CAMPBELL BIOLOGY IN FOCUS

URRY • CAIN • WASSERMAN • MINORSKY • REECE

35

The Immune System

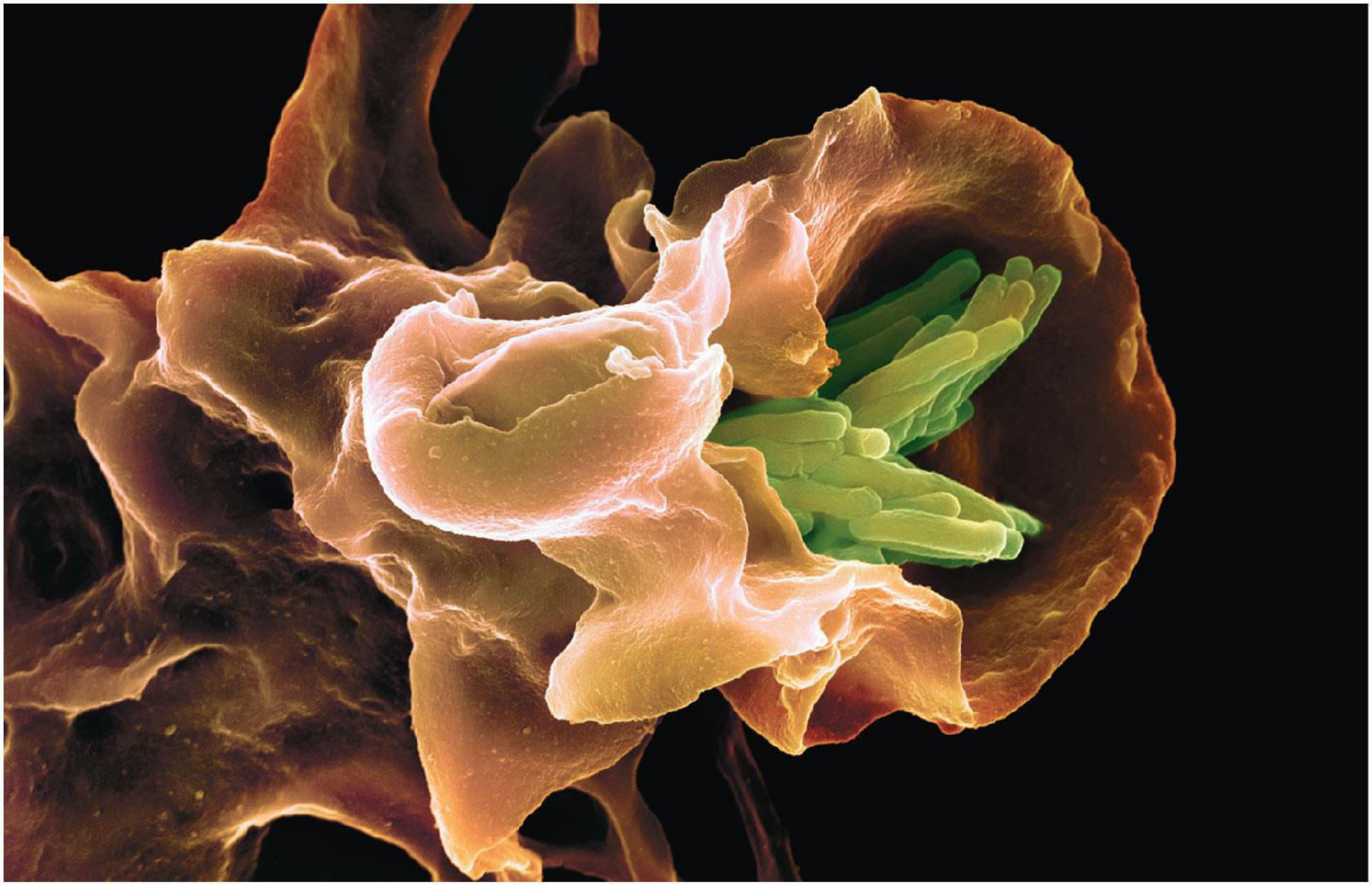
Lecture Presentations by
Kathleen Fitzpatrick and
Nicole Tunbridge,
Simon Fraser University

SECOND EDITION

Overview: Recognition and Response

- **Pathogens**, agents that cause disease, infect a wide range of animals, including humans
- The **immune system** enables an animal to avoid or limit many infections
- All animals have **innate immunity**, a defense that is active immediately upon infection
- Vertebrates also have **adaptive immunity**

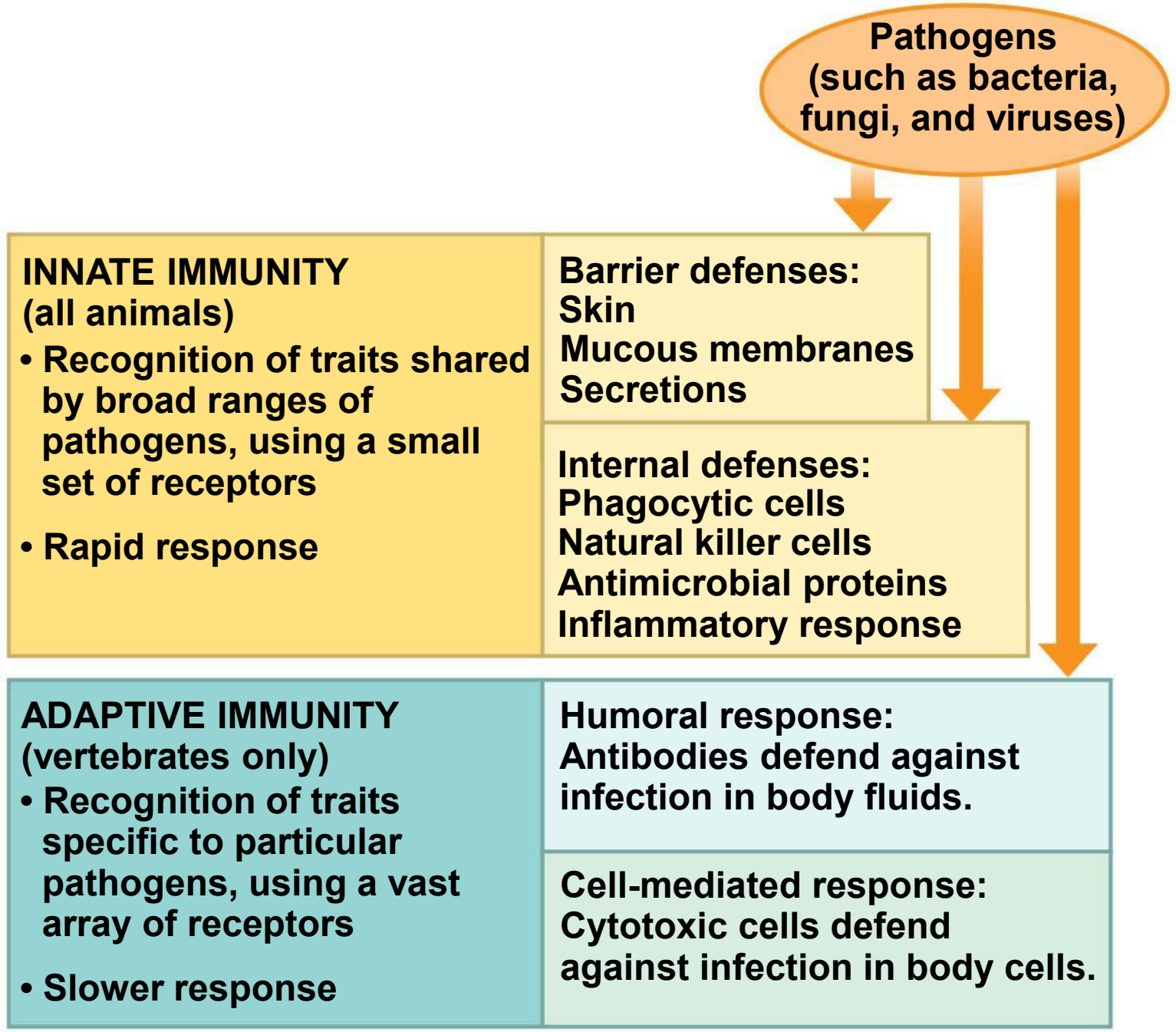
Figure 35.1



- Innate immunity includes barrier defenses
- A small set of receptor proteins bind molecules or structures common to viruses, bacteria, or other microbes
- Binding an innate immune receptor activates internal defensive responses to a broad range of pathogens

- Adaptive immunity, or acquired immunity, develops after exposure to agents such as microbes, toxins, or other foreign substances
- It involves a very specific response to pathogens

Figure 35.2



Concept 35.1: In innate immunity, recognition and response rely on traits common to groups of pathogens

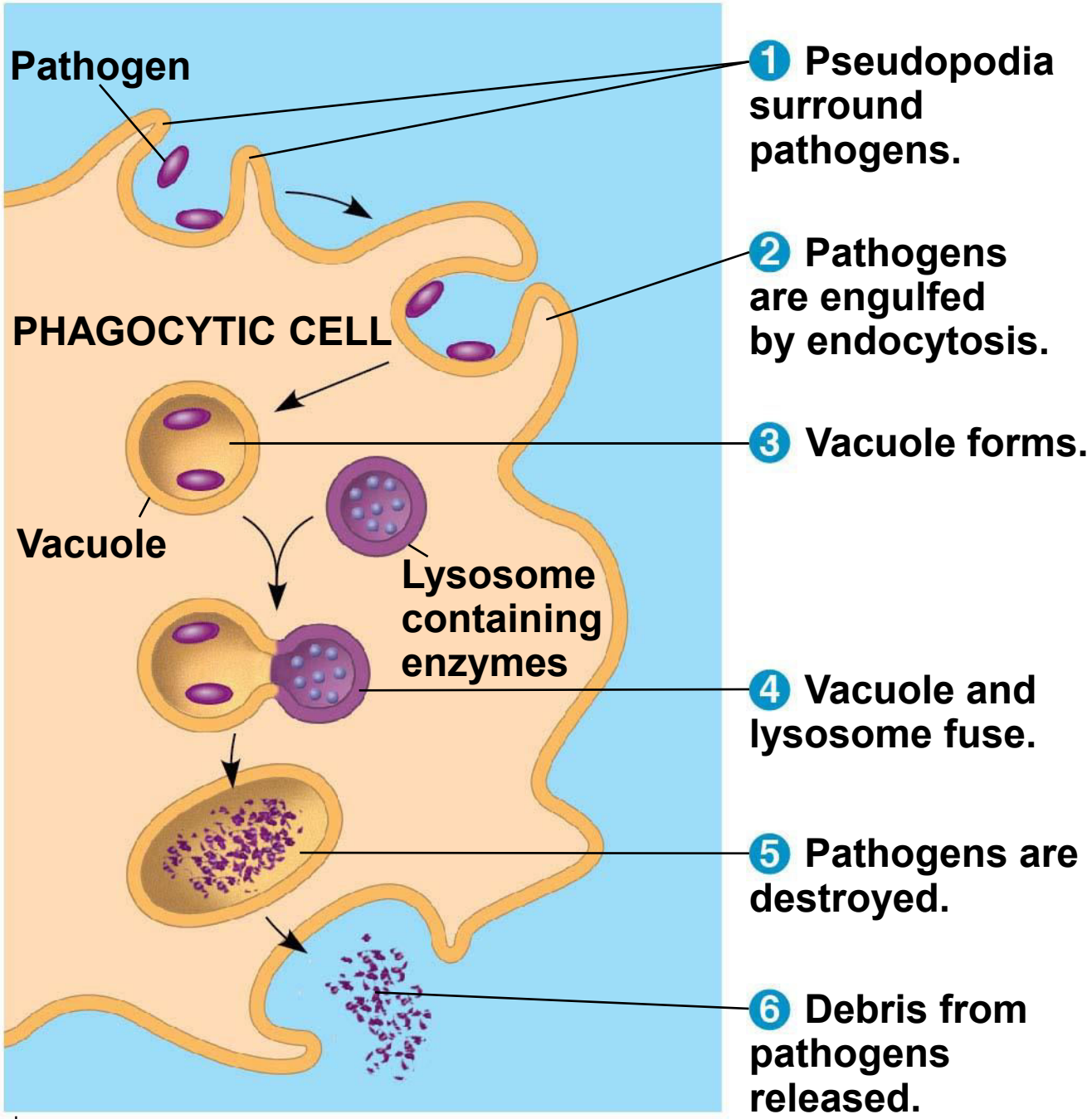
- Innate immunity is found in all animals and plants
- In vertebrates, innate immunity is an immediate response to infections and serves as the foundation of adaptive immunity

Innate Immunity of Invertebrates

- Insects rely on their exoskeleton as a physical barrier against infection
- In the digestive system, the enzyme **lysozyme** breaks down bacterial cell walls, protecting against pathogens ingested along with food
- Immune cells of insects recognize pathogens by binding to molecules specific to viruses or microorganisms
- Each recognition protein of insects recognizes a broad class of pathogens

- Hemocytes circulate within hemolymph and carry out **phagocytosis**, the ingestion and breakdown of foreign substances including bacteria
- Hemocytes also release antimicrobial peptides that disrupt the plasma membranes of fungi and bacteria

Figure 35.3



Innate Immunity of Vertebrates

- The immune system of mammals is the best understood of the vertebrates
- Innate defenses include barrier defenses, phagocytosis, and antimicrobial peptides
- Additional defenses are unique to vertebrates: natural killer cells, interferons, and the inflammatory response

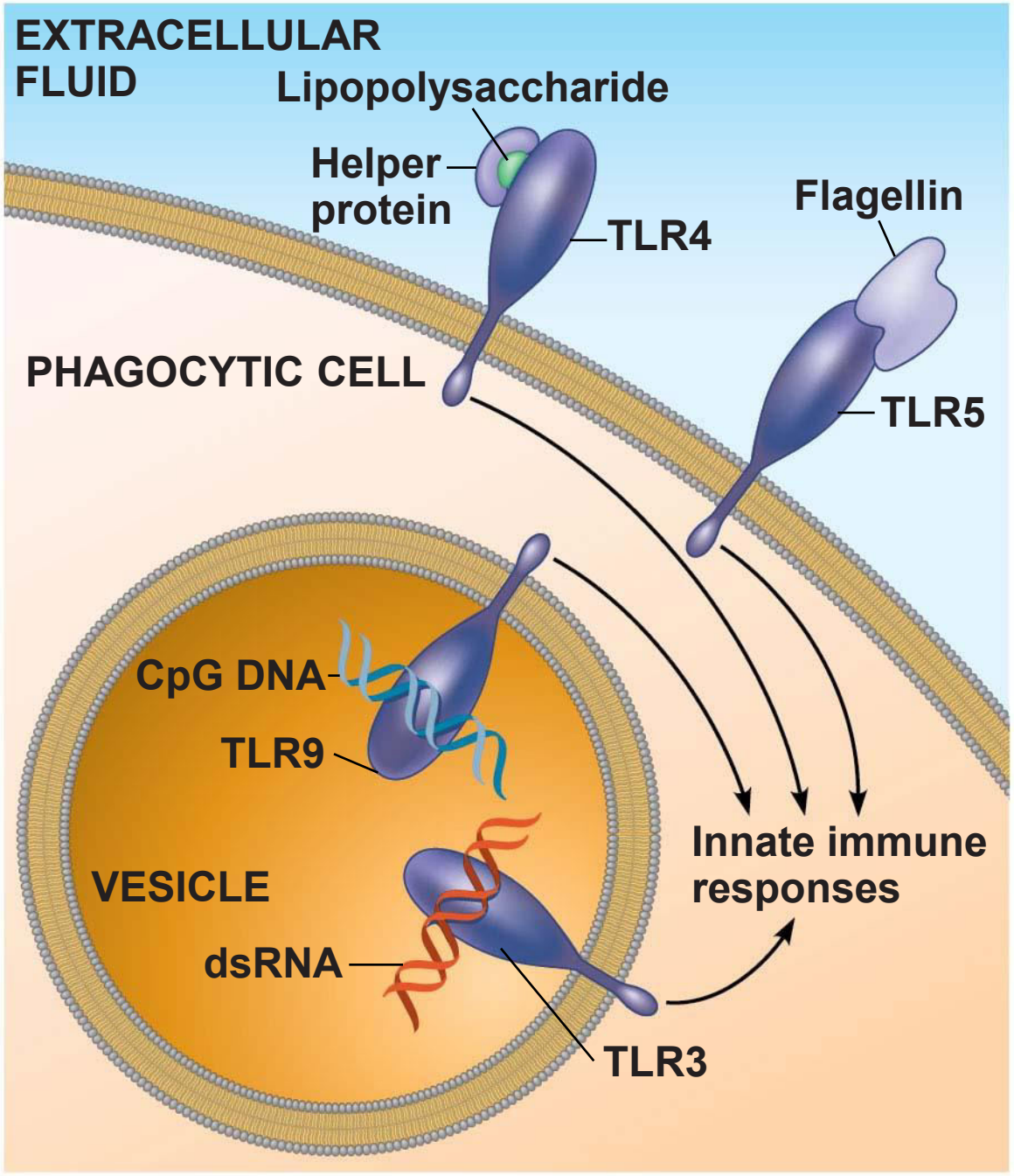
Barrier Defenses

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

Cellular Innate Defenses

- Pathogens entering the mammalian body are subject to phagocytosis
- Phagocytic cells recognize groups of pathogens by **Toll-like receptors** (**TLRs**)
- Each mammalian TLR binds to fragments of molecules characteristic to a set of pathogens

Figure 35.4



- There are two main types of phagocytic cells in mammals
  - **Neutrophils** circulate in the blood and are attracted by signals from infected tissues
  - **Macrophages** are found throughout the body

- Two additional types of cells with roles in innate defense
  - Dendritic cells stimulate development of adaptive immunity in cells that contact the environment (such as skin)
  - Eosinophils discharge destructive enzymes

- Cellular innate defenses in vertebrates also involve **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
- Many cellular innate defenses involve the lymphatic system

Antimicrobial Peptides and Proteins

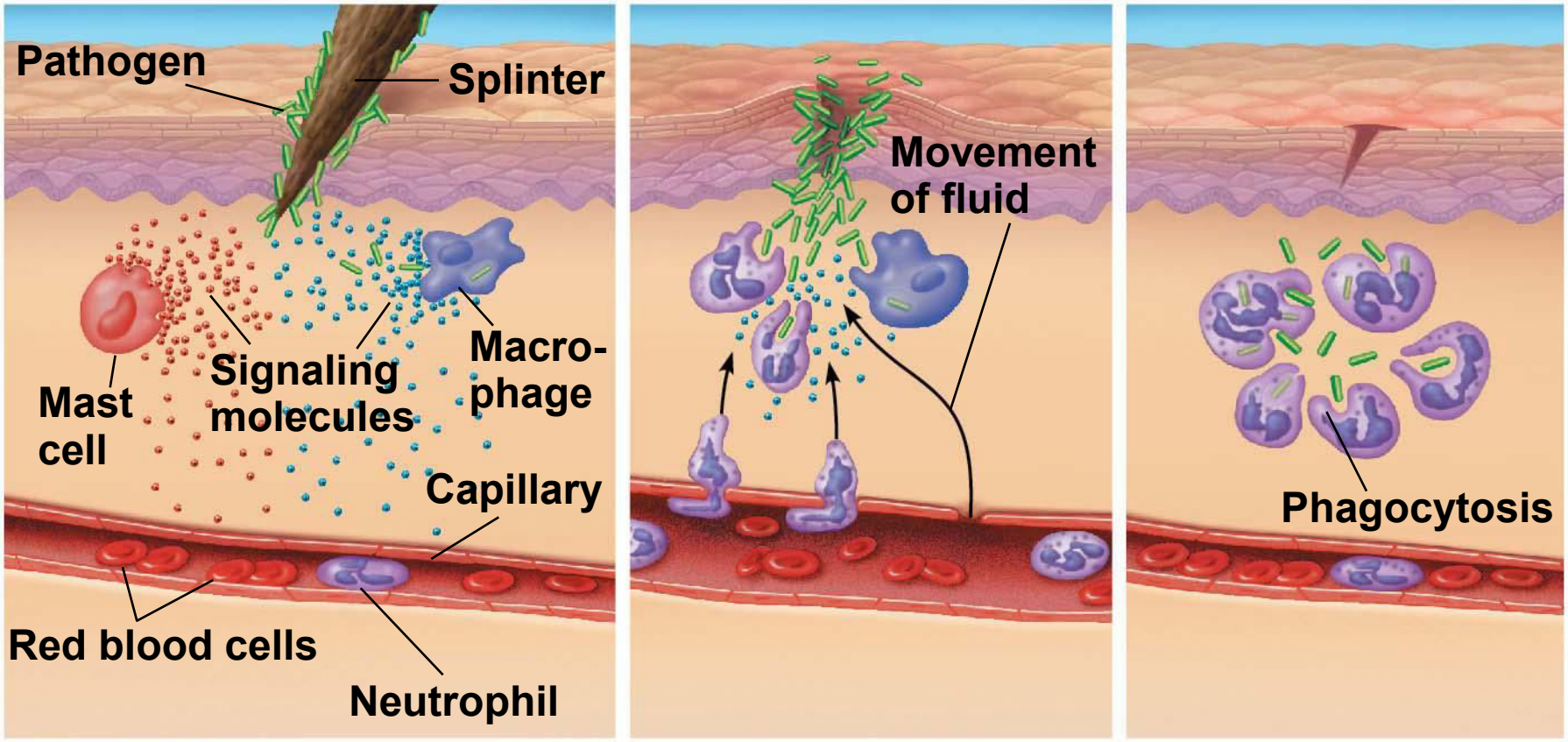
- In mammals, pathogen recognition triggers release of peptides and proteins that attack pathogens or impede their reproduction
- **Interferons** provide innate defense, interfering with viruses and helping activate macrophages
- The **complement system** consists of about 30 proteins that are activated by substances on microbe surfaces
- Activation can lead to lysis of invading cells

Inflammatory Response

- The **inflammatory response**, such as pain and swelling, is brought about by molecules released upon injury of infection
- Activated macrophages and neutrophils release **cytokines**, signaling molecules that modulate the immune response and promote blood flow to the site of injury or infection
- Mast cells release **histamine**, which triggers blood vessels to dilate and become more permeable

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

Figure 35.5



1 Histamines and cytokines released. Capillaries dilate.

2 Antimicrobial peptides enter tissue. Neutrophils are recruited.

3 Neutrophils digest pathogens and cell debris. Tissue heals.

- Inflammation can be either local or systemic (throughout the body)
- Fever is a systemic inflammatory response triggered by substances released by macrophages
- *Septic shock* is a life-threatening condition caused by an overwhelming inflammatory response
- Chronic inflammation can also threaten human health

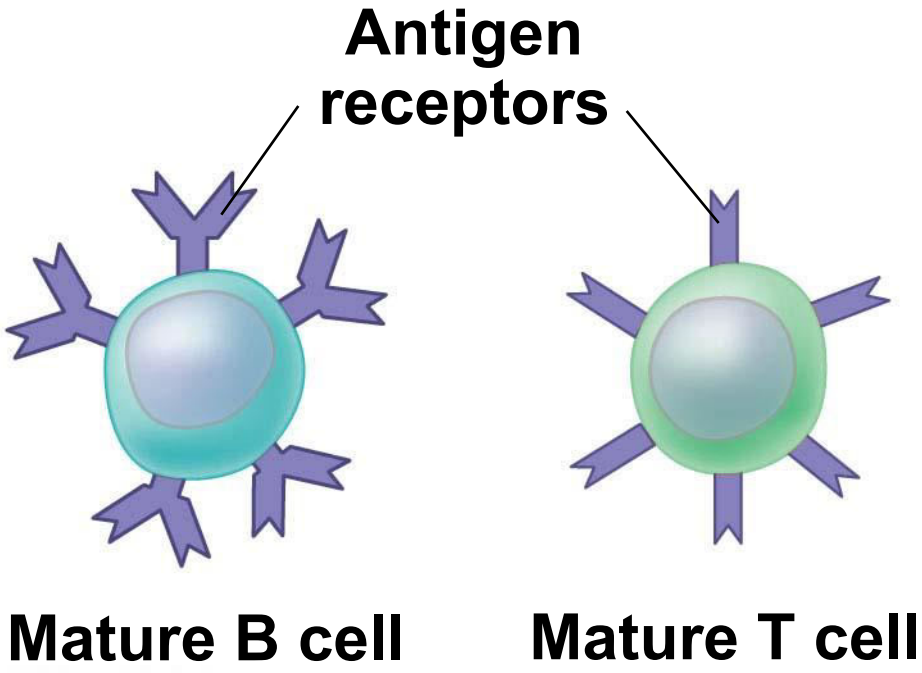
Evasion of Innate Immunity by Pathogens

- Adaptations have evolved in some pathogens that enable them to avoid destruction by phagocytic cells
- The outer capsule of some bacteria interferes with molecular recognition
- Tuberculosis (TB) resists breakdown within lysosomes after being engulfed by a host cell

Concept 35.2: In adaptive immunity, receptors provide pathogen-specific recognition

- The adaptive response relies on two types of **lymphocytes**, or white blood cells
- Lymphocytes that mature in the **thymus** above the heart are called **T cells**, and those that mature in bone marrow are called **B cells**

Figure 35.UN01

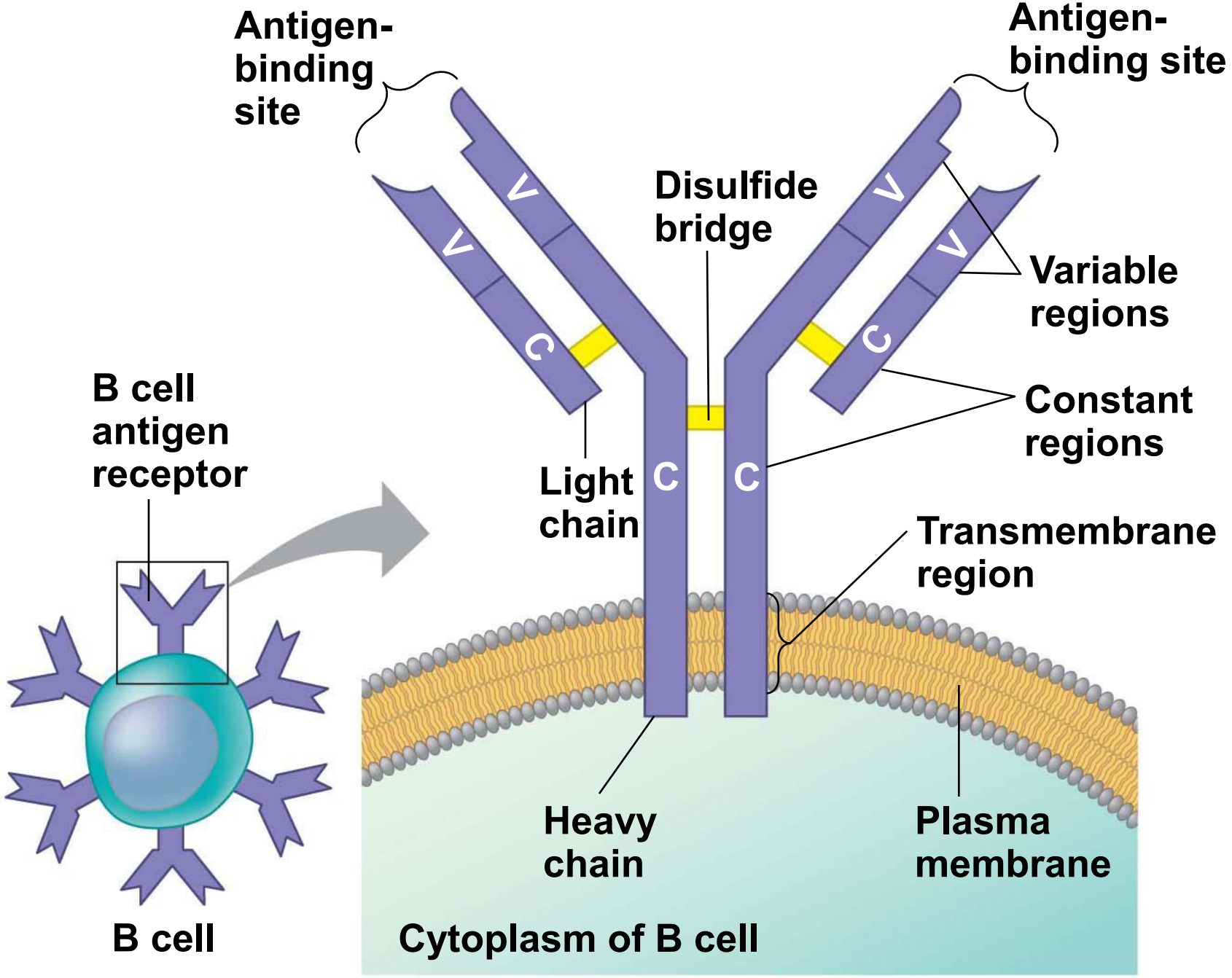


- **Antigens** are substances that can elicit a response from a B or T cell
- Recognition occurs when a B or T cell binds to an antigen, via an **antigen receptor**
- The immune system produces millions of different antigen receptors, but the receptors on a single B cell or T cell are all identical to one another
- The small accessible part of an antigen that binds to an antigen receptor is called an **epitope**

Antigen Recognition by B Cells and Antibodies

- Each B cell antigen receptor is a Y-shaped molecule with two identical **heavy chains** and two identical **light chains**
- The constant (C) regions of the chains vary little among B cells, whereas the variable (V) regions differ greatly
- Together, the V regions of the heavy and light chains form an antigen-binding site

Figure 35.6



- Binding of a B cell antigen receptor to an antigen is an early step in B cell activation
- This gives rise to cells that secrete a soluble form of the protein called an **antibody** or **immunoglobulin** (**Ig**)
- Secreted antibodies are similar to B cell receptors but are not membrane bound
- The antibodies, rather than B cells themselves, defend against pathogens

Animation: Antibodies

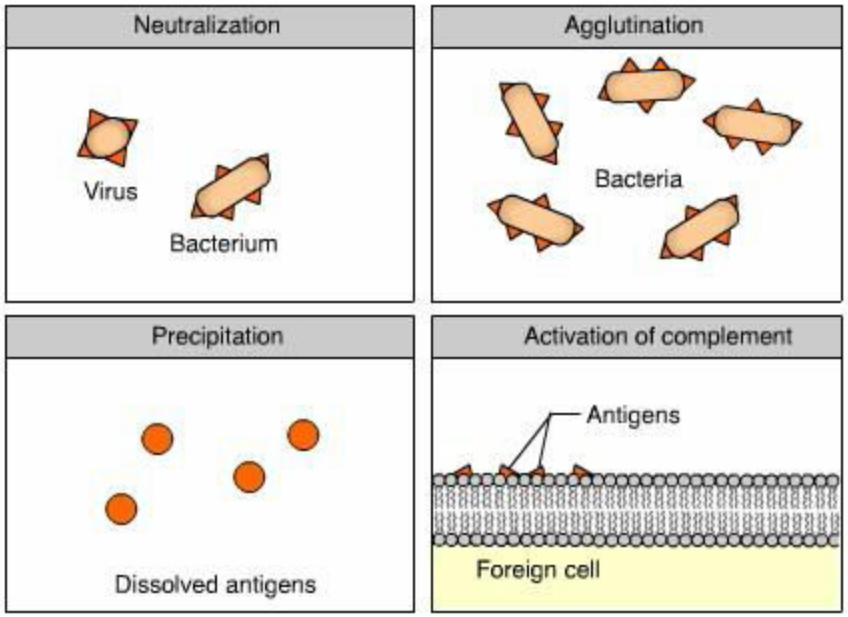
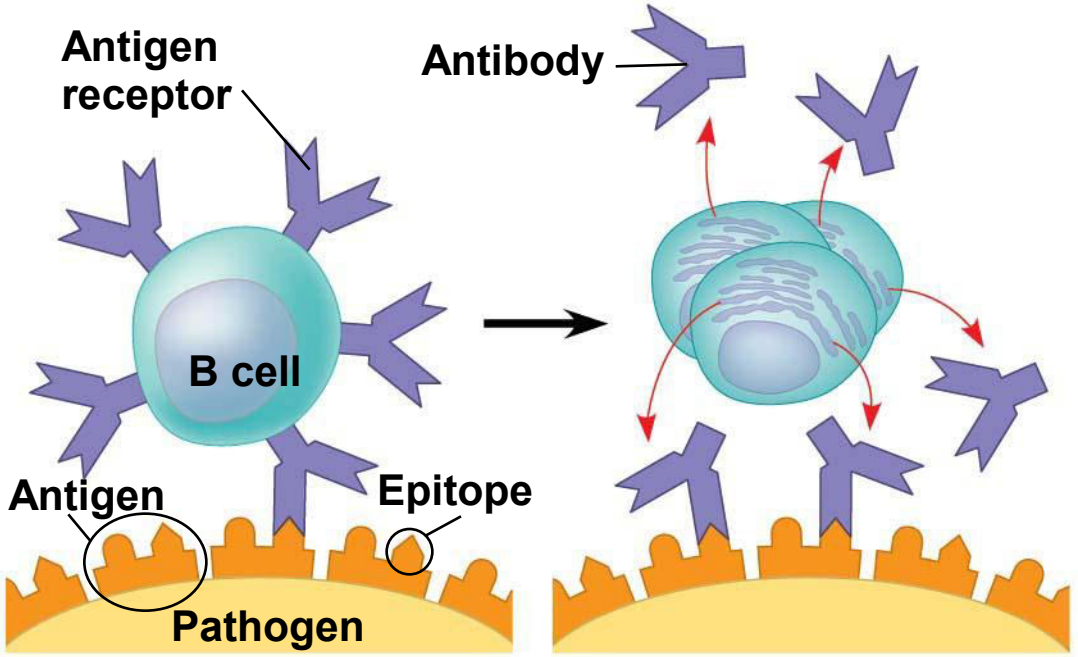
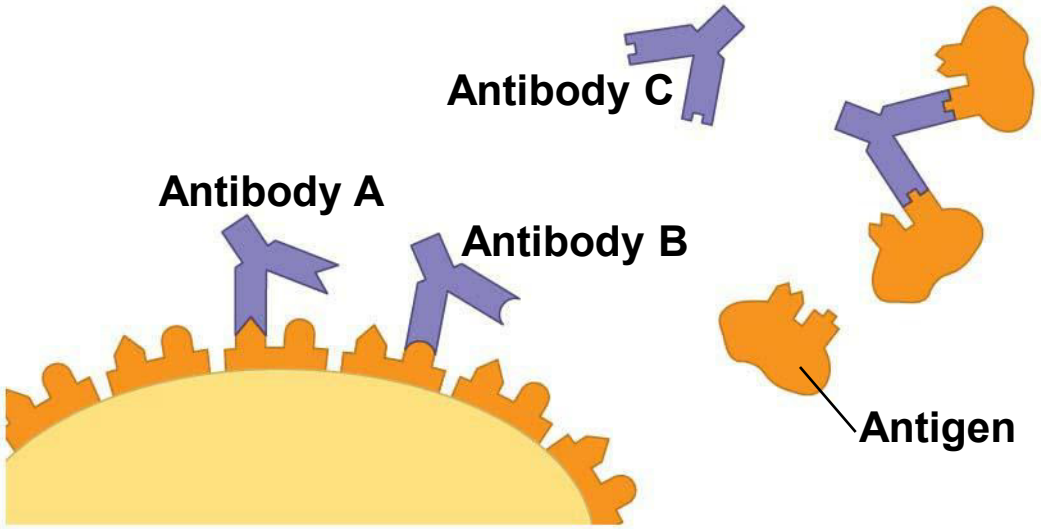


Figure 35.7

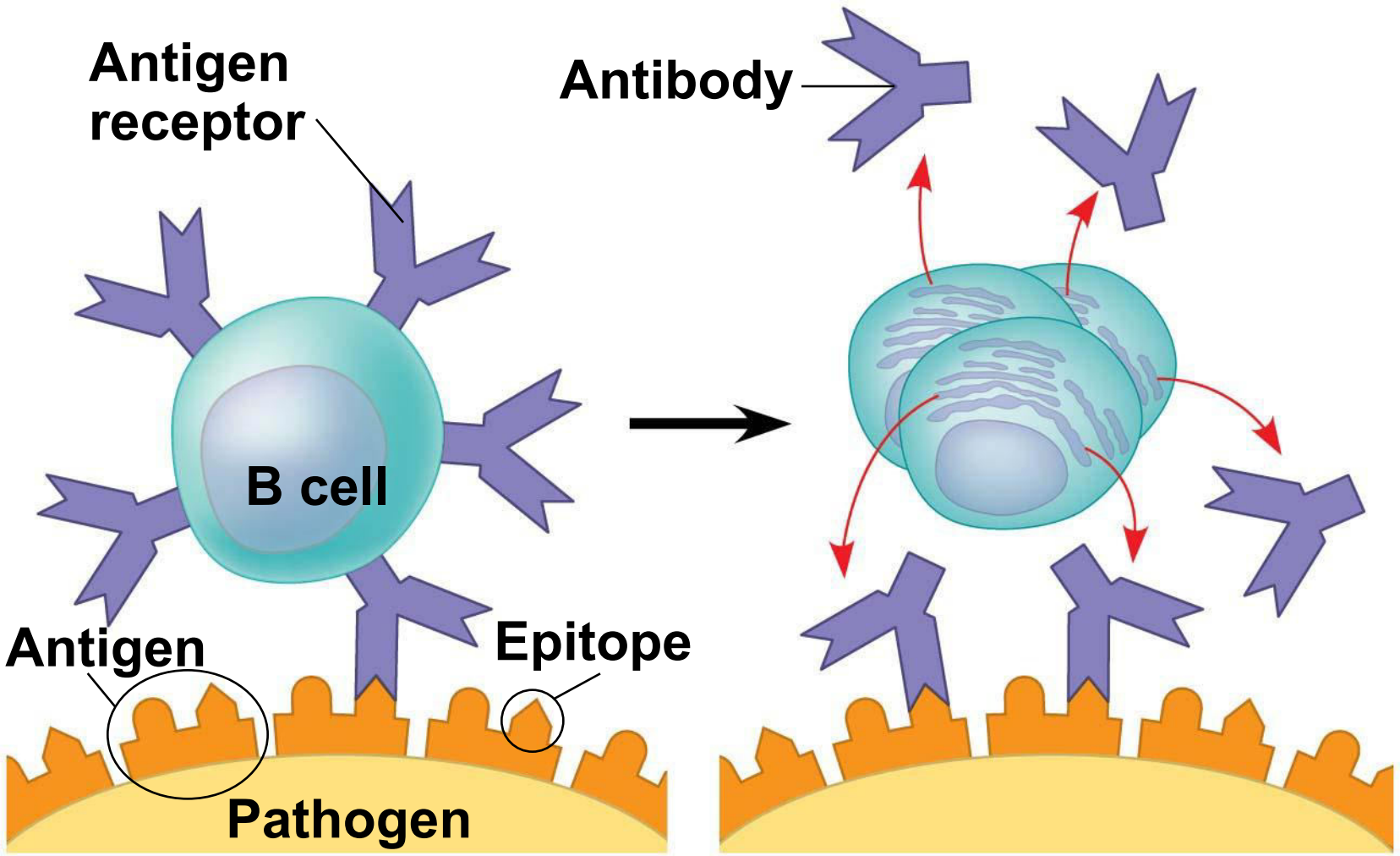


(a) B cell antigen receptors and antibodies



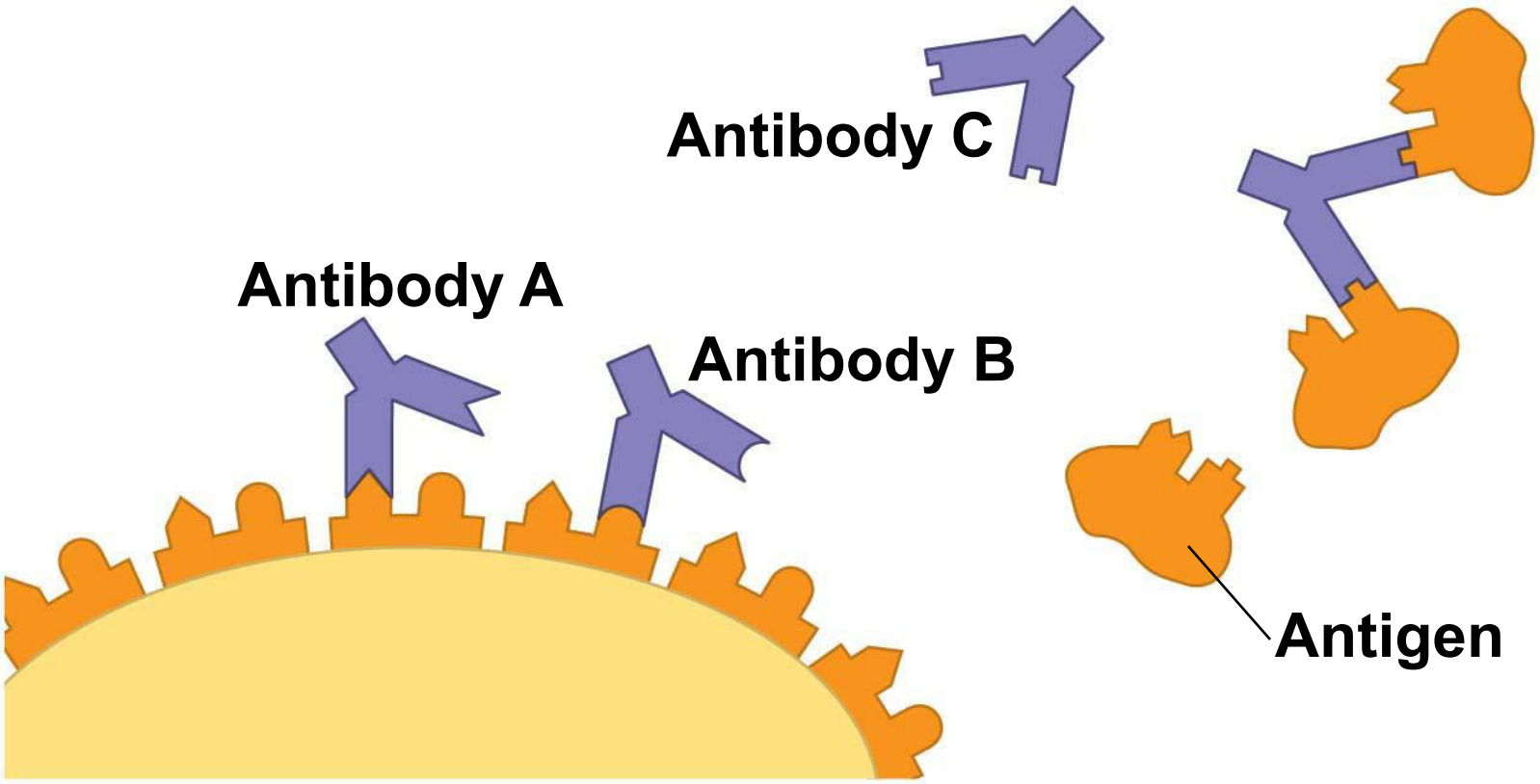
(b) Antigen receptor specificity

Figure 35.7-1



(a) B cell antigen receptors and antibodies

Figure 35.7-2

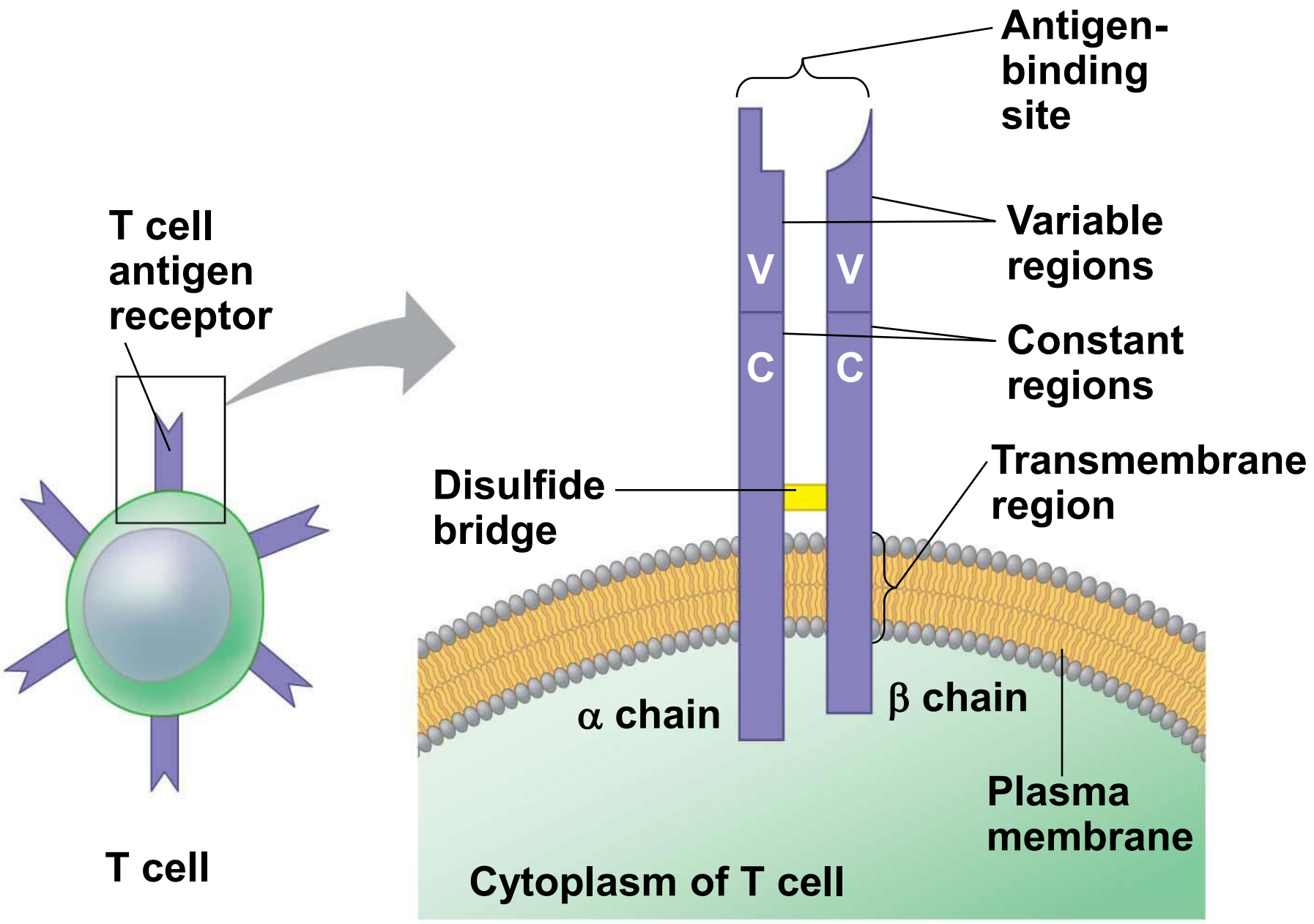


(b) Antigen receptor specificity

Antigen Recognition by T Cells

- Each T cell receptor consists of two different polypeptide chains (called α and β)
- The tips of the chain form a variable (V) region; the rest is a constant (C) region
- The V regions of the α and β chains together form an antigen-binding site

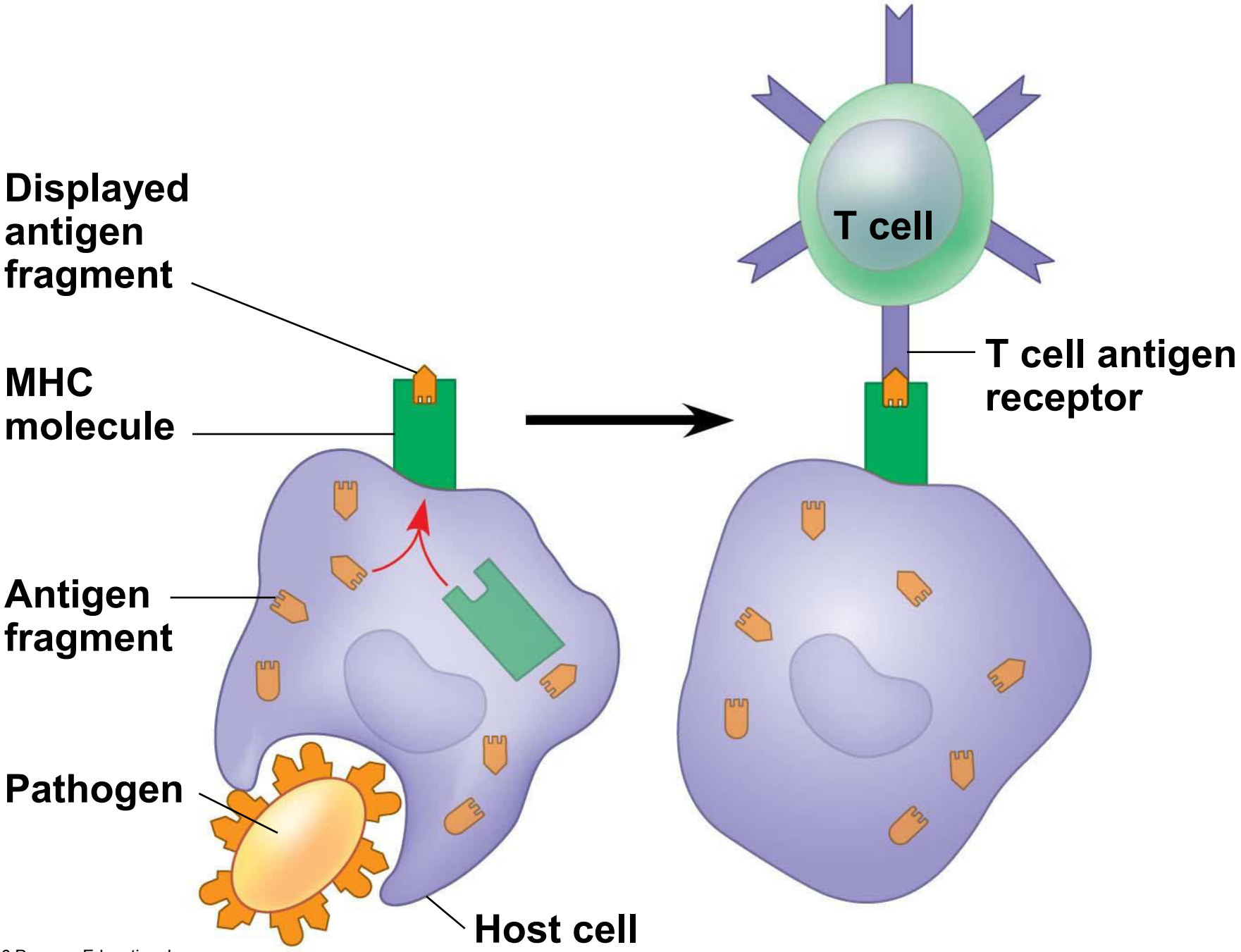
Figure 35.8



- T cells bind only to antigen fragments displayed or presented on a host cell
- **MHC** (**major histocompatibility complex**) molecules are host proteins that display the antigen fragments on the cell surface

- In infected cells, antigens are cleaved into smaller peptides by enzymes
- MHC molecules bind and transport the antigen fragments to the cell surface, a process called **antigen presentation**
- A T cell can then bind both the antigen fragment and the MHC molecule
- This interaction is necessary for the T cell to participate in the adaptive immune response

Figure 35.9



B Cell and T Cell Development

- The adaptive immune system has four major characteristics
  - Diversity of lymphocytes and receptors
  - Self-tolerance; lack of reactivity against an animal's own molecules
  - Proliferation of B and T cells after activation
  - Immunological memory

Generation of B Cell and T Cell Diversity

- By combining variable elements, the immune system assembles millions of different receptors
- The capacity to generate diversity is built into the structure of Ig genes
- 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

- For example, a receptor light-chain gene contains a variable (V) segment, a joining (J) segment, and a constant (C) segment
- The gene contains one C segment, 40 different V segments, and 5 different J segments
- These can be combined in 200 different ways
- The number of heavy-chain combinations is even greater

Figure 35.10

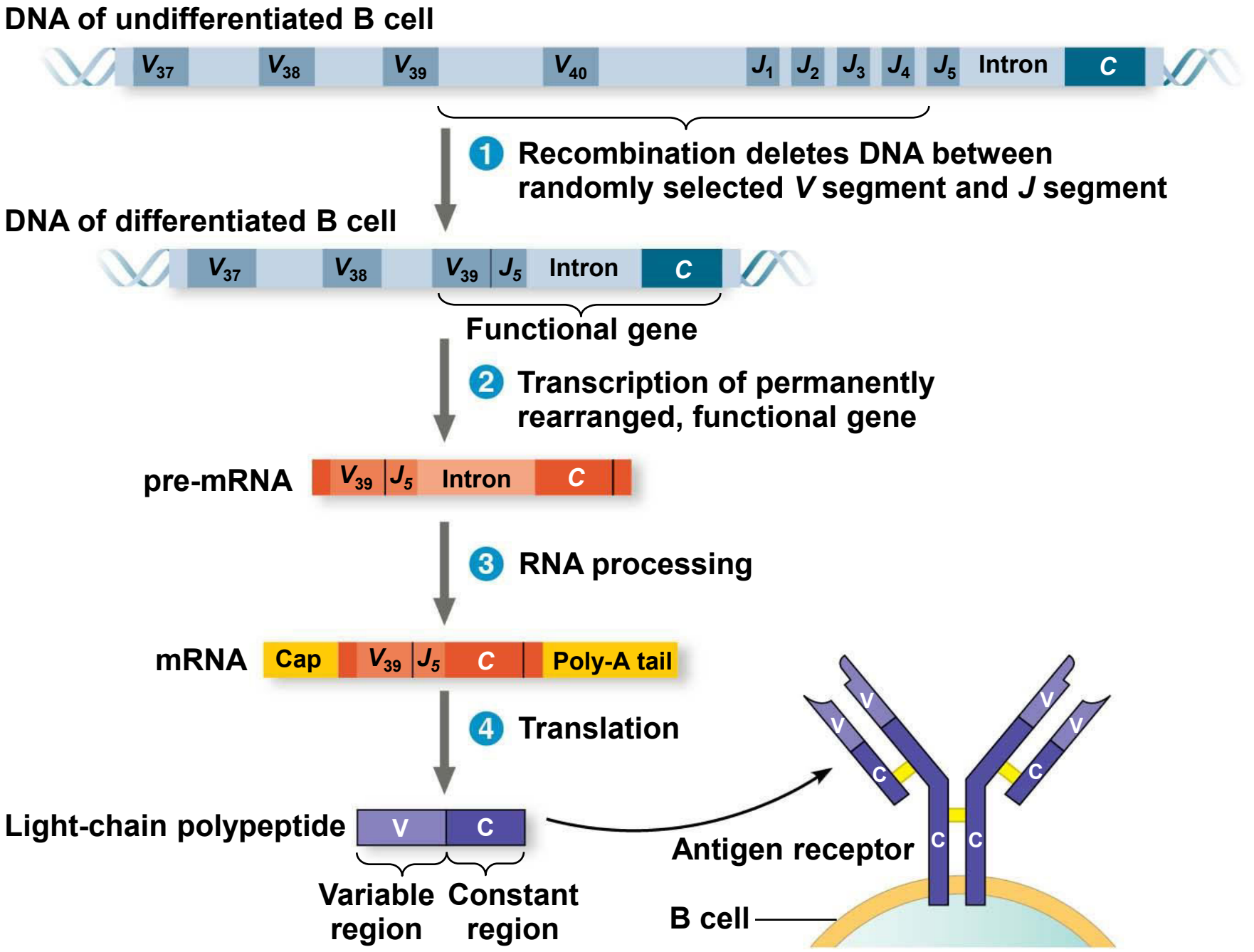


Figure 35.10-1

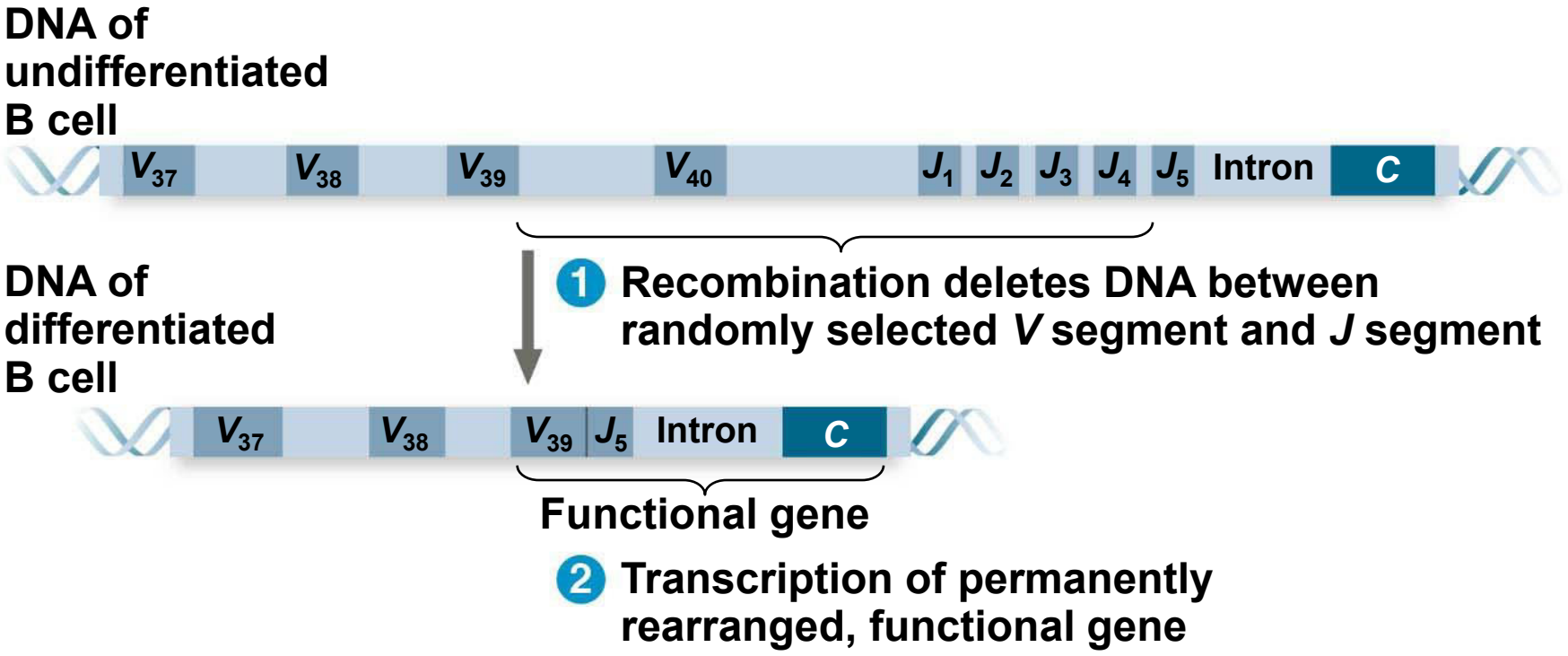
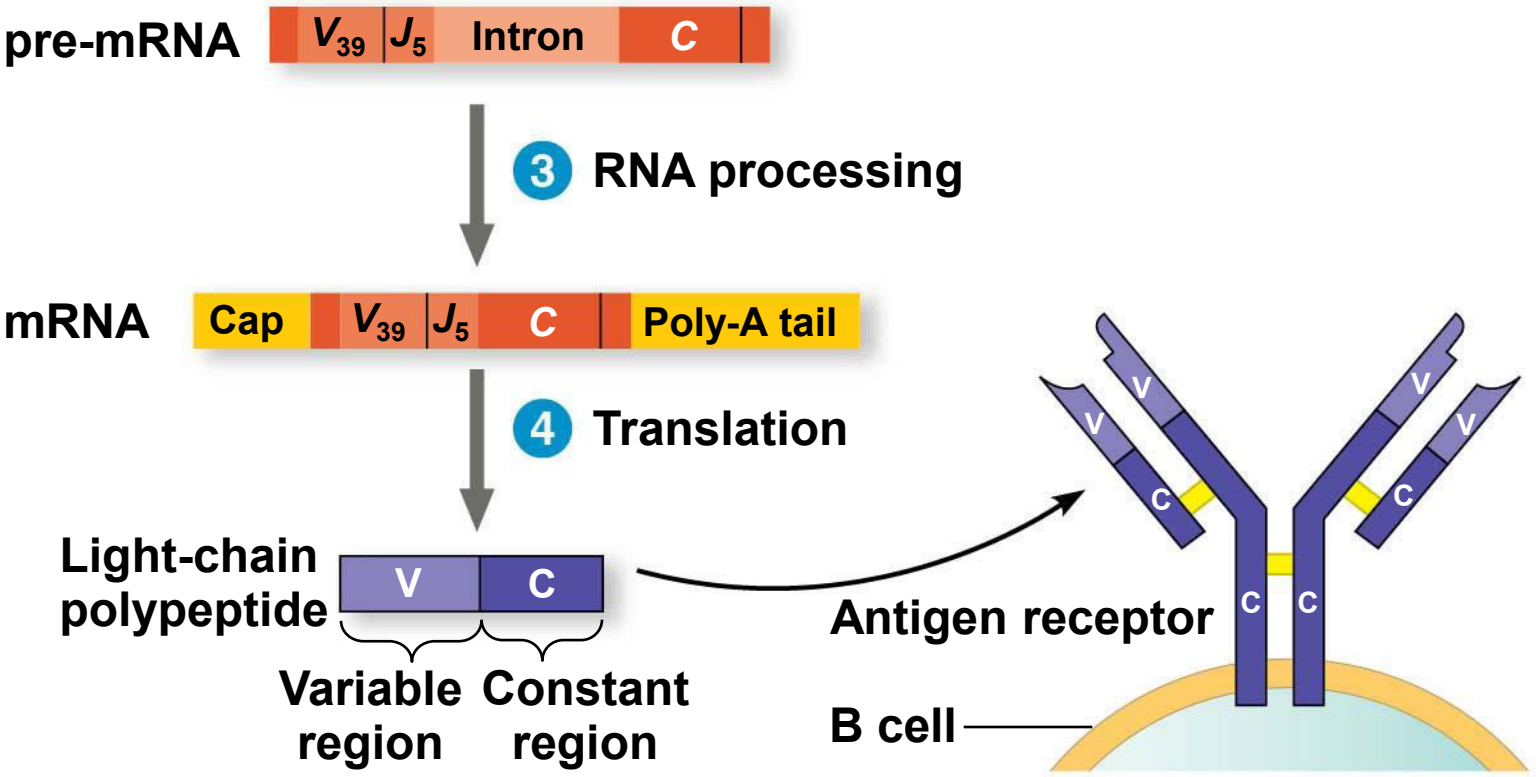


Figure 35.10-2



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 only a tiny fraction of antigen receptors are specific for a given 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 to produce a clone of identical cells (called **clonal selection**)
- Some cells become short-lived activated **effector cells** that act immediately against the antigen
- For B cells, the effector forms are **plasma cells**, which secrete antibodies
- Long-lived **memory cells** give rise to effector cells if the same antigen is encountered again

Animation: Role of B Cells

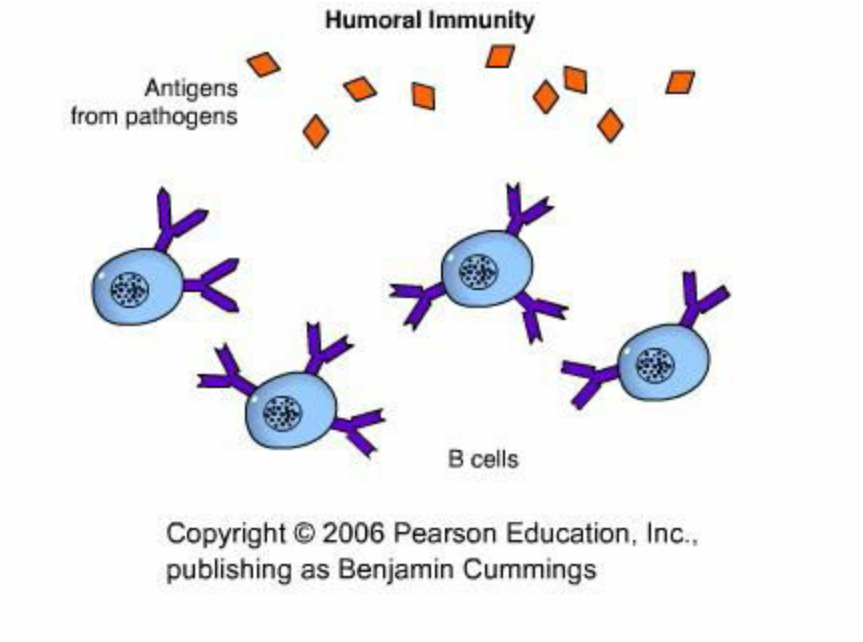
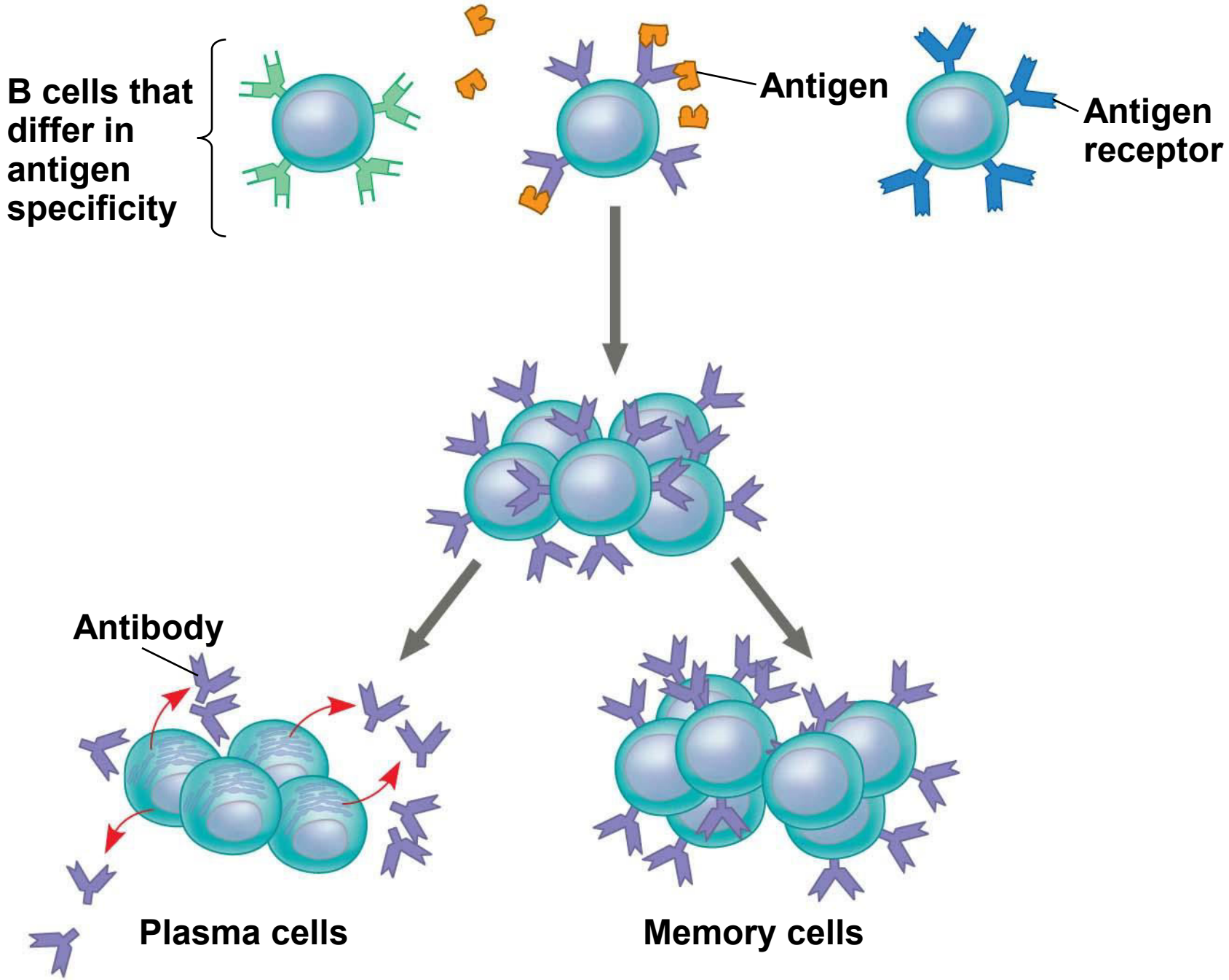


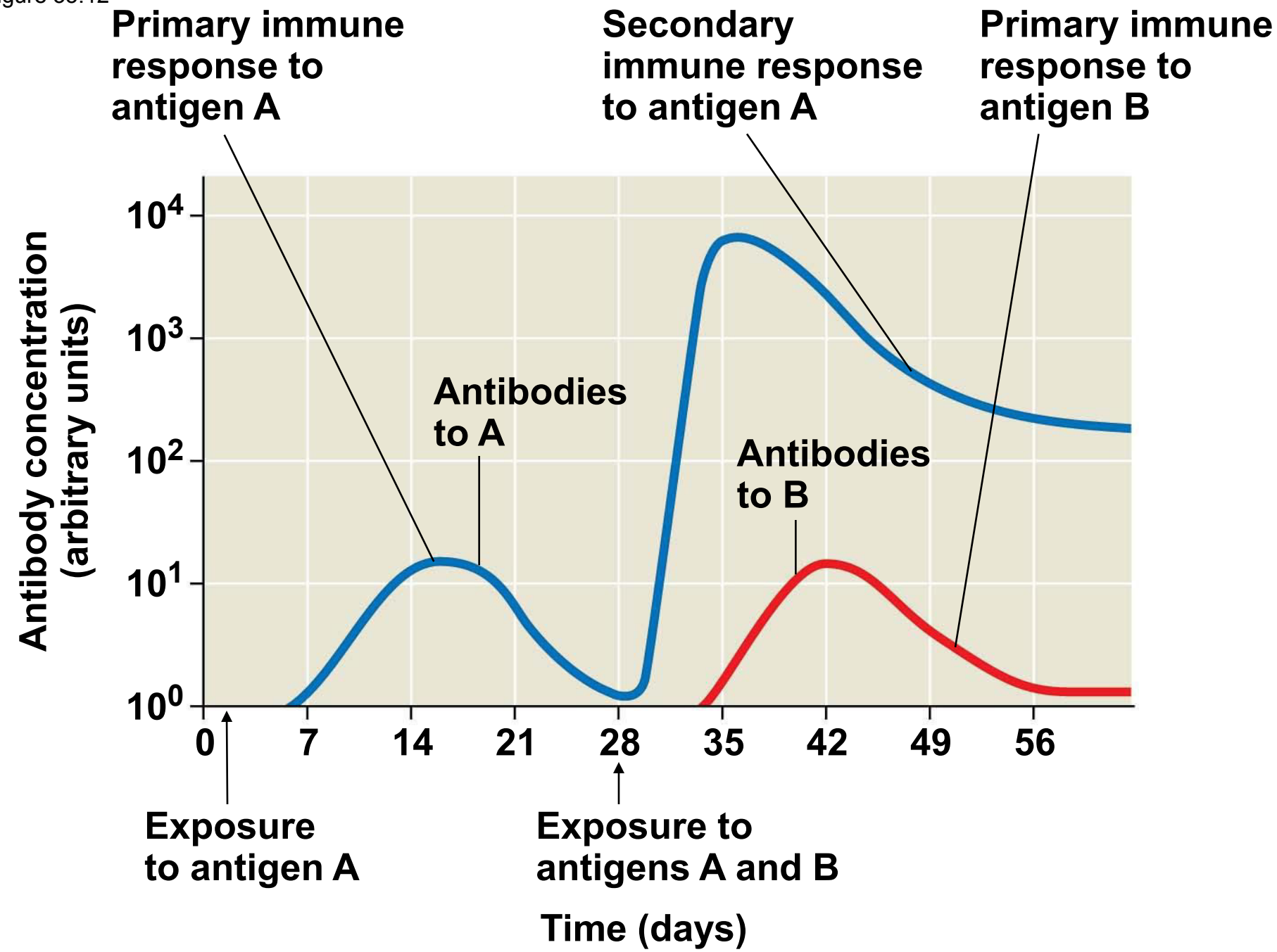
Figure 35.11



Immunological Memory

- Immunological memory is responsible for long-term protection against diseases, due to a prior infection
- The first exposure to a specific antigen represents the **primary immune response**
- During this time, selected B and T cells give rise to their effector forms
- In the **secondary immune response**, memory cells facilitate a faster, stronger, and longer response
- Immunological memory can span many decades

Figure 35.12



Concept 35.3: Adaptive immunity defends against infection of body fluids and body cells

- B and T lymphocytes produce a humoral immune response and a cell-mediated immune response
- In the **humoral immune response**, antibodies help neutralize or eliminate toxins and pathogens in the blood and lymph
- In the **cell-mediated immune response** specialized T cells destroy infected host cells

Helper T Cells: Activating Adaptive Immunity

- A type of T cell called a **helper T cell** triggers both the humoral and cell-mediated immune responses
- To produce this response
  - A foreign molecule must be bound by the antigen receptor of the helper T cell
  - An antigen must be displayed on the surface of an antigen-presenting cell
- **Antigen-presenting cells** have class I and class II MHC molecules on their surfaces

- Antigen-presenting cells are recognized based on their class II MHC molecules
- Antigen receptors on the surface of helper T cells bind to the antigen and the class II MHC molecule
- Signals are then 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

Figure 35.13-s1

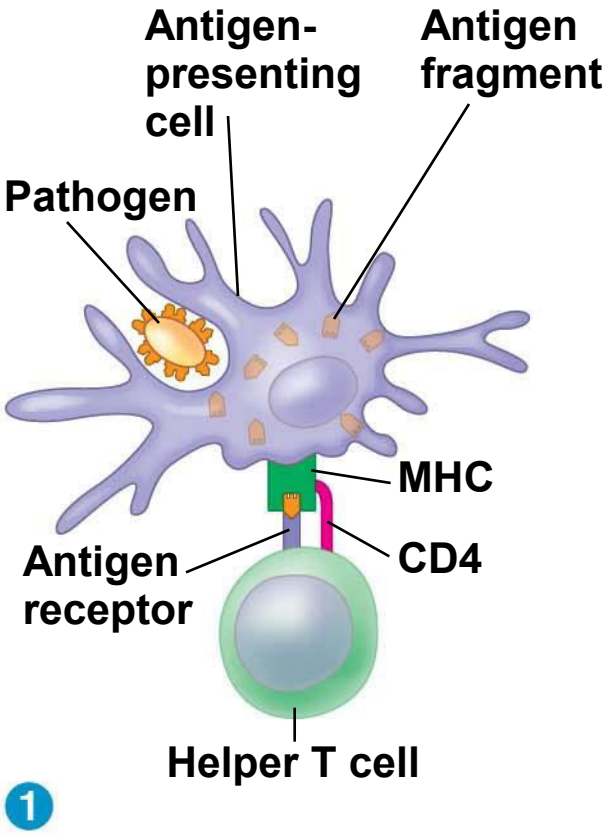


Figure 35.13-s2

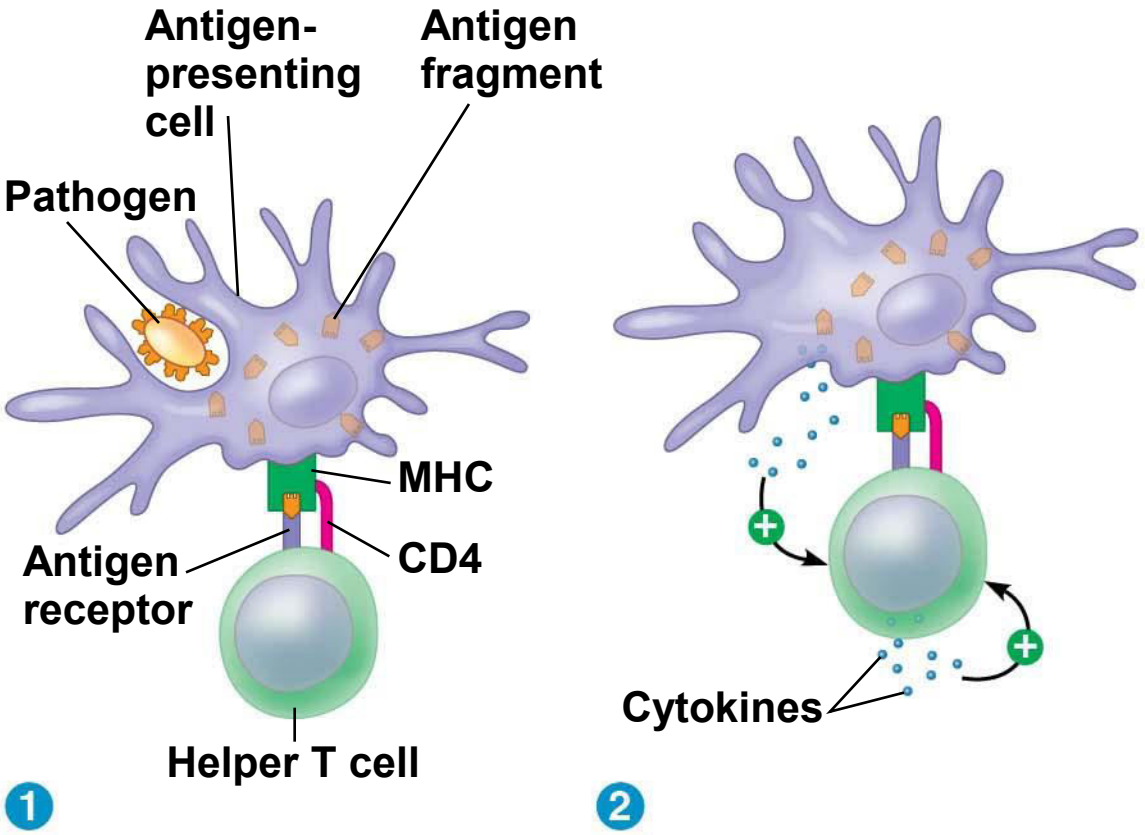
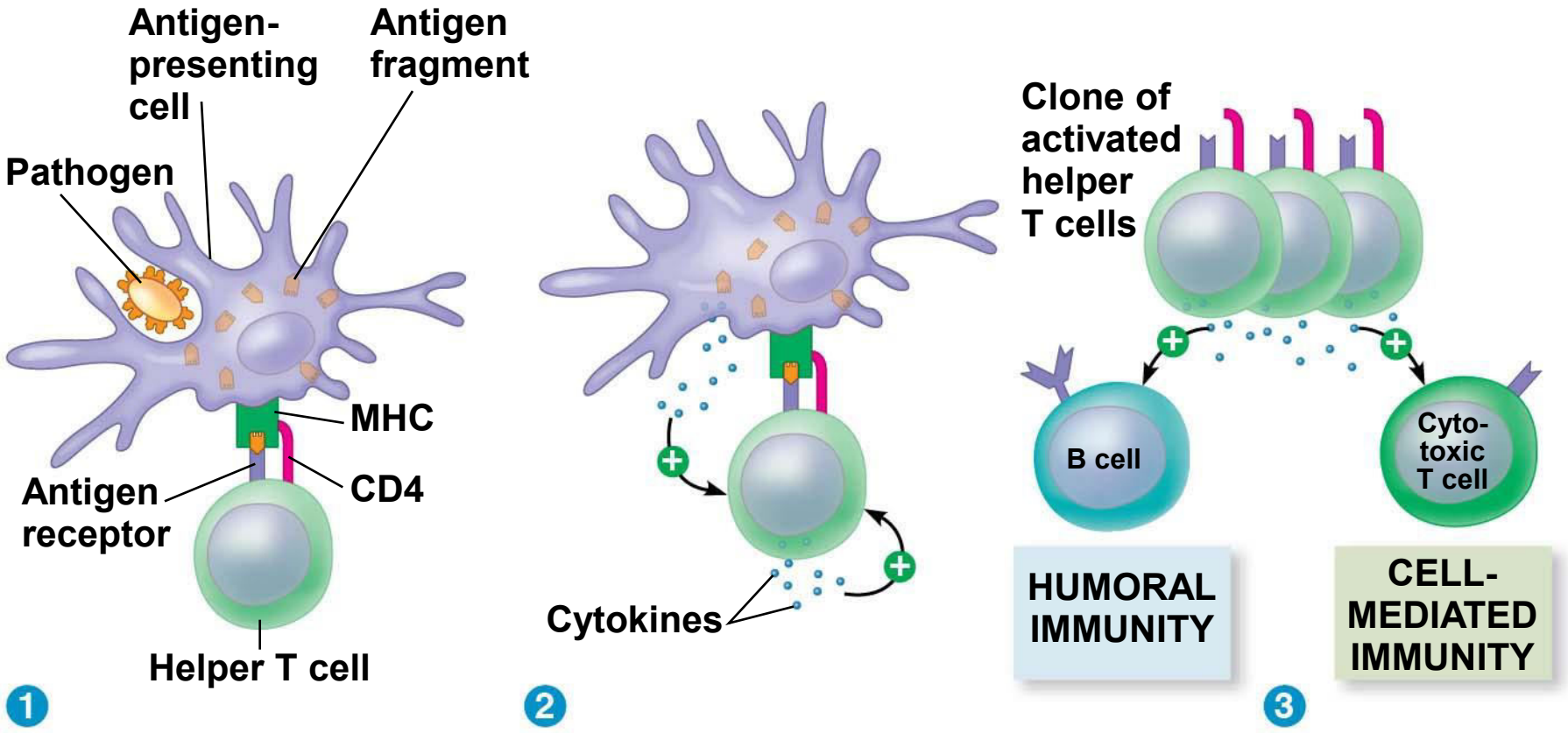


Figure 35.13-s3



B Cells and Antibodies: A Response to Extracellular Pathogens

- The humoral response is characterized by secretion of antibodies by clonally selected B cells
- Activation of B cells involves helper T cells and proteins on the surface of pathogens
- A single activated B cell gives rise to thousands of identical plasma cells

Figure 35.14-s1

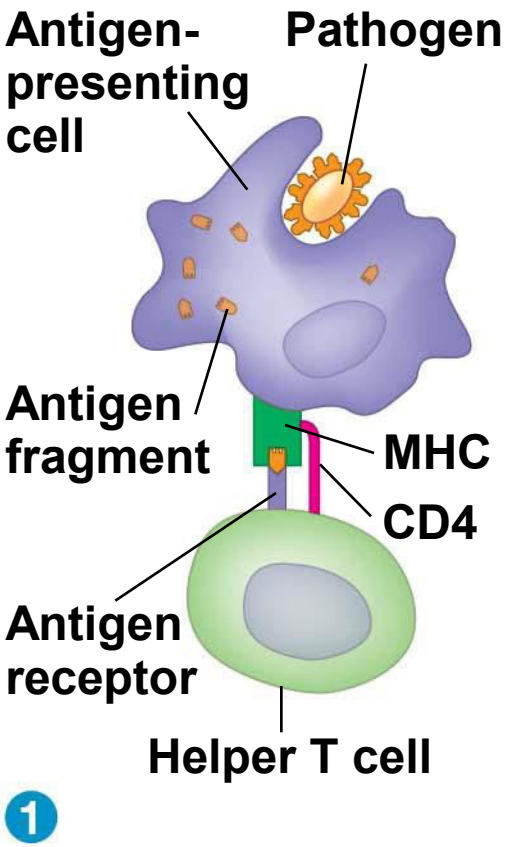


Figure 35.14-s2

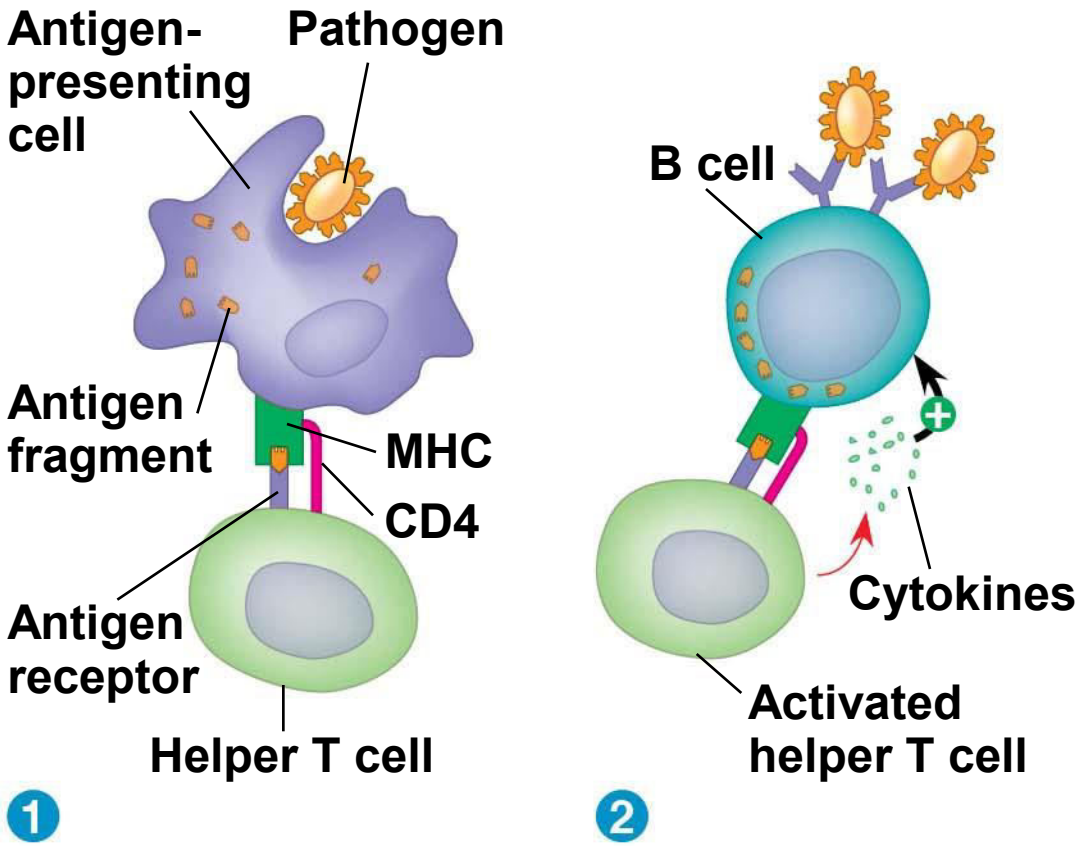
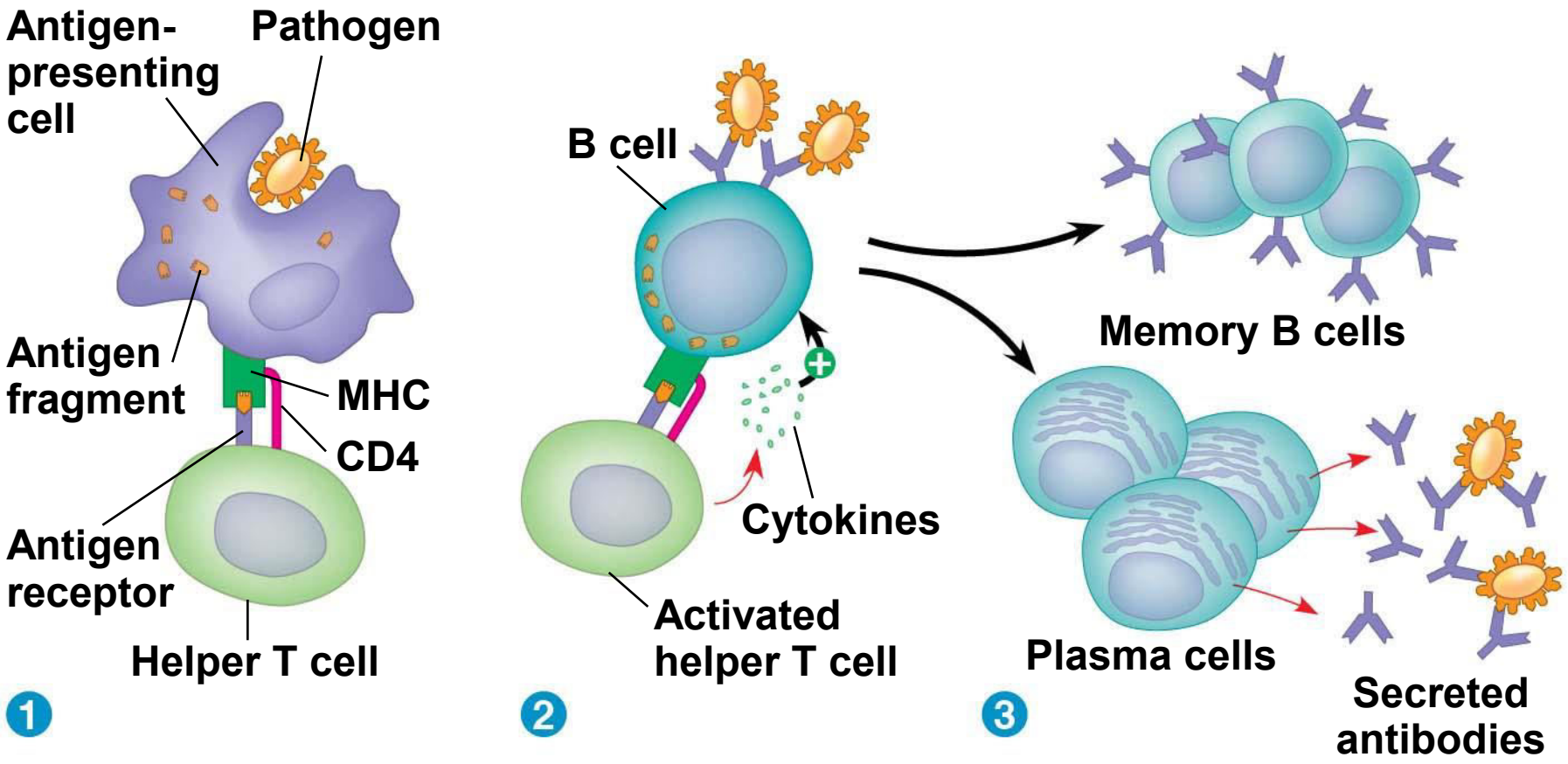


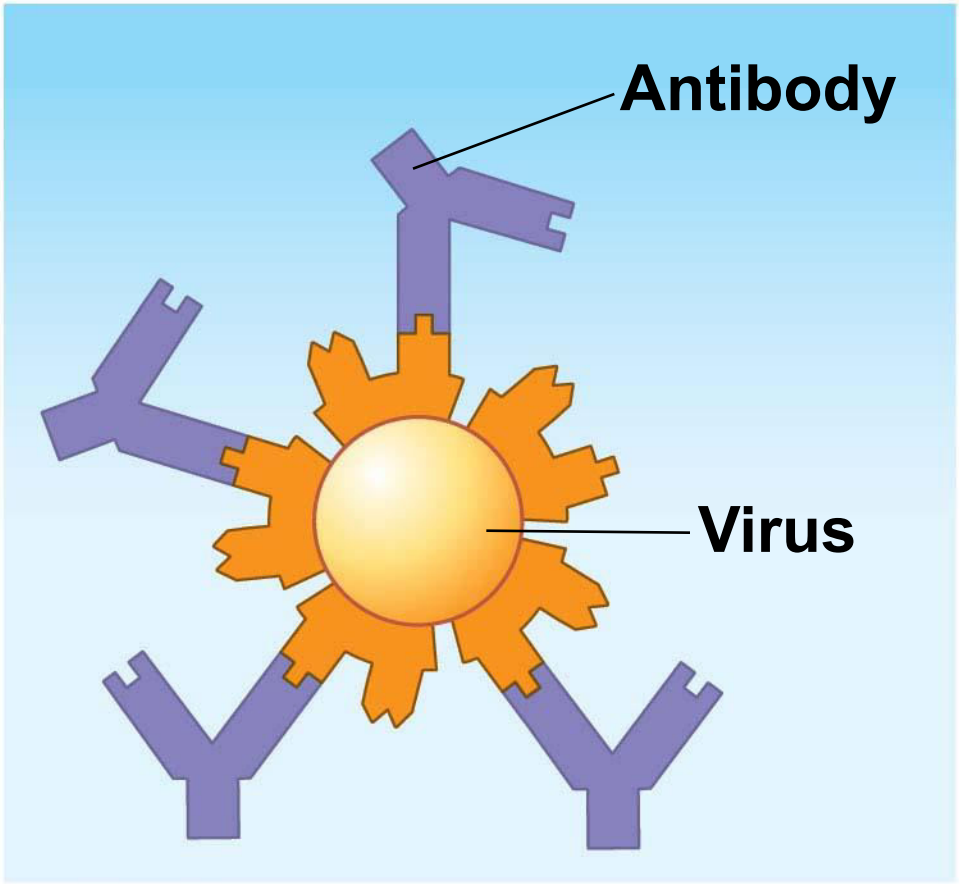
Figure 35.14-s3



- 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

- Antigen-antibody complexes may bind to a complement protein
- A cascade of subsequent events leads to formation of a pore in the membrane of the foreign cell, leading to its lysis

Figure 35.15



- B cells can express five different forms (or classes) of immunoglobulin (Ig) with similar antigen-binding specificity but different heavy-chain C regions
- One type, the B cell antigen receptor, is membrane bound
- The others are soluble and include those found in blood, tears, saliva, and breast milk

Cytotoxic T Cells: A Response to Infected Host Cells

- **Cytotoxic T cells** are the effector cells in the cell-mediated immune response
- Cytotoxic T cells recognize fragments of foreign proteins produced by infected cells and possess an accessory protein that binds to class I MHC molecules
- The activated cytotoxic T cell secretes proteins that disrupt the membranes of target cells and trigger apoptosis

Animation: Cytotoxic T Cells

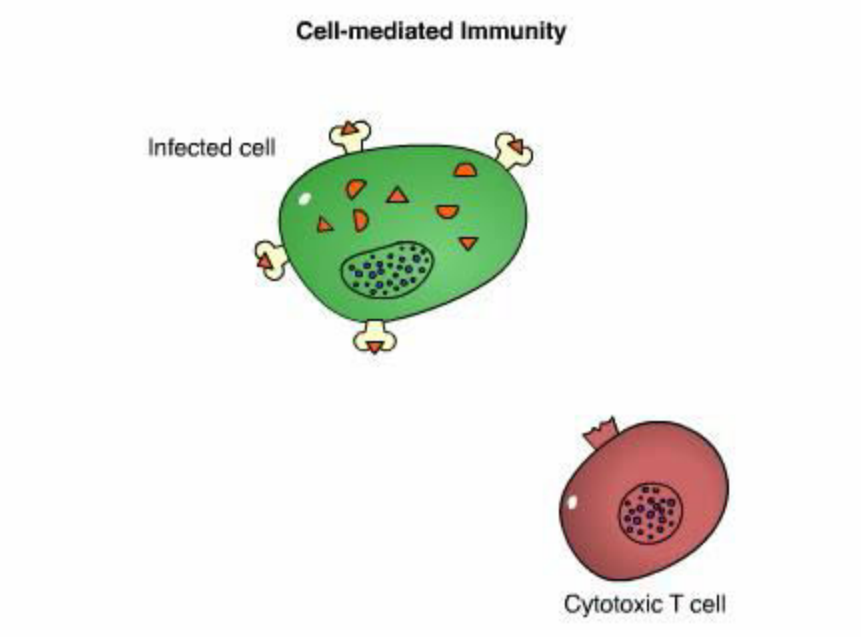


Figure 35.16-s1

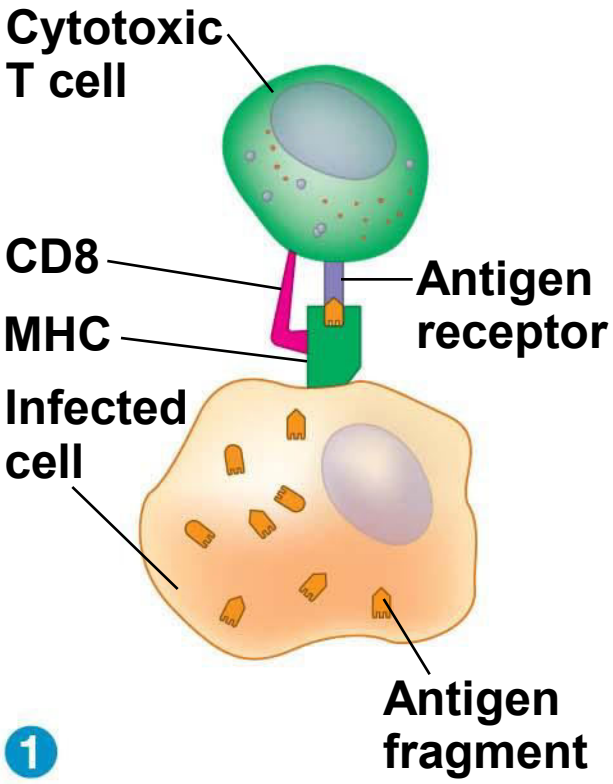


Figure 35.16-s2

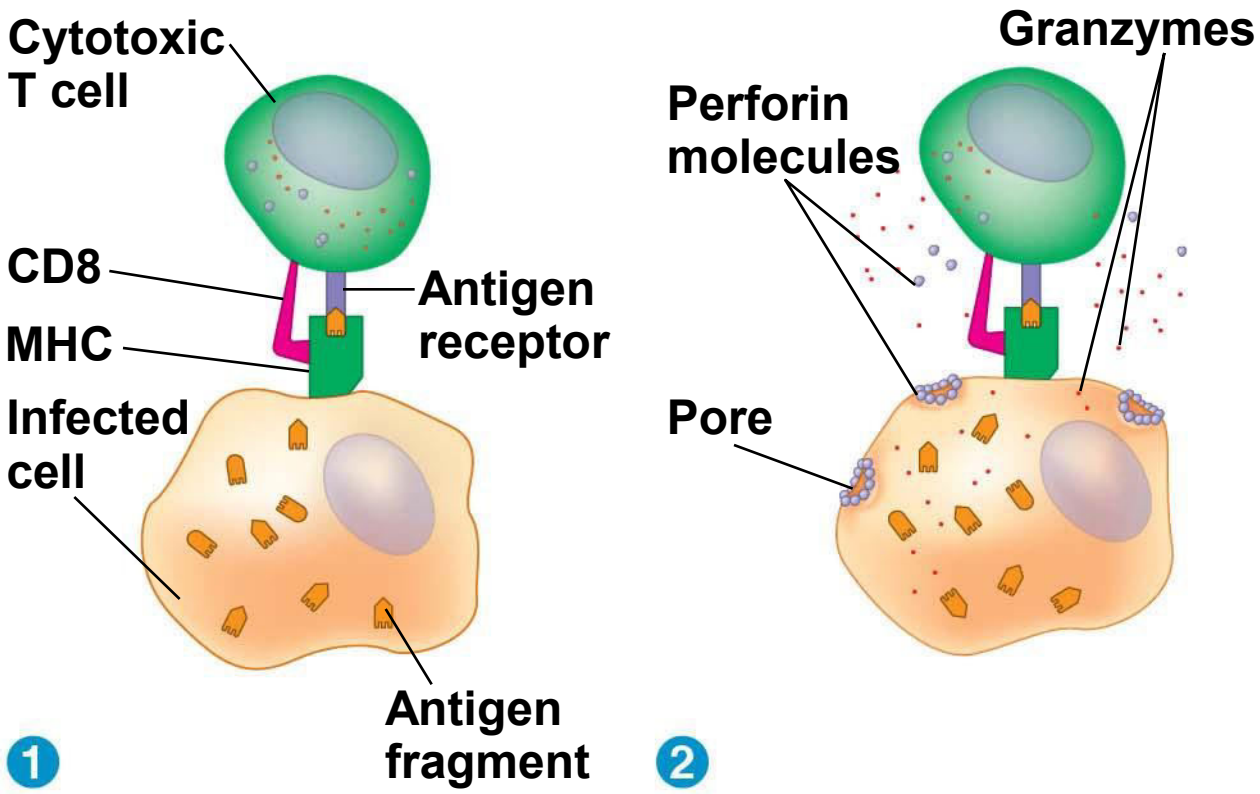
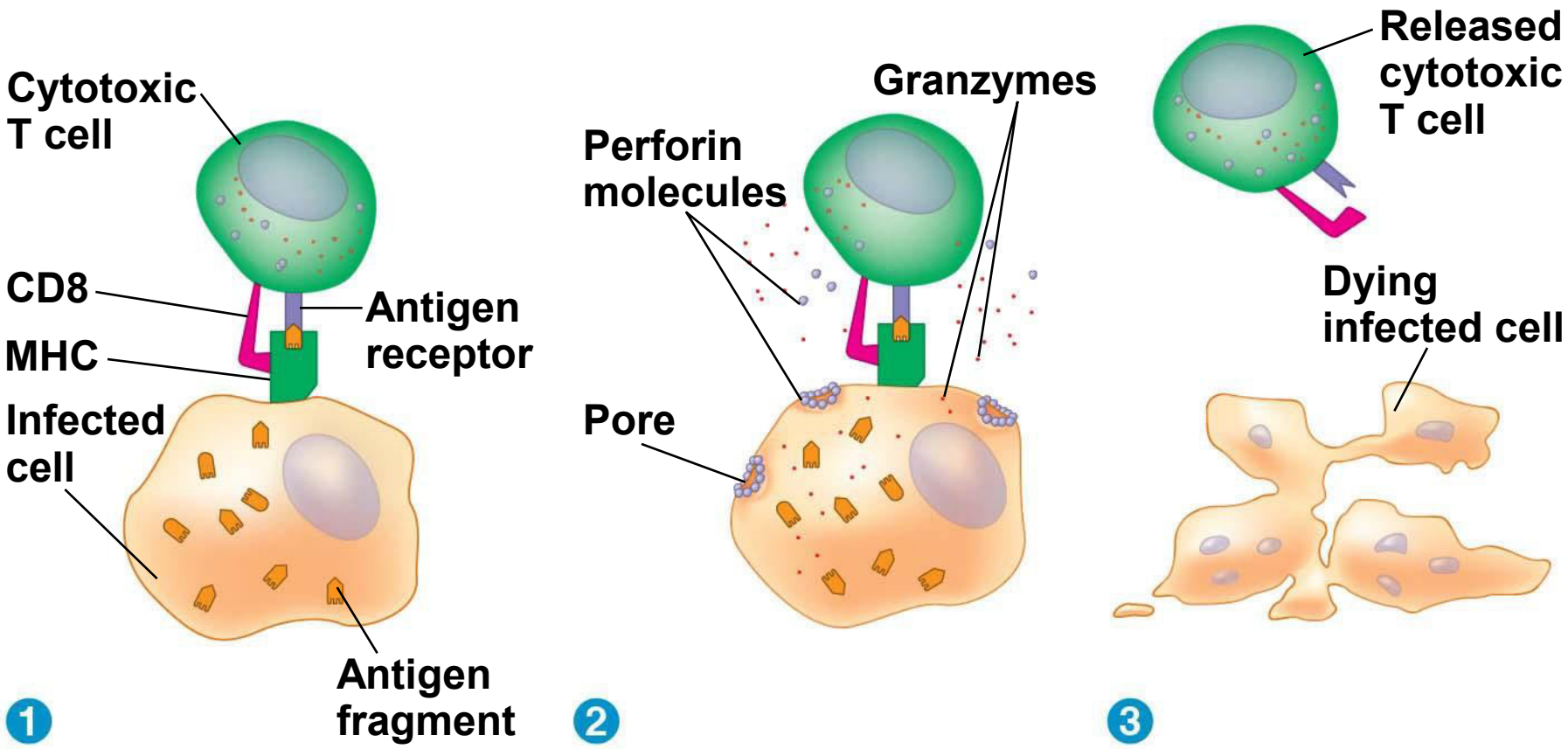


Figure 35.16-s3



Summary of the Humoral and Cell-Mediated Immune Responses

- Both the humoral and cell-mediated responses can include primary and secondary immune responses
- Memory cells enable the secondary response

Figure 35.17

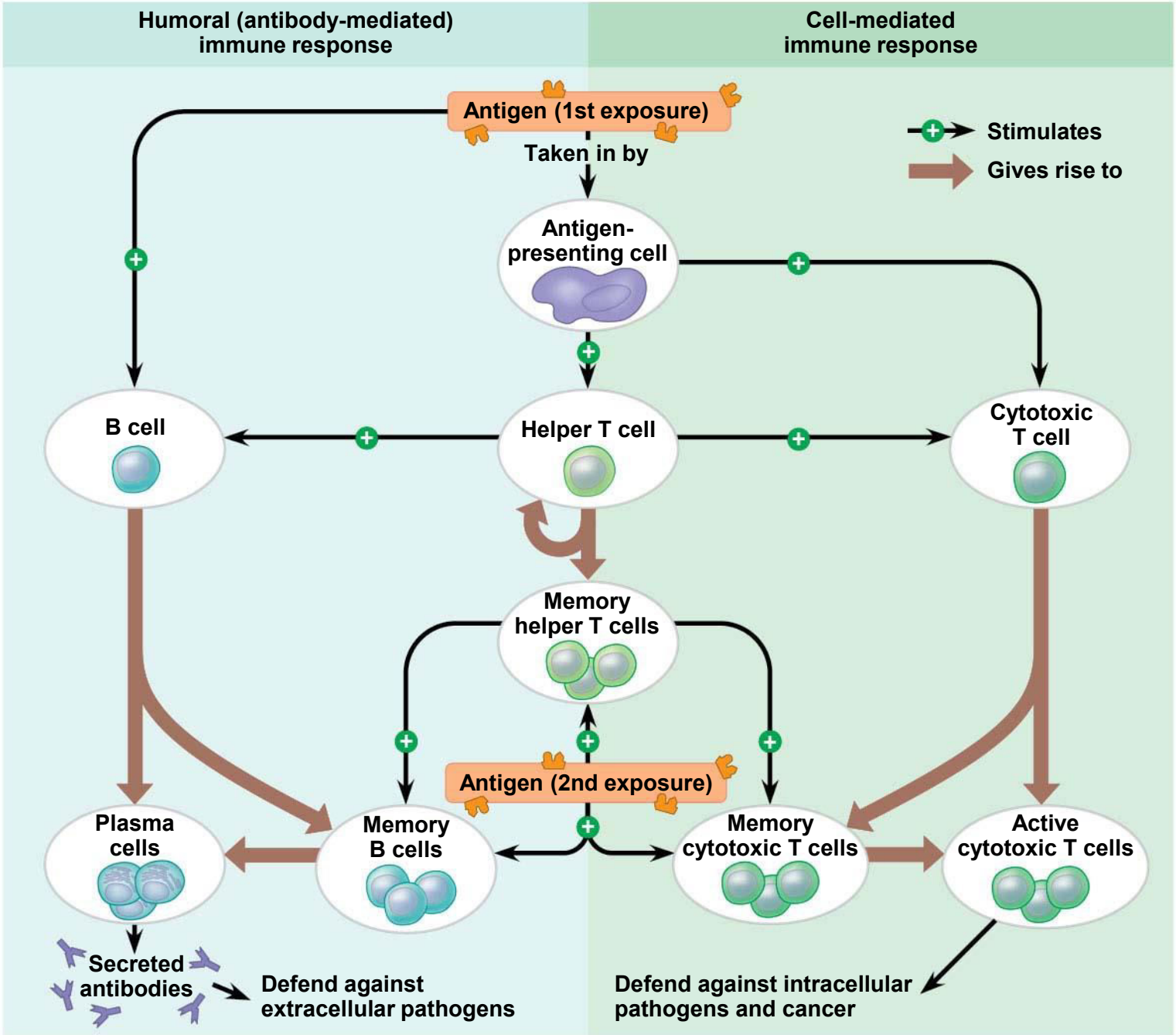


Figure 35.17-1

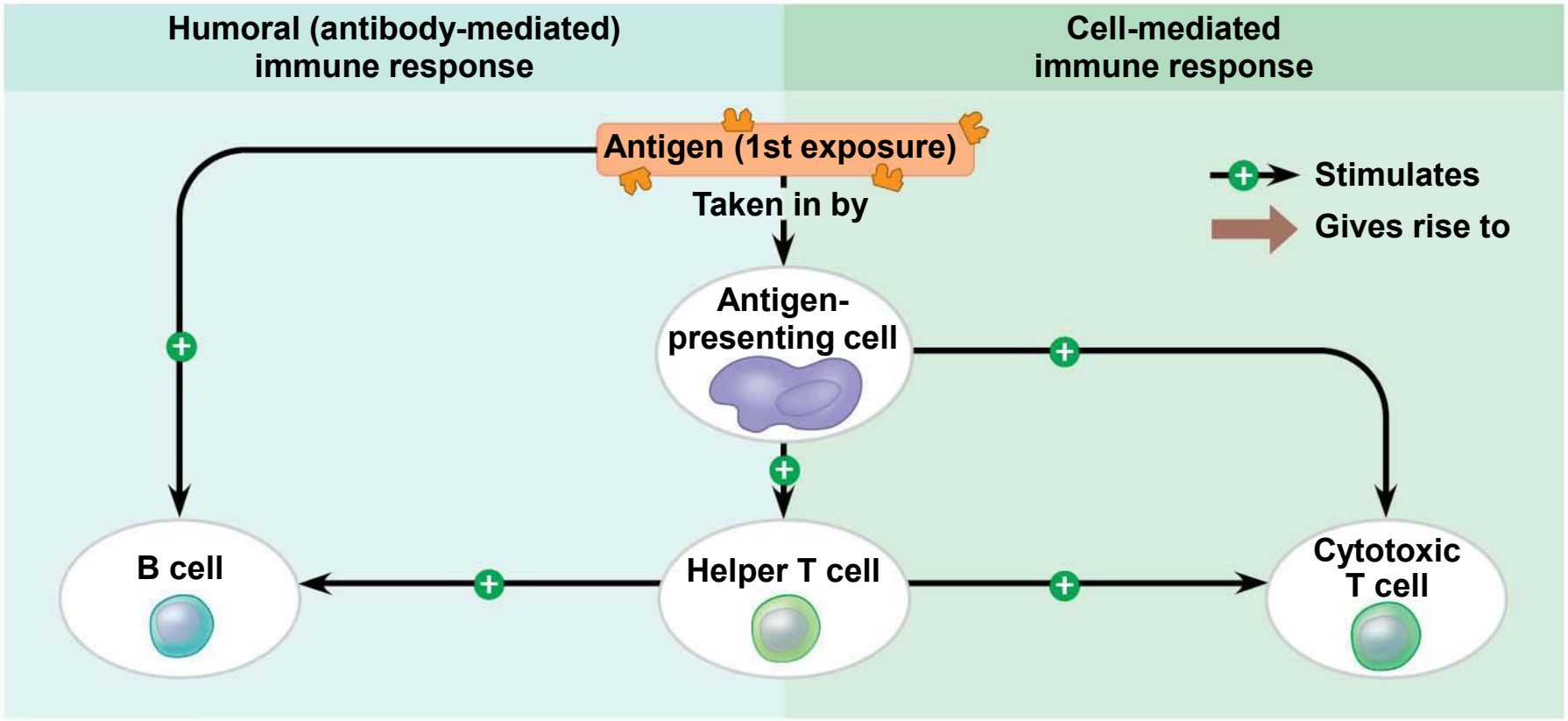
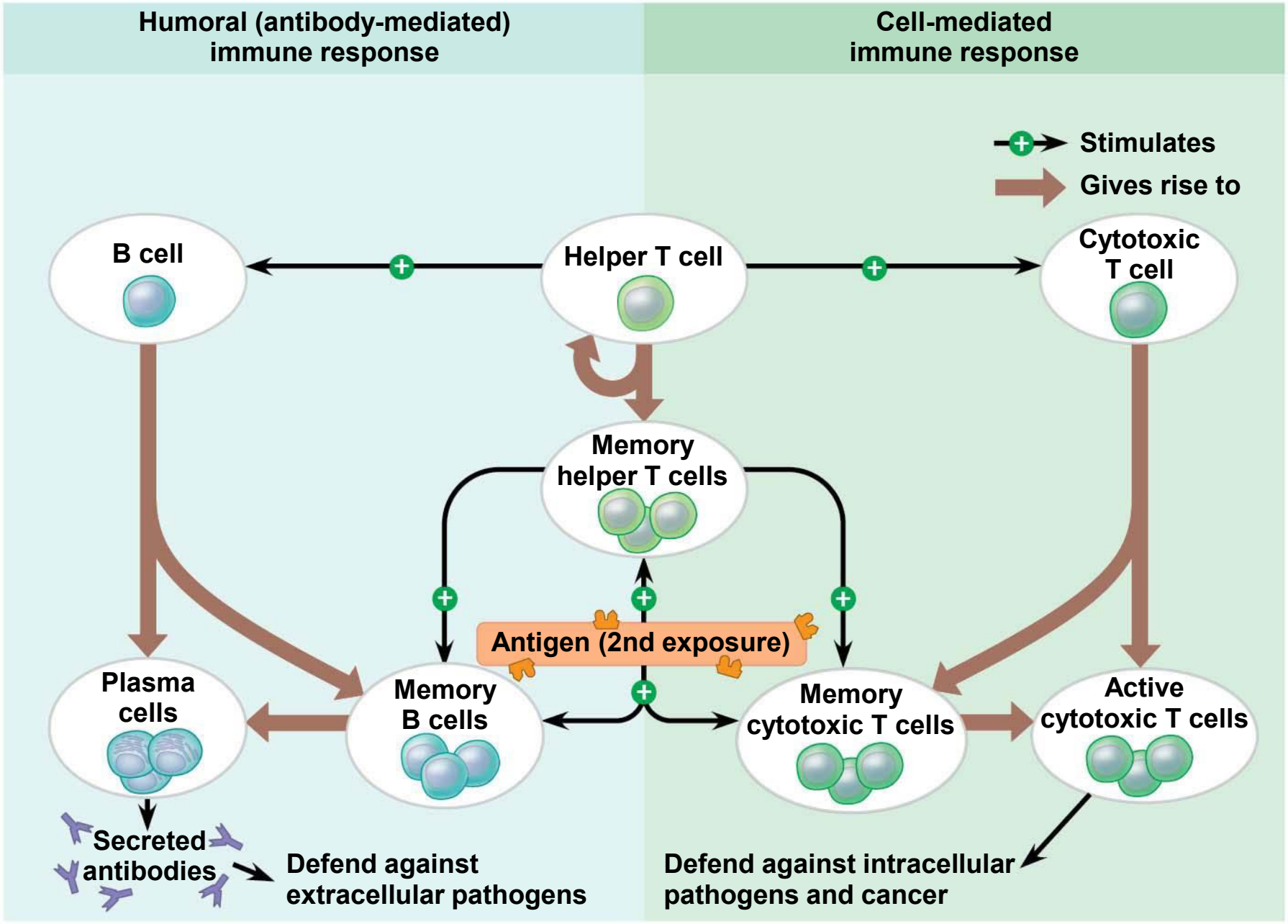


Figure 35.17-2



Active and Passive Immunity

- Active immunity occurs naturally when a pathogen infects the body
- Passive immunity provides immediate, short-term protection
- It is conferred naturally when antibodies cross the placenta from mother to fetus or pass from mother to infant in breast milk
- Both active and passive immunity can be induced artificially

- Active immunity is induced when antigens are introduced into the body in vaccines
- In this process of **immunization**, inactivated bacterial toxins or weakened or killed pathogens are introduced
- Passive immunity can be conferred artificially by injecting antibodies into a nonimmune person

Antibodies as Tools

- Polyclonal antibodies, produced following exposure to an 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
- Monoclonal antibodies have provided the basis for many recent advances in medical diagnosis and treatment

Immune Rejection

- Cells transferred from one person to another can be destroyed (rejected) by the recipient's immune defenses
- To minimize rejection, physicians use donor tissue that closely matches the MHC molecules of the recipient
- Recipients also take medicines that suppress their immune responses

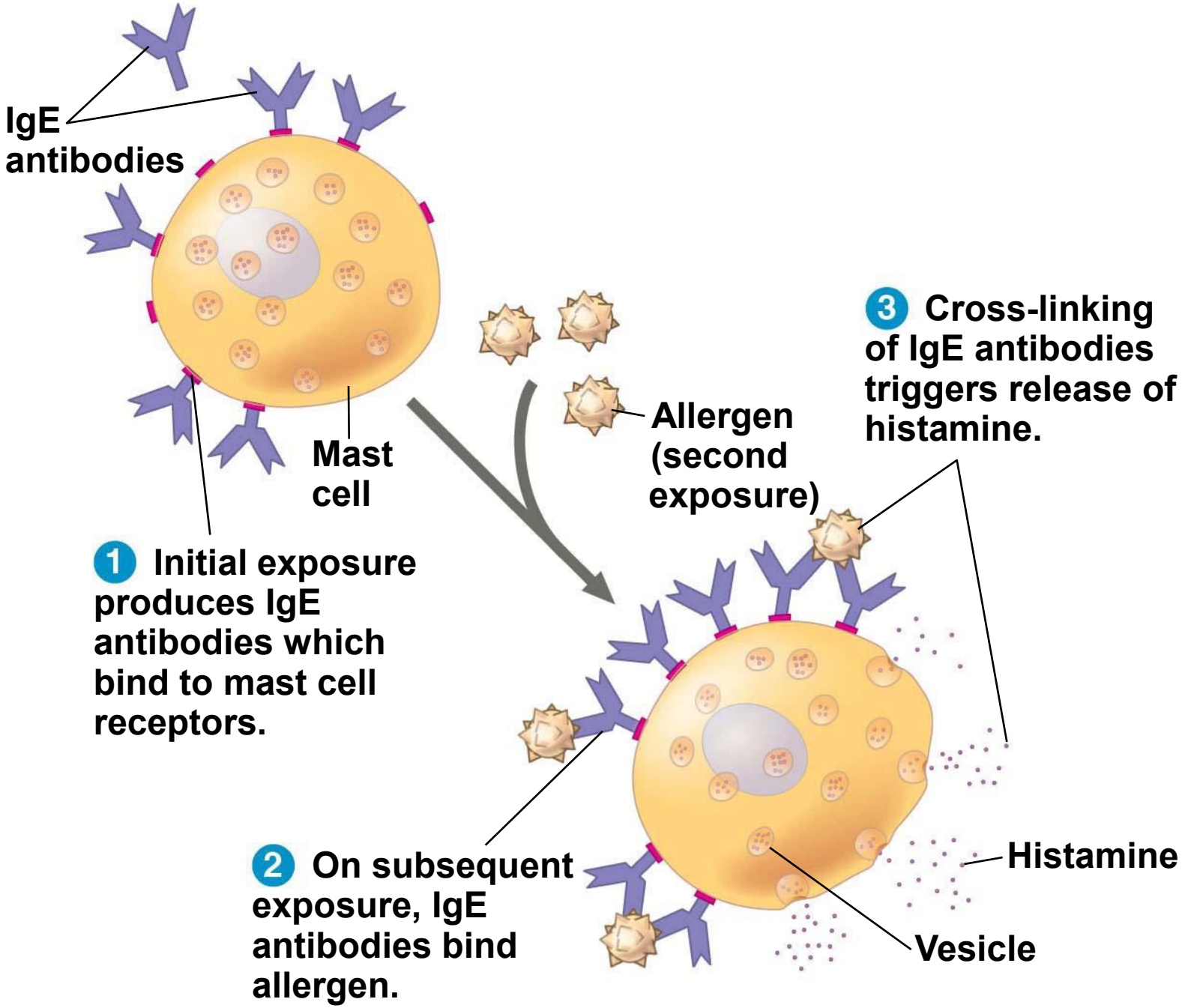
Disruptions in Immune System Function

- Although adaptive immunity protects against many pathogens, it is not fail-safe

Allergies

- Allergies are exaggerated (hypersensitive) responses to antigens called **allergens**
- In localized allergies such as hay fever, plasma cells secrete antibodies specific for antigens on the surface of pollen grains
- This triggers immune cells in connective tissue to release histamine and other inflammatory chemicals
- Antihistamines block receptors for histamine and diminish allergy symptoms

Figure 35.18

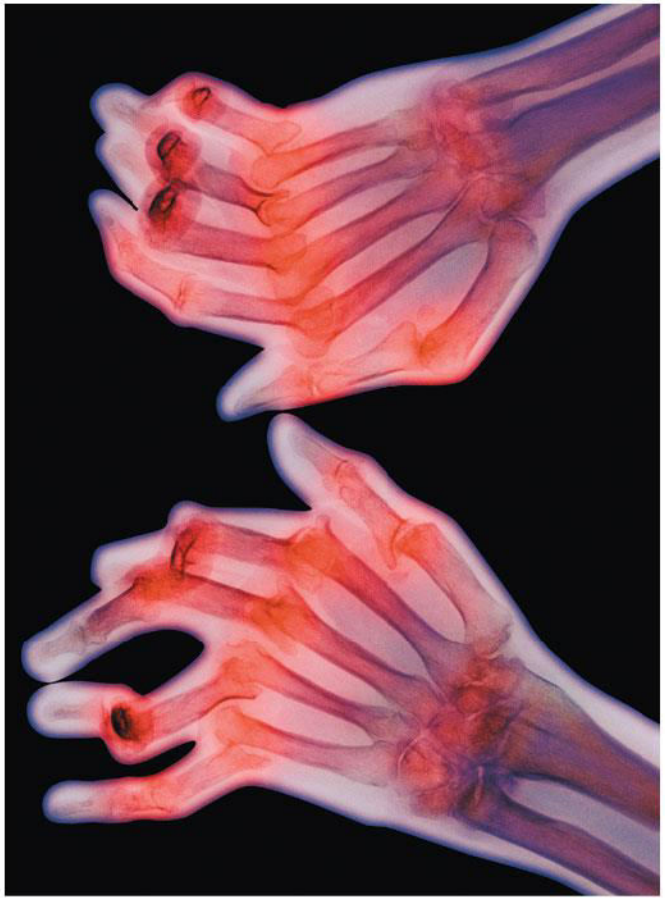


- An acute allergic response can lead to anaphylactic shock, a life-threatening reaction
- Substances that can trigger anaphylactic shock in allergic individuals include bee venom, penicillin, peanuts, and shellfish
- People with these hypersensitivities often carry epinephrine to counteract the allergic response

Autoimmune Diseases

- In individuals with **autoimmune diseases**, the immune system targets certain molecules of the body
- Autoimmune diseases include systemic lupus erythematosus, rheumatoid arthritis, type 1 diabetes, and multiple sclerosis
- Genes, heredity, and environment all influence susceptibility to autoimmune disorders

Figure 35.19



Immune System Avoidance

- Mechanisms to thwart immune responses have evolved in pathogens
- A pathogen may alter how it appears to the immune system by changing the epitopes it expresses
- Such changes are called antigenic variation
- This mechanism is seen in the parasite that causes sleeping sickness and in the influenza virus

- Some viruses avoid an immune response by infecting cells and then entering an inactive state called latency
- The virus (such as herpes simplex) remains latent until a stimulus reactivates it
- Stimuli include stress, fever, or menstruation

- Acquired immunodeficiency syndrome (AIDS) is caused by **HIV** (**human immunodeficiency virus**), which both attacks and escapes the immune system
- It infects helper T cells with high efficiency
- It escapes the immune system through its high mutation rate, which reduces the ability of the immune system to eliminate the infection
- It also can undergo latency

- People with AIDS (acquired immune deficiency syndrome) are highly susceptible to infections and cancers that a healthy immune system would normally defeat
- Unprotected sex and transmission via HIV-contaminated needles account for the majority of HIV infections
- HIV cannot be cured, but drugs have been developed to slow HIV replication and progression to AIDS

Cancer and Immunity

- The frequency of certain cancers increases when adaptive immunity is impaired
- 15–20% of all human cancers involve viruses
- The immune system can act as a defense against viruses that cause cancer and against cancer cells that harbor viruses
- In 2006, a vaccine was released that acts against human papillomavirus (HPV), a virus associated with cervical cancer

Figure 35.UN02-1

Day	Number of Parasites (in millions) per mL of Blood
4	0.1
6	0.3
8	1.2
10	0.2
12	0.2
14	0.9
16	0.6
18	0.1
20	0.7
22	1.2
24	0.2

Data from L. J. Morrison et al., Probabilistic order in antigenic variation of *Trypanosoma brucei*, *International Journal for Parasitology* 35:961–972 (2005) and L.J. Morrison et al., Antigenic variation in the African trypanosome: molecular mechanisms and phenotypic complexity, *Cellular Microbiology* 1:1724–1734 (2009).

Figure 35.UN02-2

Day	Antibody Specific to Glycoprotein Variant A	Antibody Specific to Glycoprotein Variant B
4	0	0
6	0	0
8	0.2	0
10	0.5	0
12	1	0
14	1	0.1
16	1	0.3
18	1	0.9
20	1	1
22	1	1
24	1	1

Data from L. J. Morrison et al., Probabilistic order in antigenic variation of *Trypanosoma brucei*, *International Journal for Parasitology* 35:961–972 (2005) and L.J. Morrison et al., Antigenic variation in the African trypanosome: molecular mechanisms and phenotypic complexity, *Cellular Microbiology* 1:1724–1734 (2009).

Figure 35.UN02-3

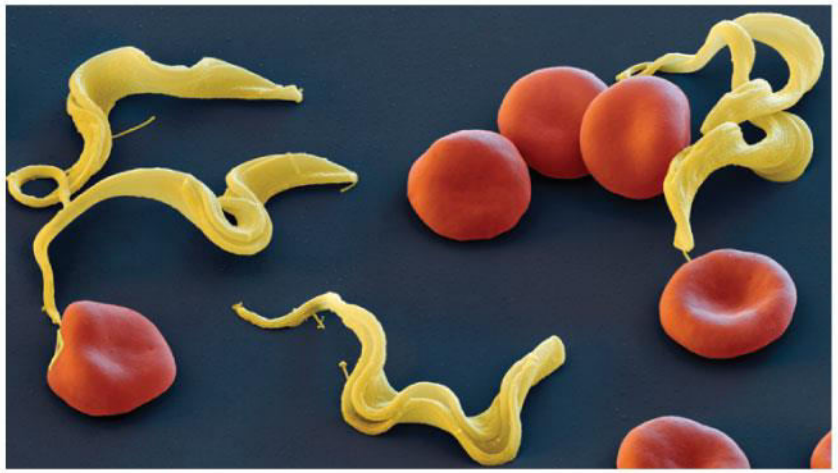


Figure 35.UN03