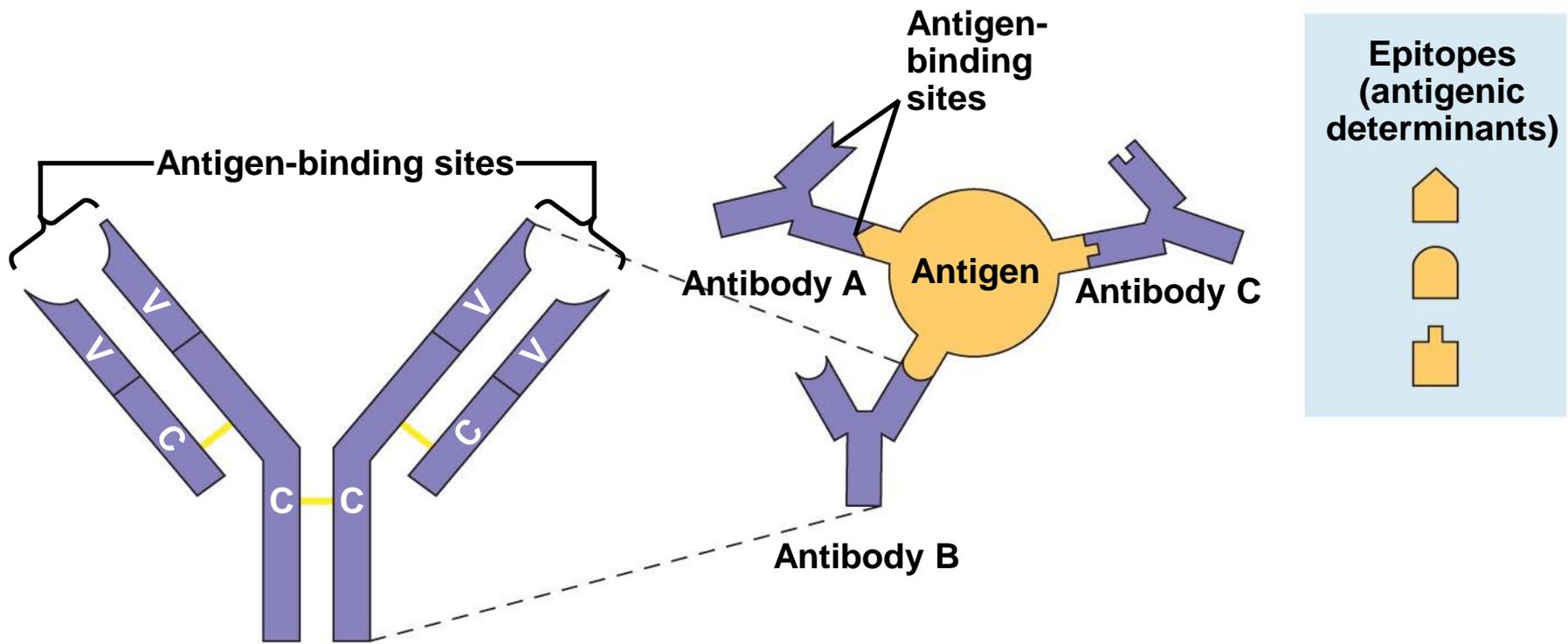
4 Lymphatic vessels return lymph to the blood via two large ducts that drain into veins near the shoulders.



Antigen Recognition by Lymphocytes

- Lymphocytes are activated by **Cytokines** which are secreted by macrophages and dendritic cells
- Lymphocyte receptors provide **pathogen-specific recognition**
- B cells and T cells have receptor proteins that can bind to foreign molecules
- Each individual lymphocyte is specialized to recognize a specific type of molecule
- An **antigen** is any foreign molecule to which a lymphocyte responds
- A single B cell or T cell has about 100,000 identical **antigen receptors**





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- All antigen receptors on a single lymphocyte recognize the same **Epitope** (or *antigenic determinant*) on an antigen
- B cells give rise to **effector cells** (or Plasma Cells), which secrete proteins called **Antibodies**

The Antigen Receptors of B Cells

- **B cell receptors** bind to specific, intact antigens
- The B cell receptor consists of two identical **heavy chains** and two identical **light chains**:
 - The tips of the chains form a *constant (C) region*, and each chain contains a *variable (V) region*, so named because its amino acid sequence varies extensively from one B cell to another
- Secreted **antibodies**, or **immunoglobulins**, are structurally similar to B cell receptors but lack transmembrane regions that anchor receptors in

The Antigen Receptors of T Cells

- Each **T cell receptor** consists of two different polypeptide chains:
 - The tips of the chain form a variable (V) region; the rest is a constant (C) region
- T cells can bind to an antigen that is free or on the surface of a pathogen
- T cells bind to antigen fragments presented on a host cell

Generation of Lymphocyte Diversity by Gene Rearrangement

- Differences in the variable region account for specificity of antigen receptors
- The *immunoglobulin (Ig)* gene encodes one chain of the B cell receptor
- Many different chains can be produced from the same Ig chain gene by rearrangement of the DNA
- **Rearranged DNA** is transcribed and translated and the antigen receptor formed

Immunoglobulin (antibody) gene rearrangement

- The capacity to generate diversity is built into the structure of the **Ig light-chain gene**.
- A receptor light chain is encoded by three gene segments:
 - a variable (**V**) segment,
 - a joining (**J**) segment
 - a constant (**C**) segment.
- The **V** and **J** segments together encode the **variable region** of the receptor chain, while the **C** segment encodes the entire constant region.

Immunoglobulin (antibody) gene rearrangement

- DNA sequencing reveals that the light-chain gene contains
 - 40 different *V* segments
 - 5 different *J* segments
 - a single *C* segment
- These alternative copies of the *V* and *J* segments are arranged within the gene in a series .
- Because a functional gene is built from one copy of each type of segment, the pieces can be combined in **200** ($40 V \times 5J \times 1 C$) different ways.
 - The number of different heavy-chain genes is even

DNA of undifferentiated B cell



1 DNA deleted between randomly selected V and J segments

DNA of differentiated B cell



Functional gene

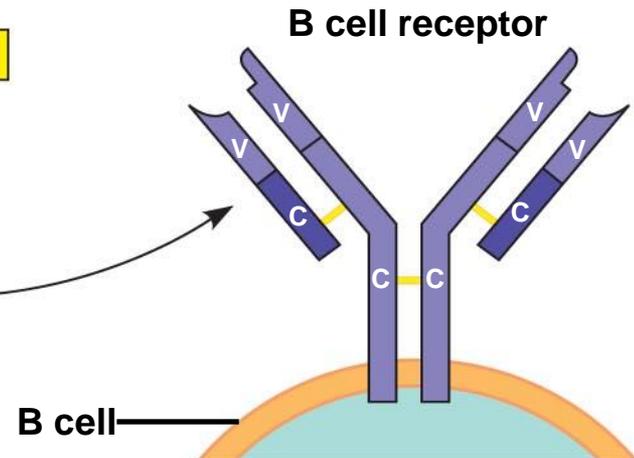
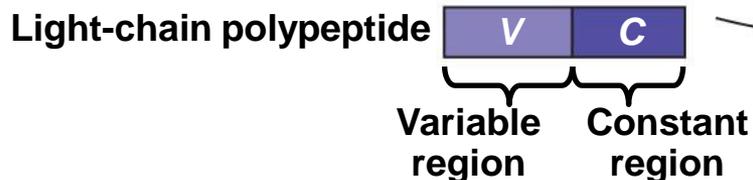
2 Transcription



3 RNA processing



4 Translation



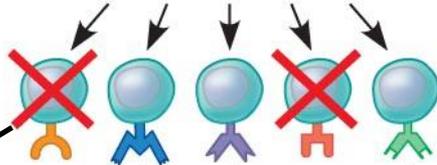
Origin of Self-Tolerance

- Antigen receptors are generated by **random rearrangement of DNA**
- As lymphocytes **mature** in ***bone marrow*** or the ***thymus***, they are tested for self-reactivity
- Lymphocytes with receptors specific for the body's own molecules are destroyed by apoptosis, or rendered nonfunctional

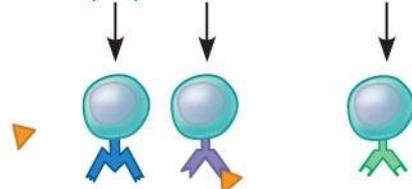
Stem cell



Cell division and gene rearrangement

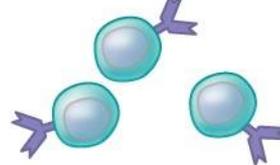


Elimination of self-reactive B cells

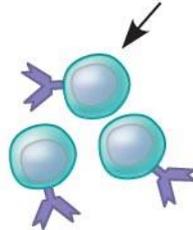


Antigen

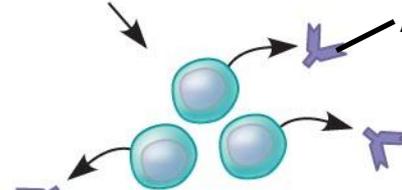
Clonal selection



Formation of activated cell populations



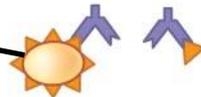
Memory cells



Antibody

Effector B cells

Microbe



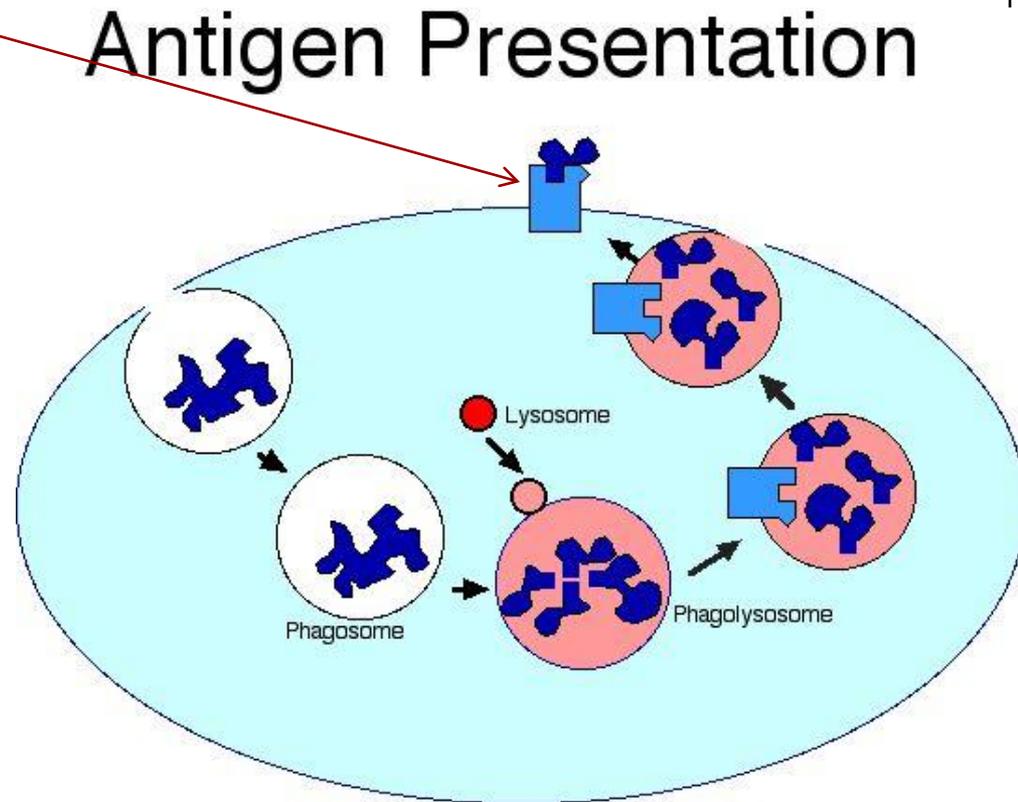
Receptors bind to antigens

Clonal Selection

- In the body there are few lymphocytes with antigen receptors for any particular **epitope**
- The binding of a mature lymphocyte to an antigen induces the lymphocyte to **divide** rapidly
 - This proliferation of lymphocytes is called “**clonal selection**”
- Two types of clones are produced:
 - short-lived activated **Effector cells**
 - long-lived **Memory cells**

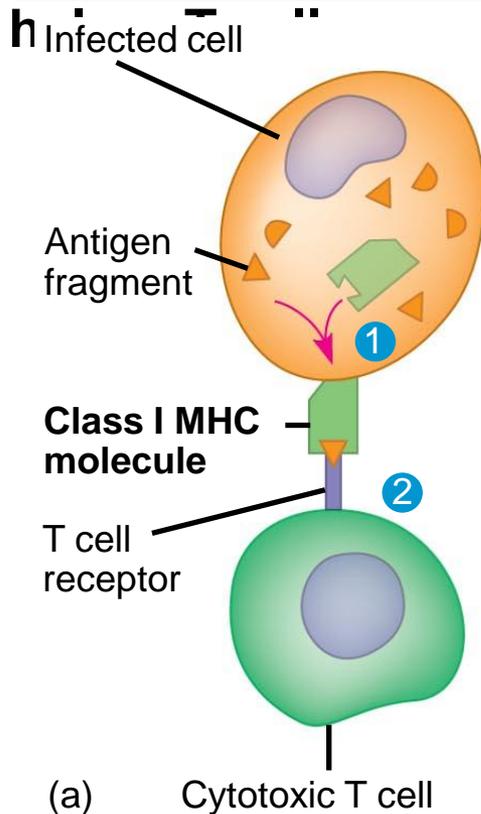
Antigen Presentation

- In infected cells, MHC molecules bind and transport antigen fragments to the cell surface, a process called “antigen presentation”
 - These antigen fragments are bound to cell-surface proteins called **MHC molecules** (*Major Histocompatibility Complex*; they are so named because they



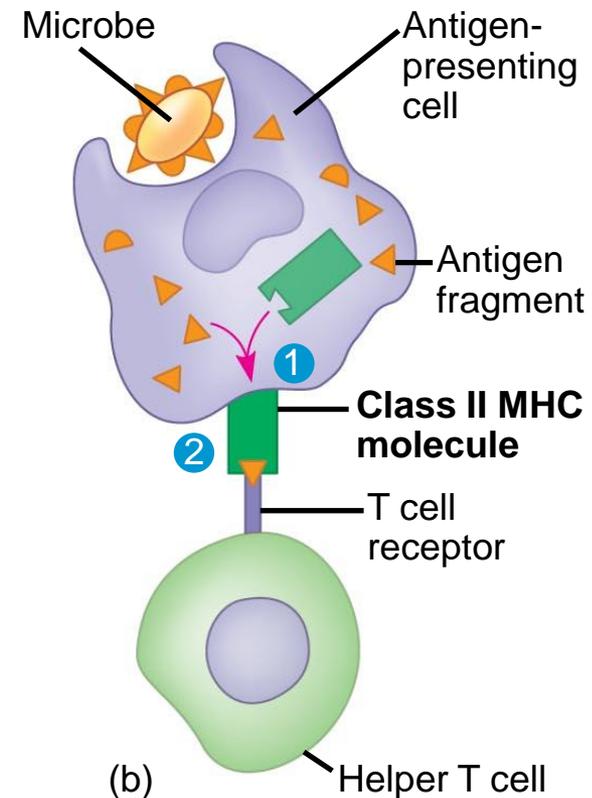
Antigen Presentation

- Different classes of MHC molecules:
 - **Class I MHC molecules:** are found on almost all nucleated cells of the body and display antigens to **cytotoxic T cells**
 - **Class II MHC molecules** are located mainly on dendritic cells, macrophages, and B cells that display to **cytotoxic T cells** and



1 Antigen associates with MHC molecule

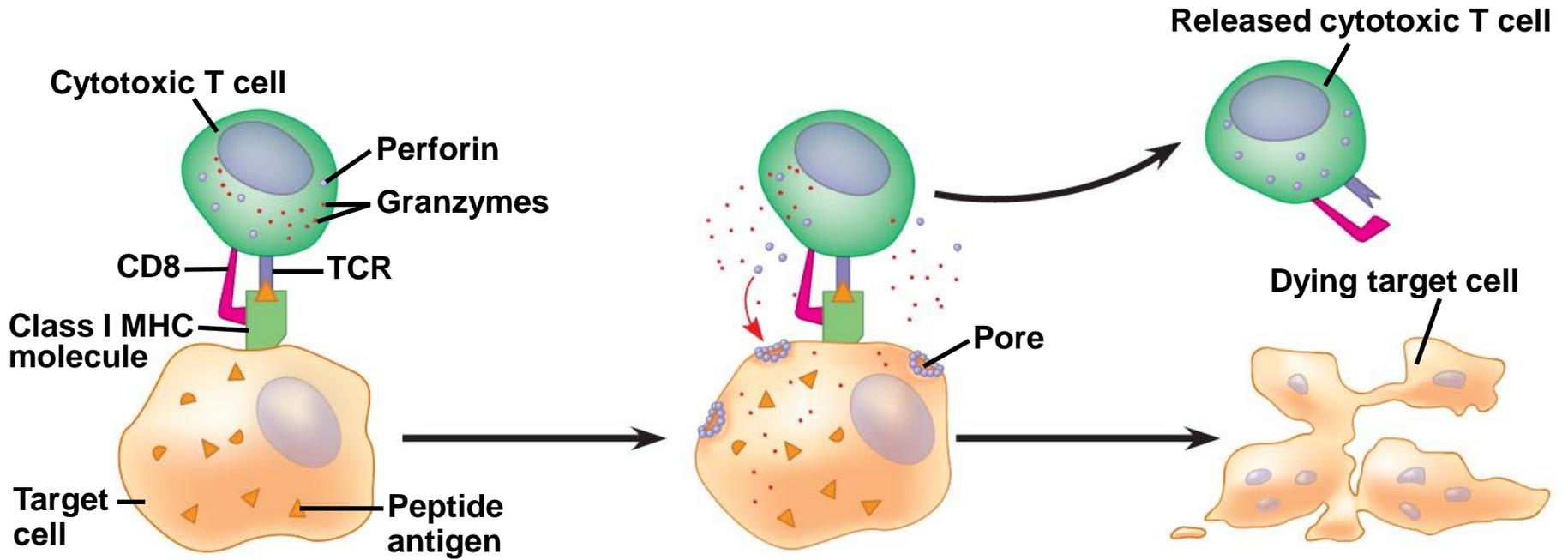
2 T cell recognizes combination



Cytotoxic T Cells related to class I MHC

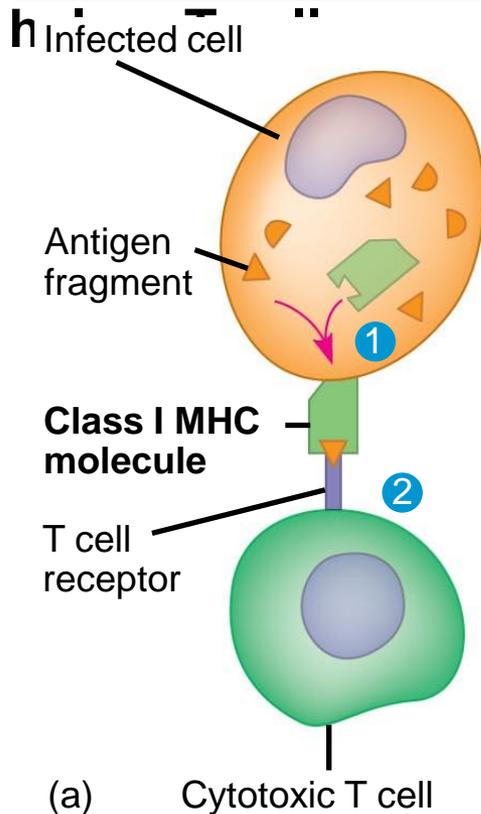
- **Cytotoxic T cells** are the **effector cells** in cell-mediated immune response
 - Cytotoxic T cells make **CD8**, a surface protein that greatly enhances interaction between a target cell and a cytotoxic T cell
 - Binding to a **class I MHC complex** on an infected cell activates a cytotoxic T cell and makes it an active killer
- The activated cytotoxic T cell secretes proteins that destroy the infected target cell :
 1. they attach to the cells to be killed and release proteins called **perforins** that create holes in the cell membrane of the target cell, with consequent cell lysis.
 2. they attach to a cell and kill it by triggering

The killing action of cytotoxic T cells



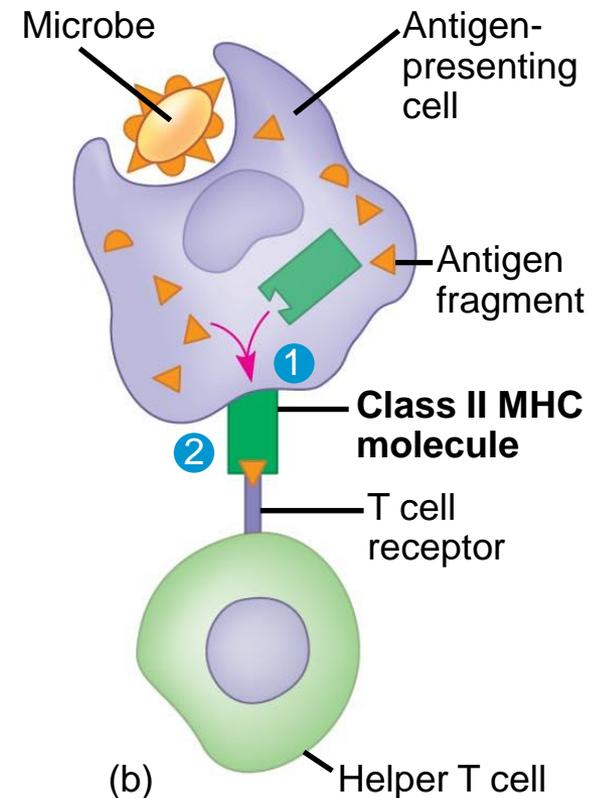
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1 Antigen associates with MHC molecule

2 T cell recognizes combination

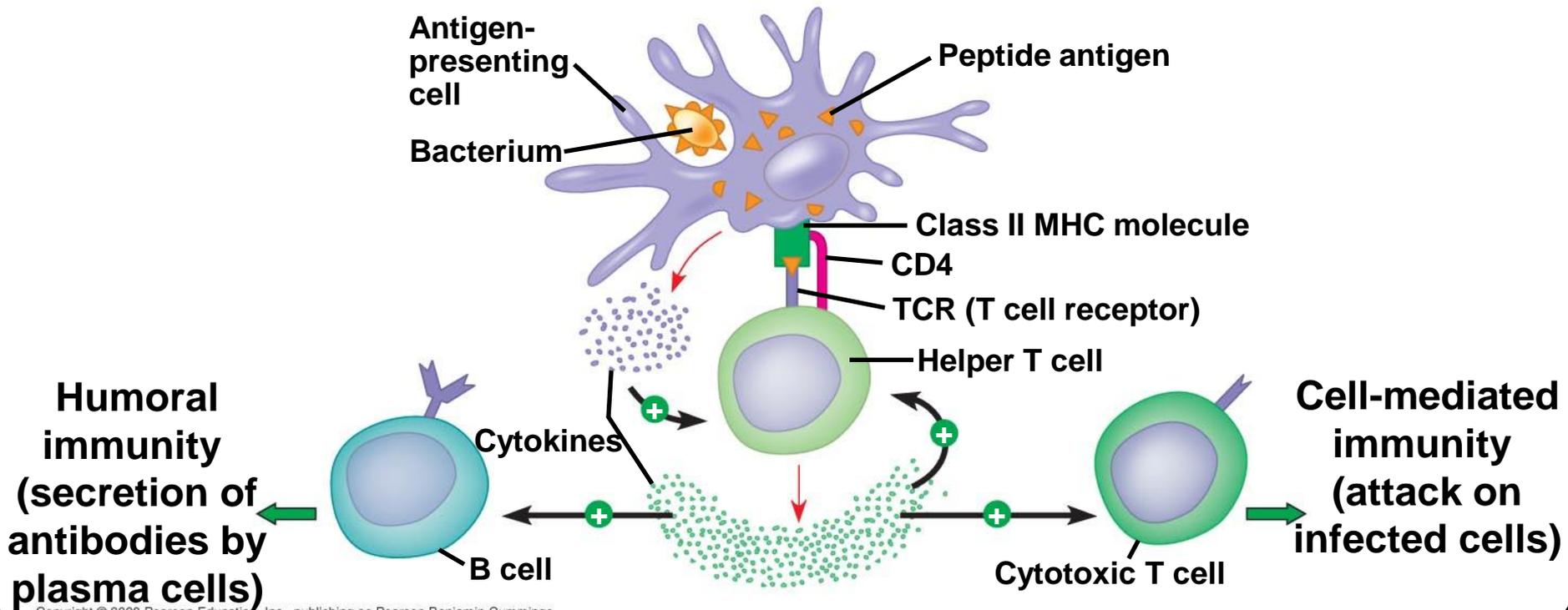


Helper T Cells related to class II MHC

- The two main subpopulations of T cells are:
 - **Helper T Cells**
 - **Cytotoxic T lymphocytes (CTLs).**
- ***Helper T cells*** have a marker called CD4 on their surfaces and are, hence, called **CD4⁺ T cells** binds to the class II MHC molecule
- This binding keeps the **helper T cell** joined to the antigen-presenting cell while ***activation occurs***
- Activated helper T cells secrete ***cytokines*** that stimulate other lymphocytes

Acquired immunity

- Acquired immunity has two responses where **Helper T cells** aid both:
 - Humoral immune response** involves activation and clonal selection of B cells, resulting in production of secreted antibodies
 - Cell-mediated immune response** involves activation

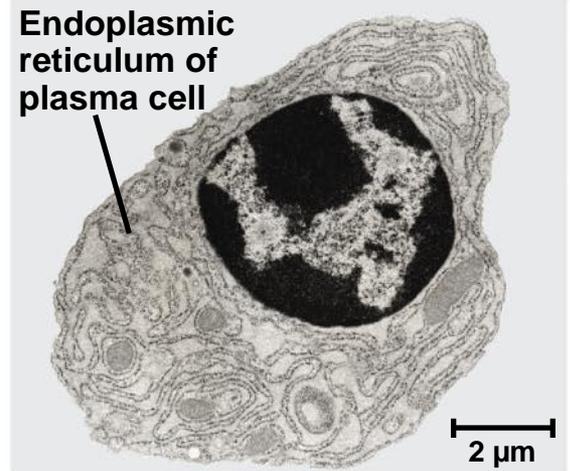
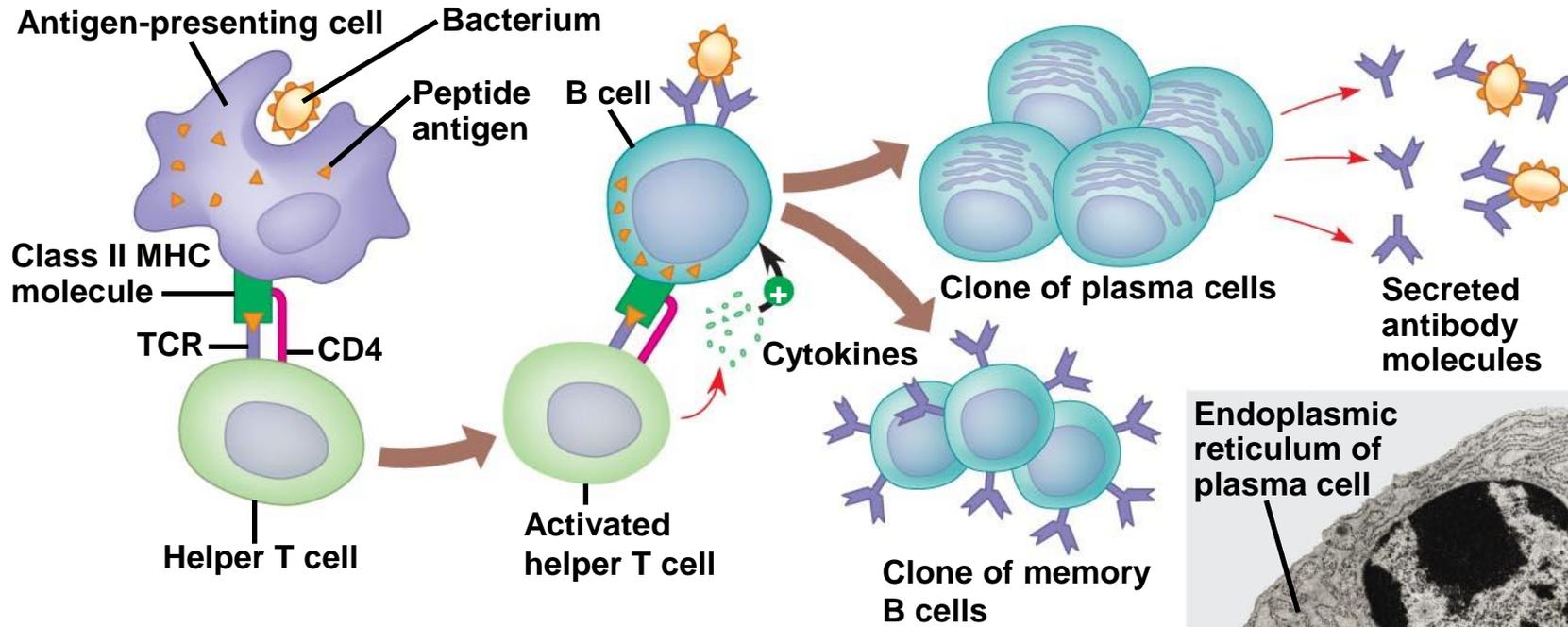


- **Helper T cells** play very important roles in the immune response by being responsible for:
 1. cytokine production (*Many of the following actions are mediated by cytokines*)
 2. interaction with B cells to promote their differentiation into effector cells
 3. activation of macrophages to phagocytose
 4. activation of cytotoxic lymphocytes
 5. induction of an inflammatory reaction
 6. respond to nearly all antigens

- The first encounter of a CD4⁺ or CD8⁺ T cell with its specific epitope is followed by amplification of that clone
 - some of the cells of this increased population become ***effector cells*** and some remain ***memory helper or memory cytotoxic T cells***, reacting rapidly to the next presentation of the same epitope

A Response to Extracellular Pathogens

- The humoral response is characterized by secretion of **antibodies by B cells**
- Activation of B cells is aided by **cytokines** and antigen binding to **helper T cells**
- Clonal selection of B cells generates antibody-secreting effector cells (**plasma cells**), the effector cells of humoral immunity

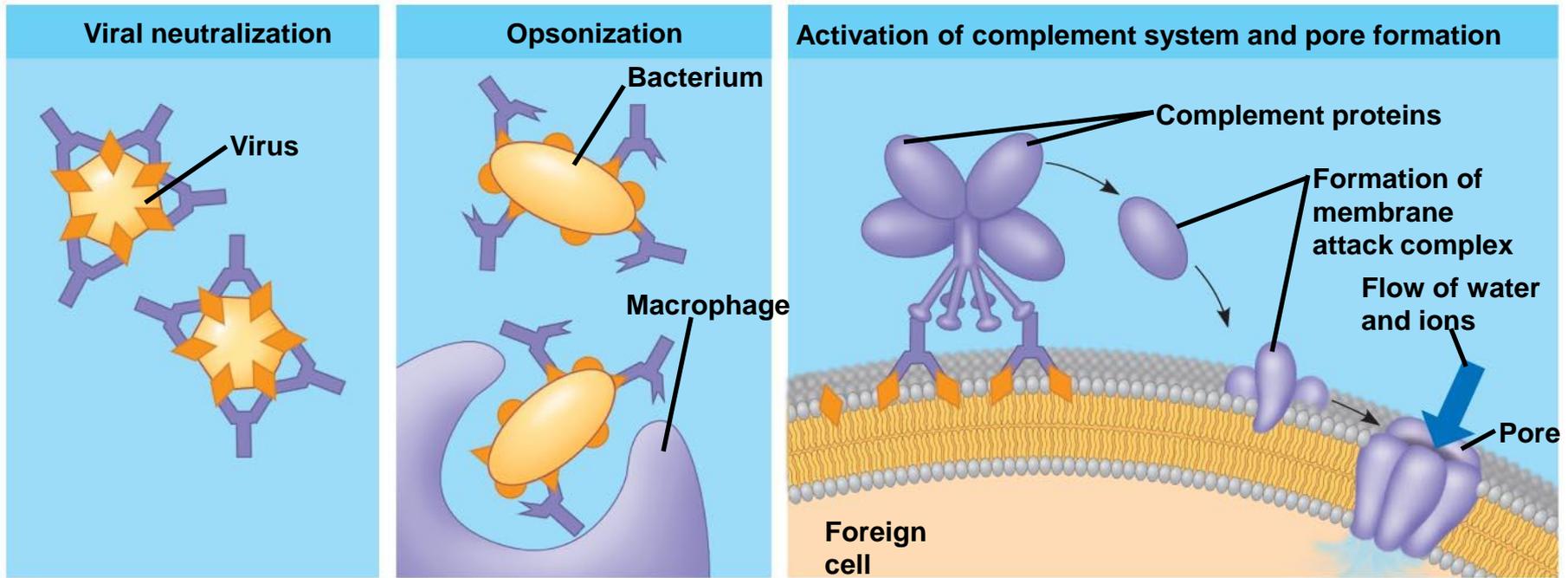


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B cell activation in the humoral immune response

Immunity

- **Neutralization:** occurs when a pathogen can no longer infect a host because it is bound to an antibody
- **Opsonization:** occurs when antibodies bound to antigens increase phagocytosis
- **Activation of complement system and pore formation:** Antibodies together with proteins of the complement system generate a membrane **attack complex** and **cell**



Antibody Classes

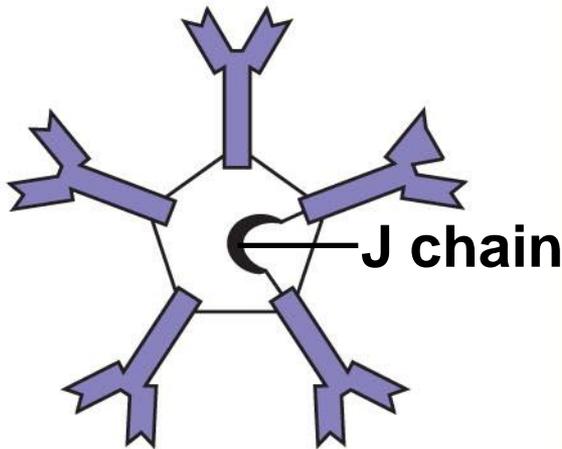
- The five major classes of antibodies, or immunoglobulins, differ in distribution and function
- **Polyclonal antibodies** are the products of many different clones of B cells following exposure to a microbial antigen
- **Monoclonal antibodies** are prepared from a single clone of B cells grown in culture

Class of Immuno- globulin (Antibody)

Distribution

Function

IgM (pentamer)



First Ig class produced after initial exposure to antigen; then its concentration in the blood declines

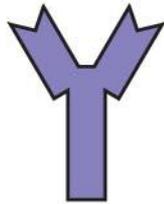
Promotes neutralization and cross-linking of antigens; very effective in complement system activation

Class of Immuno- globulin (Antibody)

Distribution

Function

IgG (monomer)



Most abundant Ig
class in blood;
also present in
tissue fluids

Promotes opsoniza-
tion, neutralization,
and cross-linking of
antigens; less effec-
tive in activation of
complement system
than IgM

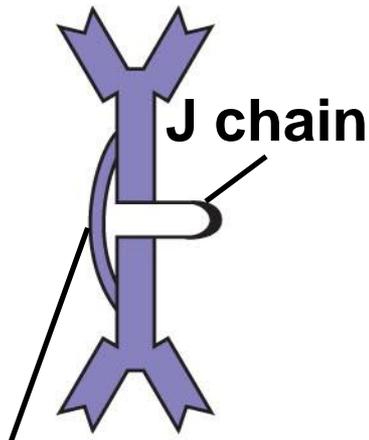
Only Ig class that
crosses placenta,
thus conferring
passive immunity
on fetus

Class of Immuno- globulin (Antibody)

Distribution

Function

**IgA
(dimer)**



**Secretory
component**

Present in
secretions such
as tears, saliva,
mucus, and
breast milk

Provides localized
defense of mucous
membranes by
cross-linking and
neutralization of
antigens

Presence in **breast
milk** confers
passive immunity
on nursing infant

Class of Immuno- globulin (Antibody)	Distribution	Function
IgE (monomer)	Present in blood at low concentrations	Triggers release from mast cells and basophils of hista- mine and other chemicals that cause allergic reactions

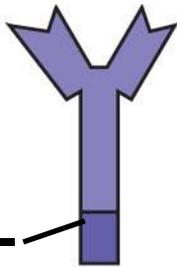


Class of Immunoglobulin (Antibody)

Distribution

Function

IgD (monomer)



Trans-
membrane
region

Present primarily on surface of B cells that have not been exposed to antigens

Acts as antigen receptor in the antigen-stimulated proliferation and differentiation of B cells (clonal selection)

Active and Passive Immunization

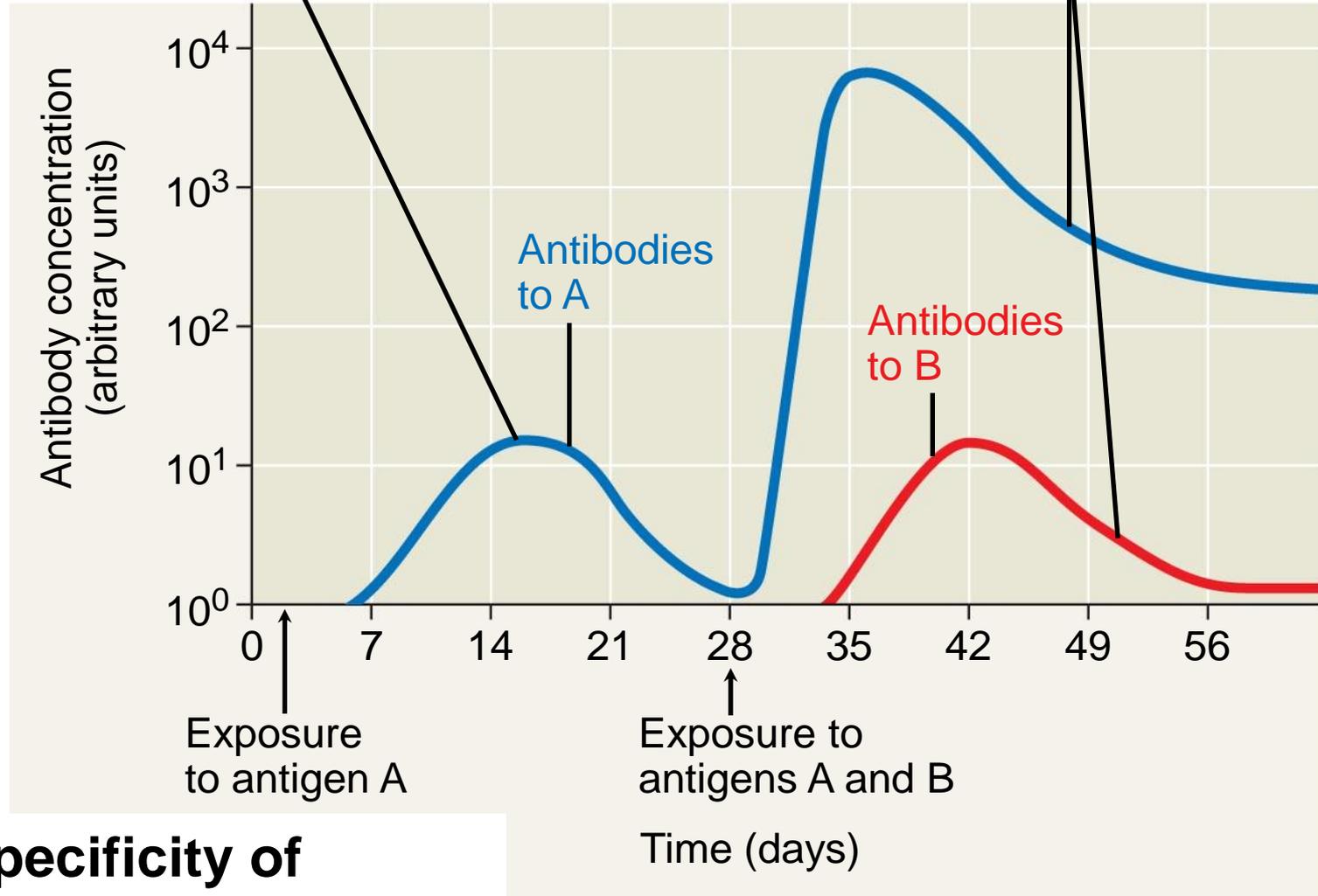
- **Active immunity** develops naturally in response to an infection
 - It can also develop following immunization, also called **vaccination**
 - In **immunization**, a nonpathogenic form of a microbe or part of a microbe elicits an immune response to an immunological memory
- **Passive immunity** provides immediate, short-term protection
 - It is conferred naturally when IgG crosses the placenta from mother to fetus or when IgA passes from mother to infant in breast milk

The exposure to a specific antigen

- The first exposure to a specific antigen represents the “**primary immune response**”
 - During this time, effector B cells (or plasma cells) are generated, and T cells are activated to their effector forms
- In the “**secondary immune response**”, memory cells facilitate a faster, more efficient response

Primary immune response to antigen A produces antibodies to A.

Secondary immune response to antigen A produces antibodies to A; primary immune response to antigen B produces antibodies to B.



The specificity of immunological memory

Examples of immune system disorders

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**

Blood Groups

- Antigens on red blood cells determine whether a person has blood type A (A antigen), B (B antigen), AB (both A and B antigens), or O (neither antigen)
- Antibodies to nonself blood types exist in the body
- ***Transfusion*** with incompatible blood leads to destruction of the transfused cells
- ***Recipient-donor combinations*** can be fatal or safe

Tissue and Organ Transplants

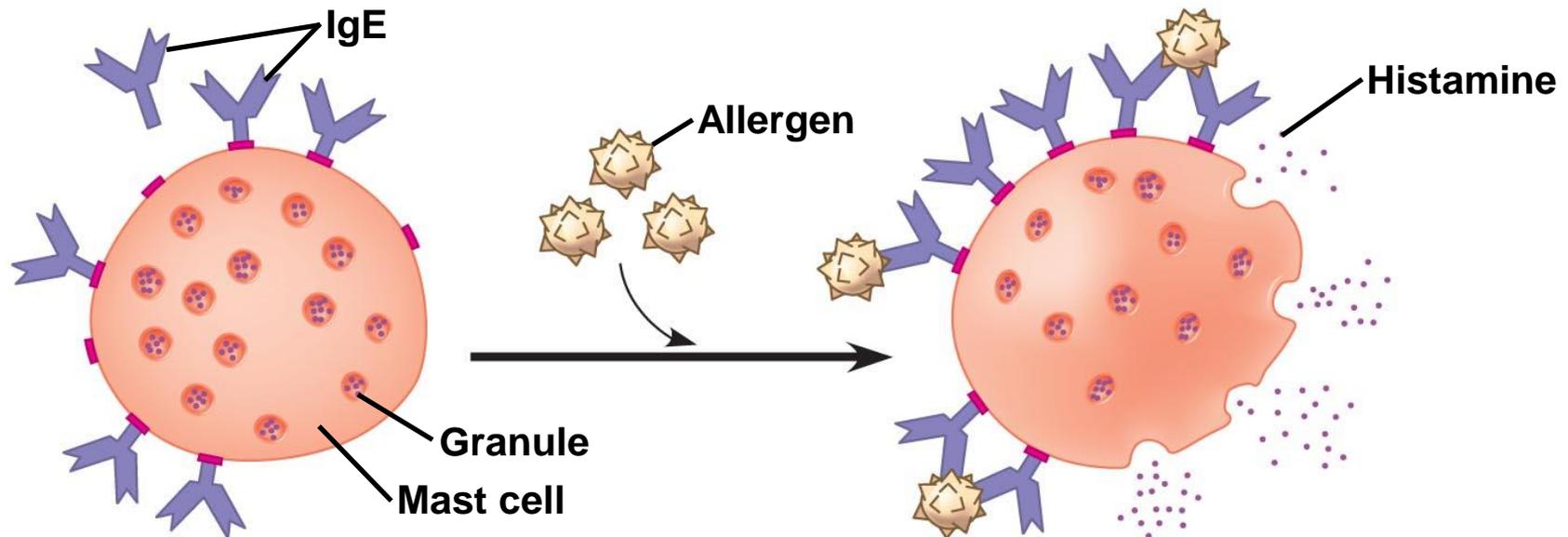
- MHC molecules are different among genetically nonidentical individuals
- Differences in MHC molecules stimulate rejection of tissue grafts and organ transplants
- Chances of successful transplantation increase if donor and recipient MHC tissue types are well matched
- **Immunosuppressive drugs** facilitate transplantation
- Lymphocytes in bone marrow transplants may cause the donor tissue to reject the recipient

Exaggerated, self-directed, or diminished immune responses can cause disease

- Disruption in immune system function can elicit or exacerbate disease
 - Some pathogens have evolved to diminish the effectiveness of host immune responses
- If the delicate balance of the immune system is disrupted the effects on the individual can range from minor to often fatal consequences
 - Allergies
 - Autoimmune Diseases
 - Immunodeficiency Diseases

Allergies

- Allergies are exaggerated (hypersensitive) responses to antigens called **allergens**
- In localized allergies such as *hay fever*, IgE antibodies produced after first exposure to an allergen attach to receptors on **mast cells**



Allergies

- The next time the allergen enters the body, it binds to mast cell–associated IgE molecules
- Mast cells release **histamine** and other mediators that cause vascular changes leading to typical allergy symptoms
- An **acute allergic response** can lead to ***anaphylactic*** shock, a life-threatening reaction that can occur within seconds of allergen exposure

Autoimmune Diseases

- In individuals with autoimmune diseases, the immune system loses tolerance for self and turns against certain molecules of the body
- Autoimmune diseases include:
 - systemic lupus erythematosus, الذئبة الحمامية الجهازية
 - rheumatoid arthritis, التهاب المفاصل الروماتويدي
 - insulin-dependent diabetes



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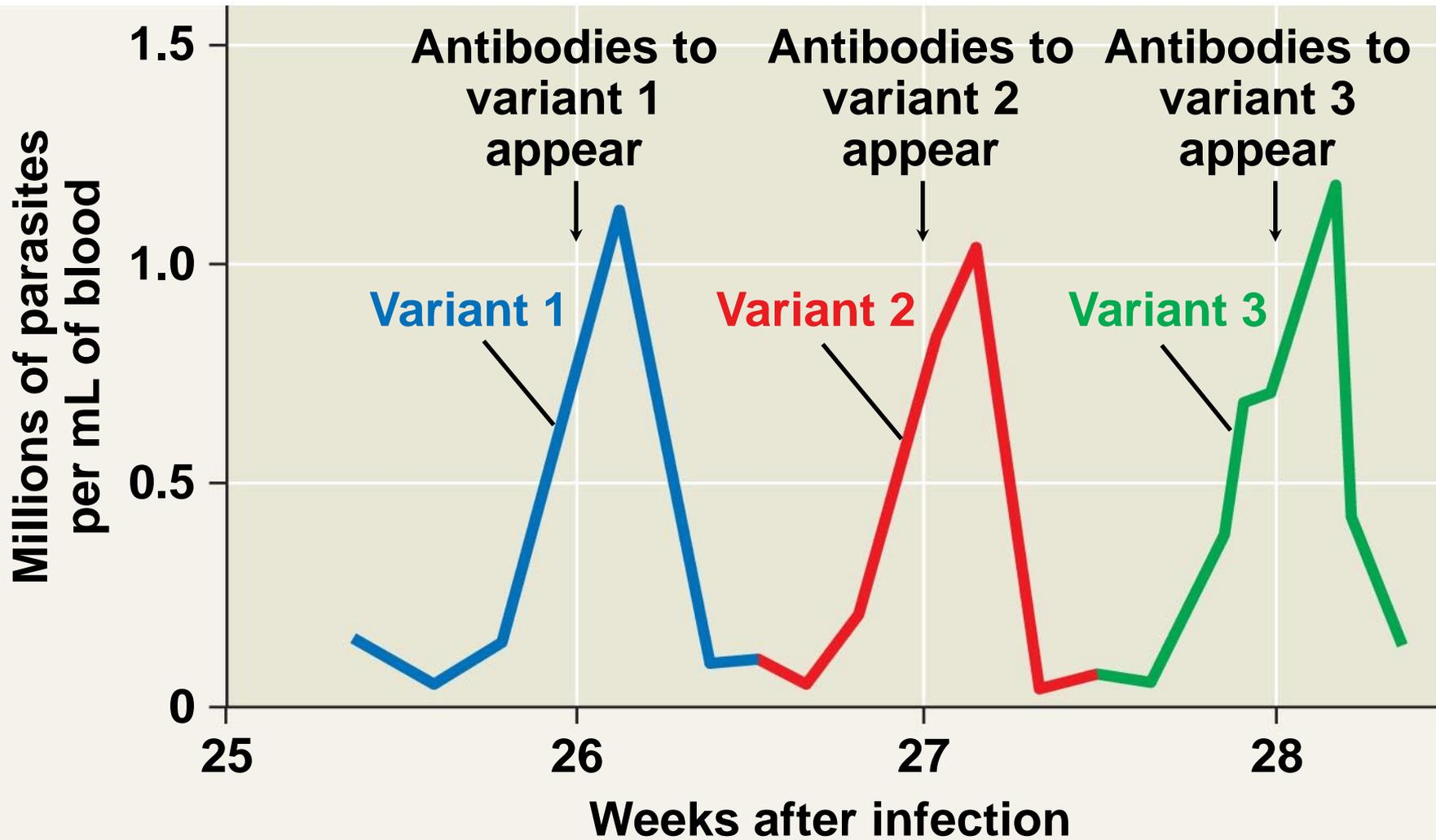
X-ray of a hand deformed by rheumatoid arthritis

Exertion, Stress, and the Immune System

- **Moderate exercise** improves immune system function
- **Psychological stress** has been shown to disrupt hormonal, nervous, and immune systems

Antigenic Variation

- Through antigenic variation, some pathogens are able to **change epitope expression** and prevent recognition
- ***The human influenza virus*** mutates rapidly, and new flu vaccines must be made each year
- Human viruses occasionally exchange genes with the viruses of domesticated animals
- This poses a danger as human immune systems are unable to recognize the new viral strain



Latency

- Some viruses may remain in a host in an inactive state called **latency**
- **Herpes simplex viruses** can be present in a human host without causing symptoms

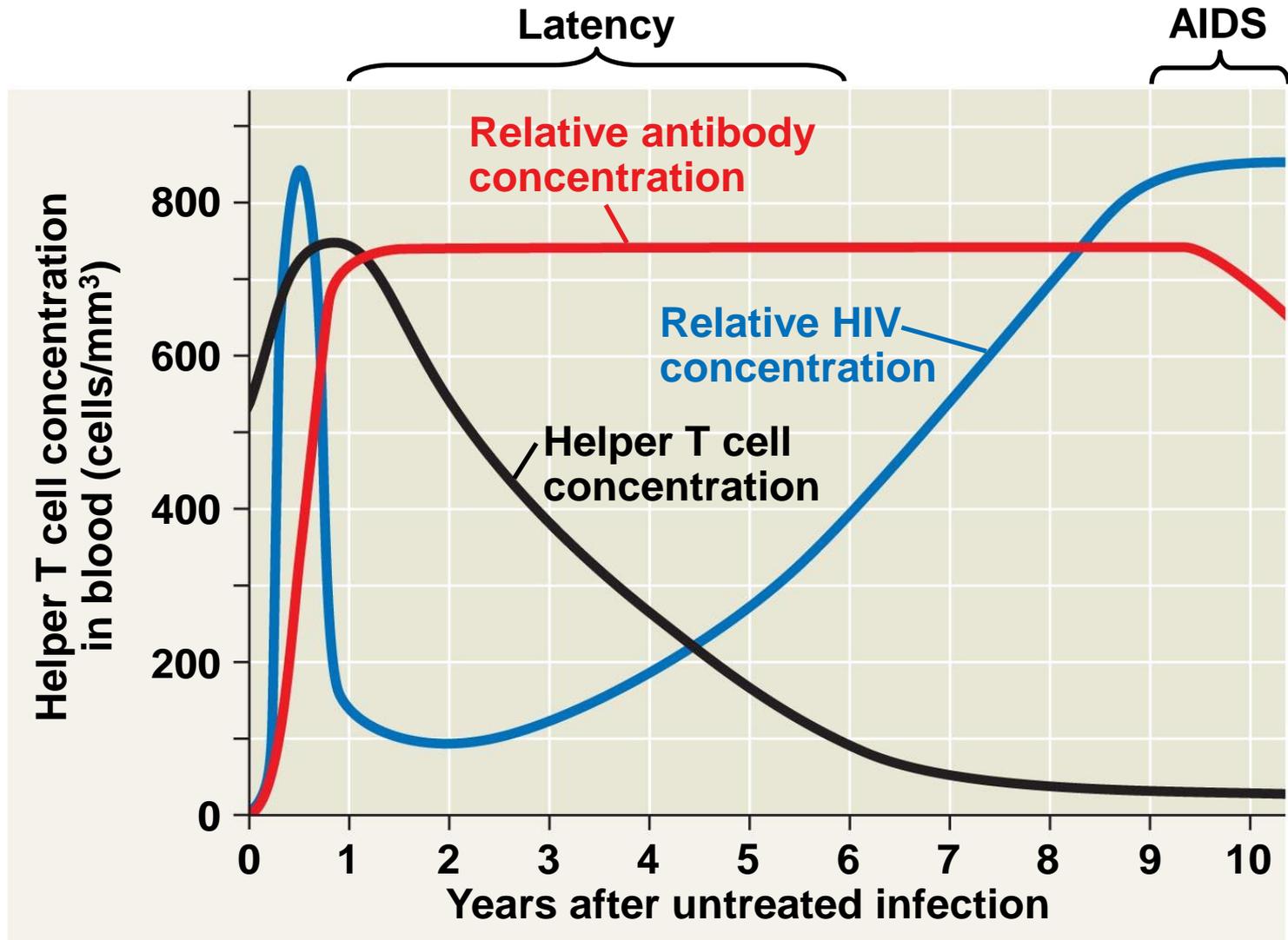
Immunodeficiency Diseases

- **Inborn immunodeficiency** results from hereditary or developmental defects that prevent proper functioning of innate, humoral, and/or cell-mediated defenses
- **Acquired immunodeficiency** results from exposure to chemical and biological agents
 - **Acquired immunodeficiency syndrome (AIDS)** is caused by a virus
- **Acquired immune system evasion by Pathogens**

HIV

- Human immunodeficiency virus (HIV) **infects helper T cells**
- The loss of helper T cells impairs both the humoral and cell-mediated immune responses and leads to AIDS
- HIV eludes the immune system because of antigenic variation and an ability to remain latent while integrated into host DNA
- People with AIDS are highly susceptible to opportunistic infections and cancers that take advantage of an immune system in collapse
- The spread of HIV is a worldwide problem
- The best approach for slowing this spread is

The progress of an untreated HIV infection



Cancer and Immunity

- The frequency of certain cancers increases when the immune response is impaired
- Two suggested explanations are
 - Immune system normally suppresses cancerous cells
 - Increased inflammation increases the risk of cancer