Immune System
(Innate and Adaptive Components)

- **Immunity—the state of protection from infectious disease —has both a less specific and more specific component.**

1. **Innate immunity:**
   - ✓ Less specific component
   - ✓ Provides the first line of defense against infection.
   - ✓ Most components of innate immunity are present before the onset of infection and constitute a set of disease-resistance mechanisms that are not specific to a particular pathogen but that include cellular and molecular components that recognize classes of molecules peculiar to frequently encountered pathogens.
   - ✓ Phagocytic cells, such as macrophages and neutrophils
   - ✓ Barriers such as skin, and a variety of antimicrobial compounds synthesized by the host all play important roles in innate immunity.
   - ✓ In contrast to the broad reactivity of the innate immune system, which is uniform in all members of a species, the specific component,

Innate Immunity Barriers and Mechanisms

Barrier	Mechanism
Anatomic	
Skin	• Mechanical barrier retards entry of microbes • Acidic environment (pH 3-5) retards growth of microbes
Mucous membrane	• Normal flora compete with microbes for attachment sites • Mucous entraps foreign microbes • Cilia propel microbes out of body
Physiologic	
Temperature	• Body temperature/fever response inhibits growth of some pathogens
Low pH	• Acidic pH of stomach kills most undigested microbes
Chemical mediators	• Lysozyme cleaves bacterial cell wall • Interferon induces antiviral defenses in uninfected cells • Complement lyses microbes or facilitates phagocytosis
Phagocytic/endocytic barriers	
	• Various cells internalize (endocytosis) and break down foreign macromolecules • Specialized cells (blood monocytes, neutrophils, tissue macrophages) internalize (phagocytose), kill and digest whole organisms
Inflammatory barriers	
	• Tissue damage and infection induce leakage of vascular fluid containing serum protein with antibacterial activity, leading to influx of phagocytic cells into the affected area

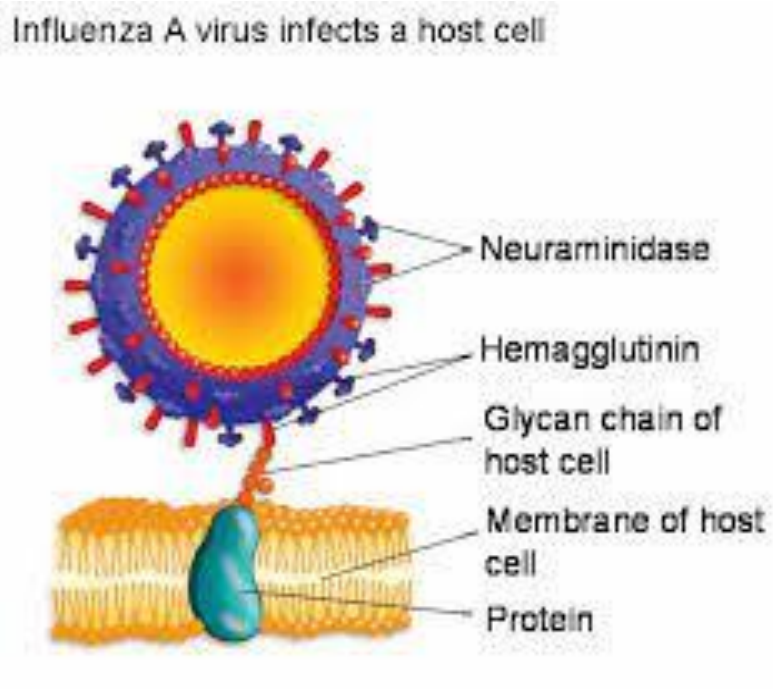
Skin and Mucosal Surfaces Provide Protective Barriers Against Infection

- Physical and anatomic barriers that tend to prevent the entry of pathogens are an organism's first line of defense against infection.
- Skin and surface of mucous membranes are included in this category because they are effective barriers to the entry of most microorganisms.
- The skin consists of two distinct layers:
  - ✓ Thinner outer layer—the **epidermis**—and a
  - ✓ Thicker layer—the **dermis.**
- The epidermis contains several layers of tightly packed epithelial cells.
- The outer epidermal layer consists of dead cells and is filled with a waterproofing protein called keratin.
- The dermis, which is composed of connective tissue, contains blood vessels, hair follicles, sebaceous glands, and sweat glands.
- The sebaceous glands are associated with the hair follicles and produce an oily secretion called **sebum.**
- Sebum consists of lactic acid and fatty acids, which maintain the pH of the skin between 3 and 5; this pH inhibits the growth of most microorganisms.
- A few bacteria that metabolize sebum live as commensals on the skin and sometimes cause a severe form of **acne.**
- One acne drug, **isotretinoin (Accutane), is a vitamin A derivative** that prevents the formation of sebum.

Mucosal Surfaces

- In the lower respiratory tract, the mucous membrane is covered by **cilia.**

- Movement of **cilia propels mucus-entrapped microorganisms** from these tracts.
- Nonpathogenic organisms tend to colonize the epithelial cells of mucosal surfaces. But, ***normal flora*** generally outcompete pathogens for attachment sites on the epithelial cell surface and for necessary nutrients.
- Some organisms have evolved ways of escaping these defense mechanisms and thus are able to invade the body through mucous membranes.
- For example, **influenza virus** has a surface molecule that enables it to attach firmly to cells in mucous membranes of the respiratory tract, preventing the virus from being swept out by the ciliated epithelial cells.



- Similarly, the organism that **causes gonorrhea** has surface projections that allow it to bind to epithelial cells in the mucous membrane of the urogenital tract.

- **Adherence of bacteria to mucous membranes is due to interactions between hairlike structures on a bacterium, called fimbriae or pili, and certain glycoproteins or glycolipids that are expressed only by epithelial cells of the mucous membrane of particular tissues.**
- **For this reason, some tissues are susceptible to bacterial invasion, whereas others are not**

Physiologic Barriers

- The physiologic barriers that contribute to innate immunity include:
  - ✓ temperature
  - ✓ pH, and
  - ✓ various soluble and
  - ✓ cell associated molecules
- Many species are not susceptible to certain diseases simply because their normal body temperature inhibits growth of the pathogens.
- Chickens, for example, have innate immunity to anthrax because their high body temperature inhibits the growth of the bacteria.
- Gastric acidity is an innate physiologic barrier to infection because very few ingested microorganisms can survive the low pH of the stomach contents.
- One reason newborns are susceptible to some diseases that do not afflict adults is that their stomach contents are less acid than those of adults.

- A variety of soluble factors contribute to innate immunity, among them the soluble proteins
  - ✓ lysozyme
  - ✓interferon
  - ✓Complement

- **Lysozyme,** a hydrolytic enzyme found in mucous secretions and in tears, is able to cleave the peptidoglycan layer of the bacterial cell wall.

- **Interferon** comprises a group of proteins produced by virus-infected cells.

- Among the many functions of the interferons is the ability to bind to nearby cells and induce a generalized antiviral state.

- **Complement,** is a group of serum proteins that circulate in an inactive state. A variety of specific and nonspecific immunologic mechanisms can convert the inactive forms of complement proteins into an active state with the ability to damage the membranes of pathogenic organisms, either destroying the pathogens or facilitating their clearance.

- Recent studies on **collectins** indicate that these surfactant proteins may kill certain bacteria directly by disrupting their lipid membranes or, alternatively, by aggregating the bacteria to enhance their susceptibility to phagocytosis.

- **Many of the molecules involved in innate immunity have the property of pattern recognition, the ability to recognize a given class of molecules.**

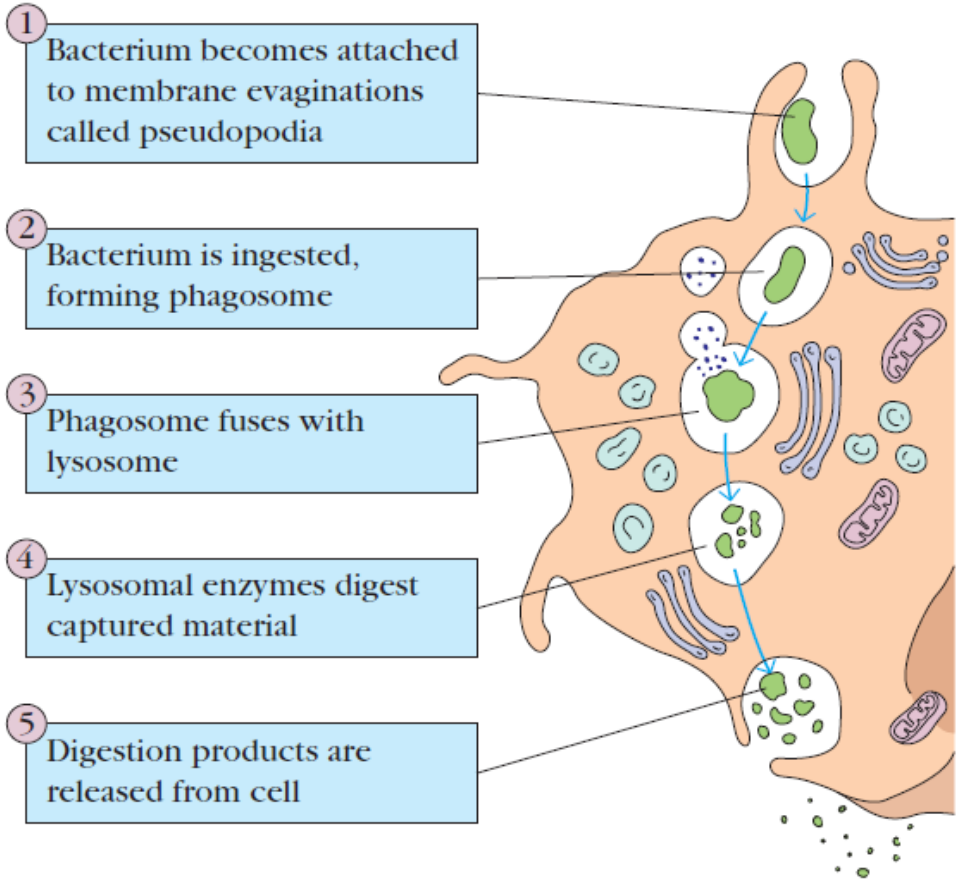
- **Because there are certain types of molecules that are unique to microbes and never found in multicellular organisms, the ability to immediately recognize and combat invaders displaying such molecules is a strong feature of innate immunity.**

- **Molecules with pattern recognition ability may be soluble, like lysozyme and the complement components or they may be cell-associated receptors.**

- **Among the class of receptors designated the toll-like receptors (TLRs), TLR2 recognizes the lipopolysaccharide (LPS) found on Gram-negative bacteria.**

Phagocytic Barrier

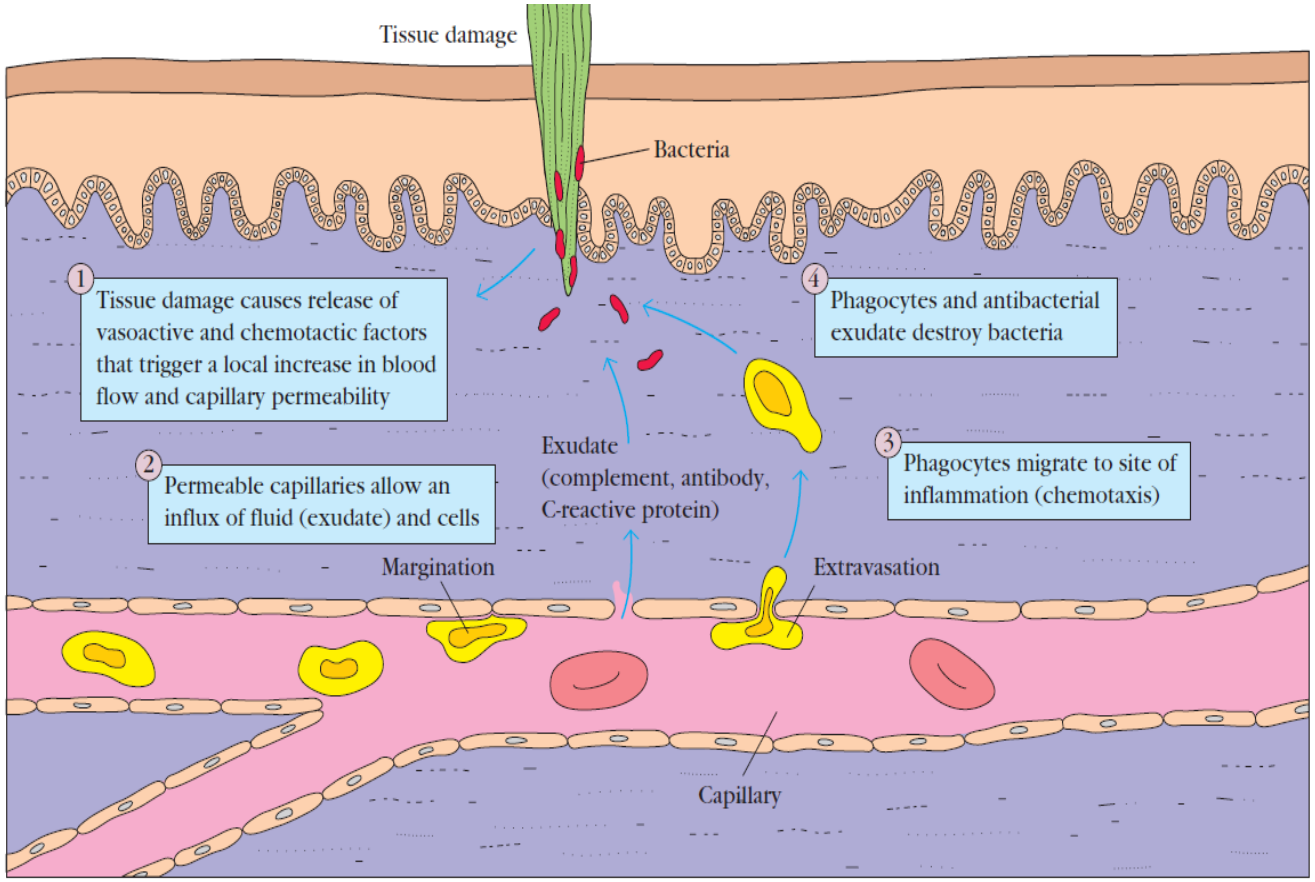
- In this system cells ingest and destroy pathogens.
- In phagocytosis, a cell's plasma membrane expands around the particulate material, which may include whole pathogenic microorganisms, to form large vesicles called **phagosomes.**
- Most phagocytosis is conducted by specialized cells, such as blood monocytes, neutrophils, and tissue macrophages.



Inflammatory Barriers

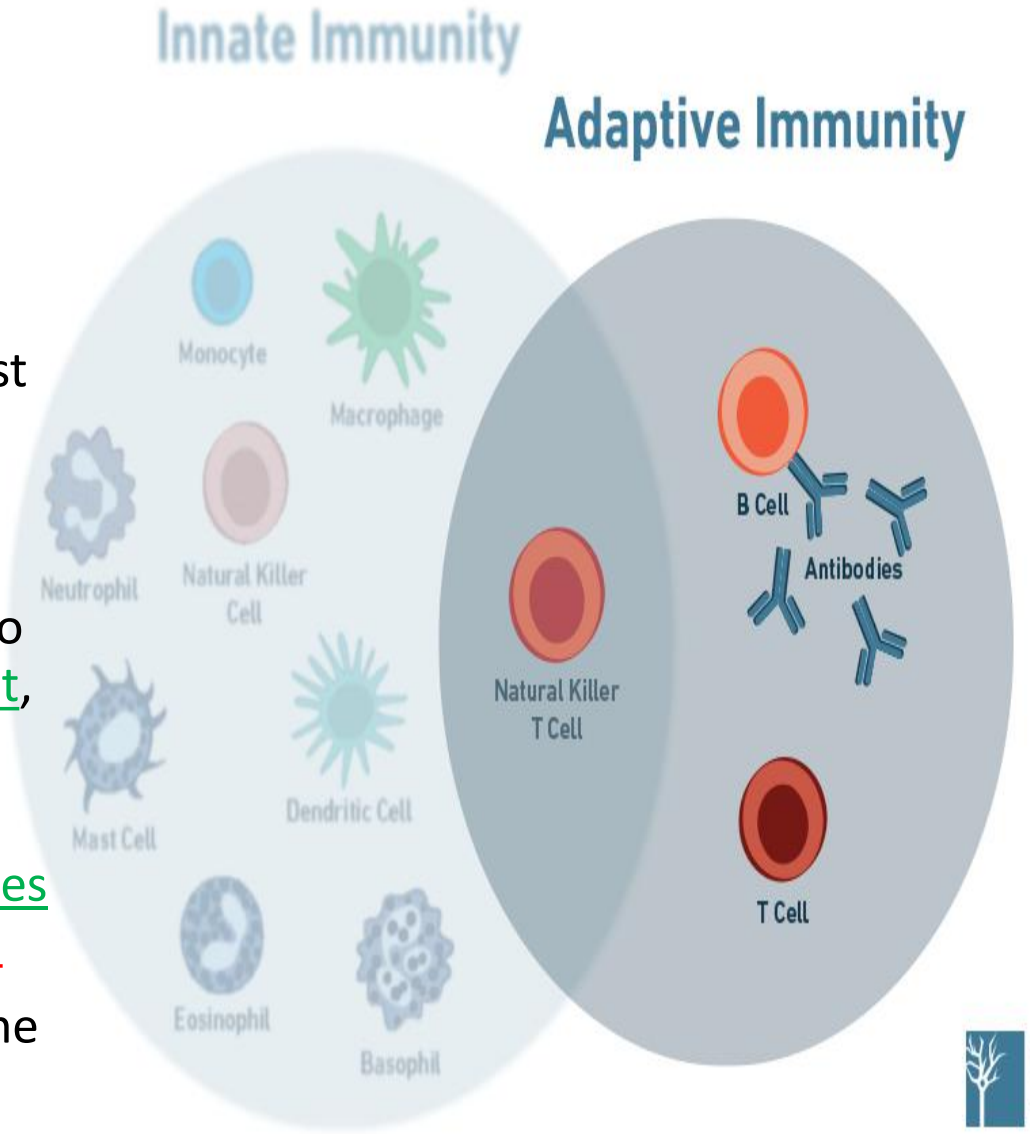
rubor (redness), *tumor* (swelling), *calor* (heat), and *dolor* (pain). fifth sign: *functio laesa*

- Represents a complex sequence of events that stimulates immune responses.
- A bacterial infection causes tissue damage with release of various vasoactive and chemotactic factors.
- These factors induce
  - ✓ increased blood flow to the area,
  - ✓ increased capillary permeability, and
  - ✓ an influx of white blood cells, including phagocytes and lymphocytes, from the blood into the tissues.
- The serum proteins contained in the exudate have antibacterial properties, and the phagocytes begin to engulf the bacteria.



2. adaptive immunity:

- Does not come into play until there is an antigenic challenge to the organism.
- It responds to the challenge with a high degree of specificity as well as the remarkable property of "memory."
- Typically, there is an adaptive immune response against an antigen within five or six days after the initial exposure to that antigen.
- Exposure to the same antigen some time in the future results in a memory response: the immune response to the second challenge occurs more quickly than the first, is stronger, and is often more effective in neutralizing and clearing the pathogen.
- The major agents of adaptive immunity are lymphocytes and the antibodies and other molecules they produce.
- Because adaptive immune responses require some time to marshal, innate immunity provides the first line of defense during the critical period just after the host's exposure to a pathogen.



Cell Signaling TECHNOLOGY®

Four characteristic attributes of Adaptive immunity

- **Antigenic specificity**
- **Diversity**
- **Immunologic memory**
- **Self/nonself recognition**

Antigenic Specificity:

- Ability to distinguish subtle differences among antigens.
- Antibodies can distinguish between two protein molecules that differ in only a single amino acid.

Diversity:

- The immune system is capable of generating tremendous *diversity* in its recognition molecules, allowing it to recognize billions of unique structures on foreign antigens.

Immunologic memory:

- Once the immune system has recognized and responded to an antigen, it exhibits *immunologic memory.*
- That is, a second encounter with the same antigen induces a heightened state of immune reactivity.
- Because of this attribute, the immune system can confer life-long immunity to many infectious agents after an initial encounter.

Self/Nonself Recognition.

- Finally, the immune system normally responds only to foreign antigens, indicating that it is capable of *self/nonself recognition.*
- The ability of the immune system to distinguish self from nonself and respond only to nonself molecules is essential, for, as described below, the outcome of an inappropriate response to self molecules can be fatal.

Interplay of innate and adaptive immunity

- **Adaptive immunity is not independent of innate immunity.**
- **The phagocytic cells crucial to nonspecific immune responses are intimately involved in activating the specific immune response.**
- **Conversely, various soluble factors produced by a specific immune response have been shown to augment the activity of these phagocytic cells.** **(antibody help phagocytic cells for opsonization).**
- **As an inflammatory response develops, for example, soluble mediators are produced that attract cells of the immune system. The immune response will, in turn, serve to regulate the intensity of the inflammatory response.** (IL-8 secreted by neutrophils, eosinophils, and basophils and attracts T-Lymphocytes)
- **Through the carefully regulated interplay of adaptive and innate immunity, the two systems work together to eliminate a foreign invader.**

Cells of adaptive immunity

B LYMPHOCYTES

- B lymphocytes mature within the bone marrow; when they leave it, each expresses a unique antigen-binding receptor on its membrane. This antigen-binding or B-cell receptor is a membrane-bound **antibody molecule.**
- When a naive B cell (one that has not previously encountered antigen) first encounters the antigen that matches its membrane bound antibody, the binding of the antigen to the antibody causes the cell to divide rapidly; its progeny differentiate into **memory B cells** and **effector B cells** called **plasma cells.**
- Memory B cells have a longer life span than naive cells, and they express the same membrane-bound antibody as their parent B cell. Plasma cells produce the antibody in a form that can be secreted and have little or no membrane-bound antibody.
- Although plasma cells live for only a few days, they secrete enormous amounts of antibody during this time*. It has been estimated that a single plasma cell can secrete more than 2000 molecules of antibody per second.* Secreted antibodies are the major effector molecules of humoral immunity.
- B cells have about 105 molecules of membrane-bound antibody per cell. All the antibody molecules on a given B cell have the same antigenic specificity and can interact directly with antigen.

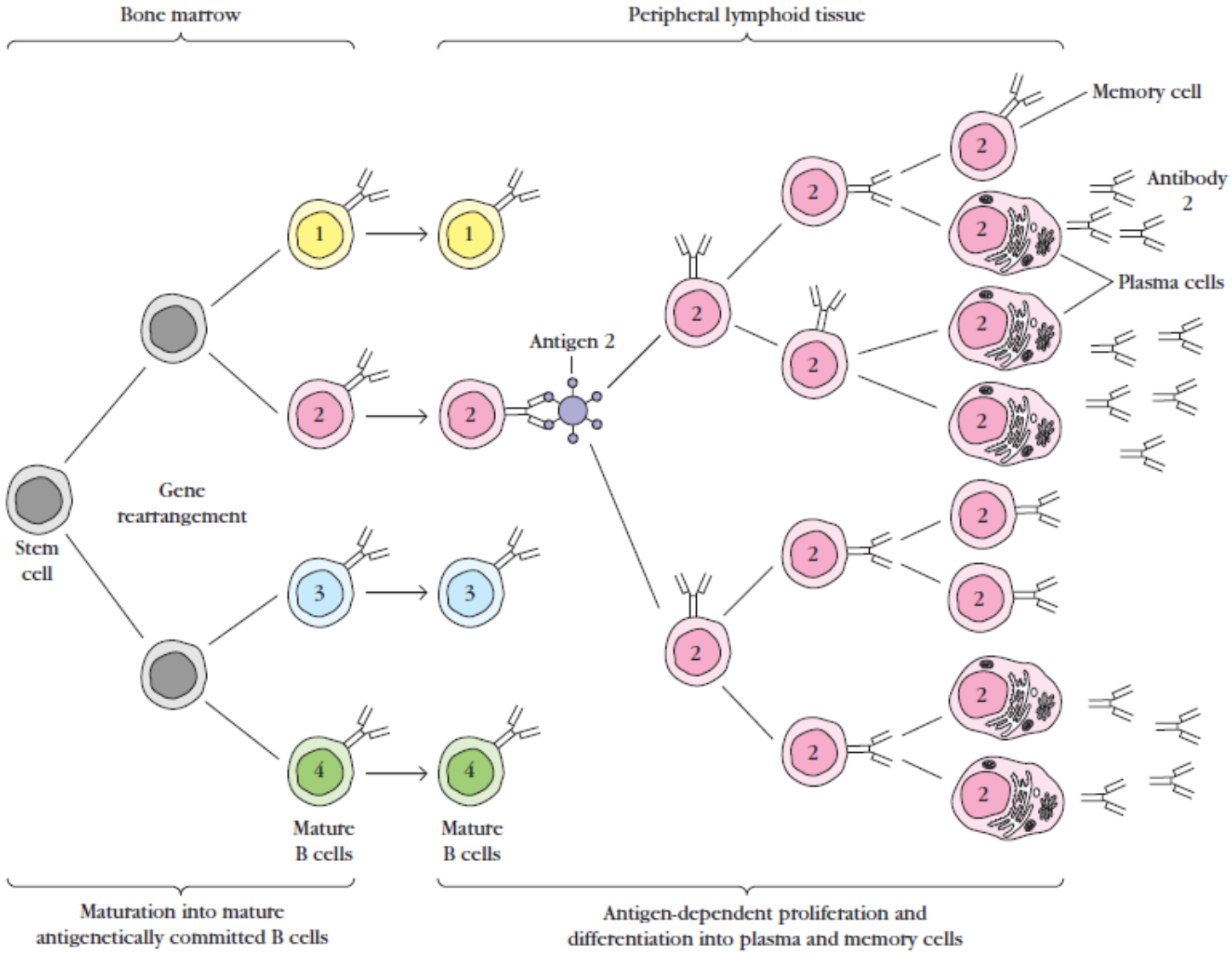


FIGURE 1-10 Maturation and clonal selection of B lymphocytes. Maturation, which occurs in the absence of antigen, produces antigenically committed B cells, each of which expresses antibody with a single antigenic specificity (indicated by 1, 2, 3, and 4). Clonal selection occurs when an antigen binds to a B cell whose membrane-bound antibody molecules are specific for epitopes on that antigen. Clonal expansion of an antigen-activated B cell (number 2 in this example) leads to a clone of memory B cells and effector B cells, called plasma cells; all cells in the expanded clone are specific for the original antigen. The plasma cells secrete antibody reactive with the activating antigen. Similar processes take place in the T-lymphocyte population, resulting in clones of memory T cells and effector T cells; the latter include activated T_H cells, which secrete cytokines, and cytotoxic T lymphocytes (CTLs).

T LYMPHOCYTES

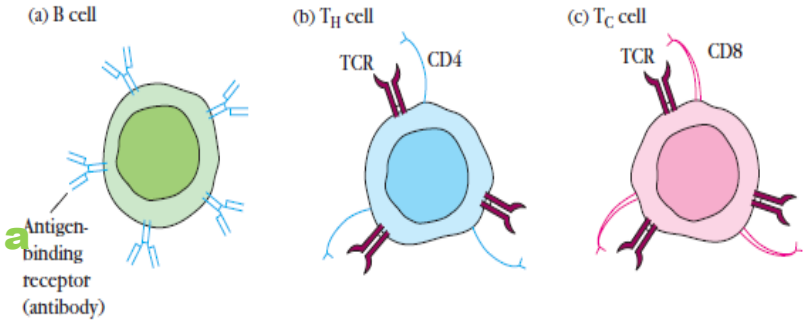
- T lymphocytes also arise in the bone marrow. Unlike B cells, which mature within the bone marrow, T cells migrate to the thymus gland to mature. During its maturation within the thymus, the T cell comes to express a unique antigen-binding molecule, called the T-cell receptor, on its membrane.

- Both types of T cells express about 105 identical molecules of the antigen binding T-cell receptor (TCR) per cell, all with the same antigenic specificity.

- Unlike membrane-bound antibodies on B cells, which can recognize antigen alone, T-cell receptors can recognize only antigen that is bound to cell-membrane proteins called major histocompatibility complex (MHC) molécules.

- MHC molécules that function in this recognition event, which is termed "antigen presentation," are polymorphic (genetically diverse) glycoproteins found on cell membranes.

- There are two major types of MHC molecules: Class I MHC molecules, which are expressed by nearly all nucleated cells of vertebrate species, consist of a heavy chain linked to a small invariant protein called β2-microglobulin.



- Class II MHC molecules, which consist of an alpha and a beta glycoprotein chain, are expressed only by antigen-presenting cells.

- When a naive T cell encounters antigen combined with a MHC molecule on a cell, the T cell proliferates and differentiates into memory T cells and various effector T cells.

- There are two well-defined subpopulations of T cells:
  - ✓ T helper (TH) and
  - ✓ T cytotoxic (TC) cells.
- T helper and T cytotoxic cells can be distinguished from one another by the presence of either CD4 or CD8 membrane glycoproteins on their surfaces.
- T cells displaying CD4 generally function as TH cells, whereas those displaying CD8 generally function as TC cells.
- After a TH cell recognizes and interacts with an antigen–MHC class II molecule complex, the cell is activated—it becomes an effector cell that secretes various growth factors known collectively as cytokines.
- The secreted cytokines play an important role in activating
  - ✓ B cells,
  - ✓ TC cells,
  - ✓ macrophages, and
  - ✓ various other cells that participate in the immune response.

- **Differences in the pattern of cytokines produced by activated TH cells result in different types of immune response.**

- **Under the influence of TH-derived cytokines, a TC cell that recognizes an antigen–MHC class I molecule complex proliferates and differentiates into an effector cell called a cytotoxic T lymphocyte (CTL).**

- **In contrast to the TC cell, the CTL generally does not secrete many cytokines and instead exhibits cell-killing or cytotoxic activity.**

- **The CTL has a vital function in monitoring the cells of the body and eliminating any that display antigen, such as virus-infected cells, tumor cells, and cells of a foreign tissue graft.**

- **Cells that display foreign antigen complexed with a class I MHC molecule are called *altered self-cells*; these are targets of CTLs.**

Antigen-presenting Cells

- Activation of both the humoral and cell-mediated branches of the immune system requires cytokines produced by TH cells.
- It is essential that activation of TH cells themselves be carefully regulated, because an inappropriate T-cell response to self-components can have fatal autoimmune consequences.
- To ensure carefully regulated activation of TH cells, they can recognize only antigen that is displayed together with class MHC II molecules on the surface of antigen-presenting cells (APCs).
- These specialized cells, which include macrophages, B lymphocytes, and dendritic cells, are distinguished by two properties:
    - (1) they express class II MHC molecules on their membranes, and
    - (2) they are able to deliver a co-stimulatory signal that is necessary for TH-cell activation.
- Antigen-presenting cells first internalize antigen, either by phagocytosis or by endocytosis, and then display a part of that antigen on their membrane bound to a class II MHC molecule.
- The TH cell recognizes and interacts with the antigen–class II MHC molecule complex on the membrane of the antigen-presenting cell.
- An additional costimulatory signal is then produced by the antigen-presenting cell, leading to activation of the TH cell.

Humoral and cell mediated immune response

Humoral Immunity

- Humoral immunity refers to immunity that can be conferred upon a nonimmune individual by administration of serum antibodies from an immune individual.
- Humoral branch of the immune system is at work in the interaction of B cells with antigen and their subsequent proliferation and differentiation into antibody-secreting plasma cells.
- Antibody functions as the effector of the humoral response by binding to antigen and neutralizing it or facilitating its elimination.
- When an antigen is coated with antibody, it can be eliminated in several ways.
- For example,
  - ✓ antibody can cross-link several antigens, forming clusters that are more readily ingested by phagocytic cells.
  - ✓ Binding of antibody to antigen on a microorganism can also activate the complement system, resulting in lysis of the foreign organism.
  - ✓ Antibody can also neutralize toxins or viral particles by coating them, which prevents them from binding to host cells.

Cell mediated Immunity

- Cell-mediated immunity can be transferred only by administration of T cells from an immune individual.
- Effector T cells generated in response to antigen are responsible for cell-mediated immunity.
- Both activated TH cells and cytotoxic T lymphocytes (CTLs) serve as effector cells in cell-mediated immune reactions.
- Cytokines secreted by TH cells can activate various phagocytic cells, enabling them to phagocytose and kill microorganisms more effectively.
- This type of cell-mediated immune response is especially important in ridding the host of bacteria and protozoa contained by infected host cells.
- CTLs participate in cell-mediated immune reactions by
  - ✓ killing altered self-cells
  - ✓ Killing of pathogen/virus infected cells and
  - ✓ killing of tumor cells.

Humoral

- B cells can recognize an epitope alone.
- Humoral branch recognizes an enormous variety of epitopes:
  - ✓ those displayed on the surfaces of bacteria or viral particles,
  - ✓ displayed on soluble proteins, glycoproteins, polysaccharides, or lipopolysaccharides that have been released from invading pathogens.

Cell mediated

- T Cells can recognize an epitope only when it is associated with an MHC molecule on the surface of antigen presenting cell or an altered self-cell.
- The cell-mediated branch (T cells) recognizes protein epitopes:
  - ✓ displayed together with MHC molecules on self-cells, including altered self-cells such as virus-infected self-cells and cancerous cells.

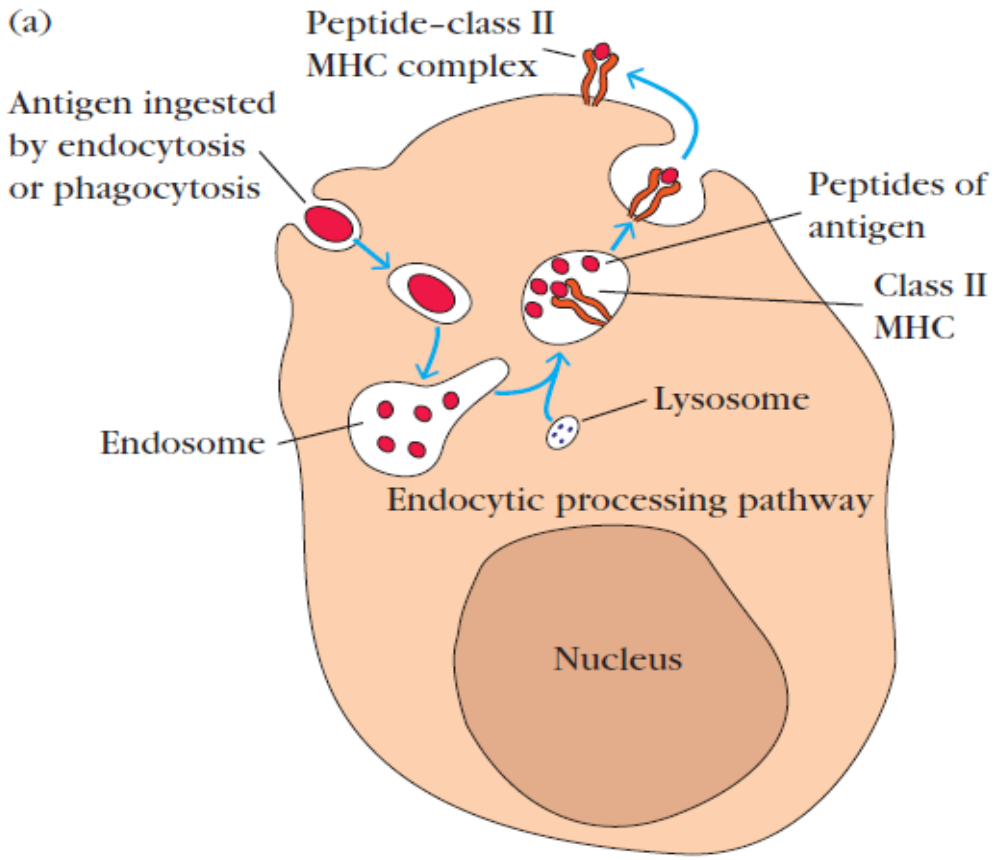
Thus, four related but distinct cell-membrane molecules are responsible for antigen recognition by the immune system:

- Membrane-bound antibodies on B cells
- T-cell receptors
- Class I MHC molecules
- Class II MHC molecules

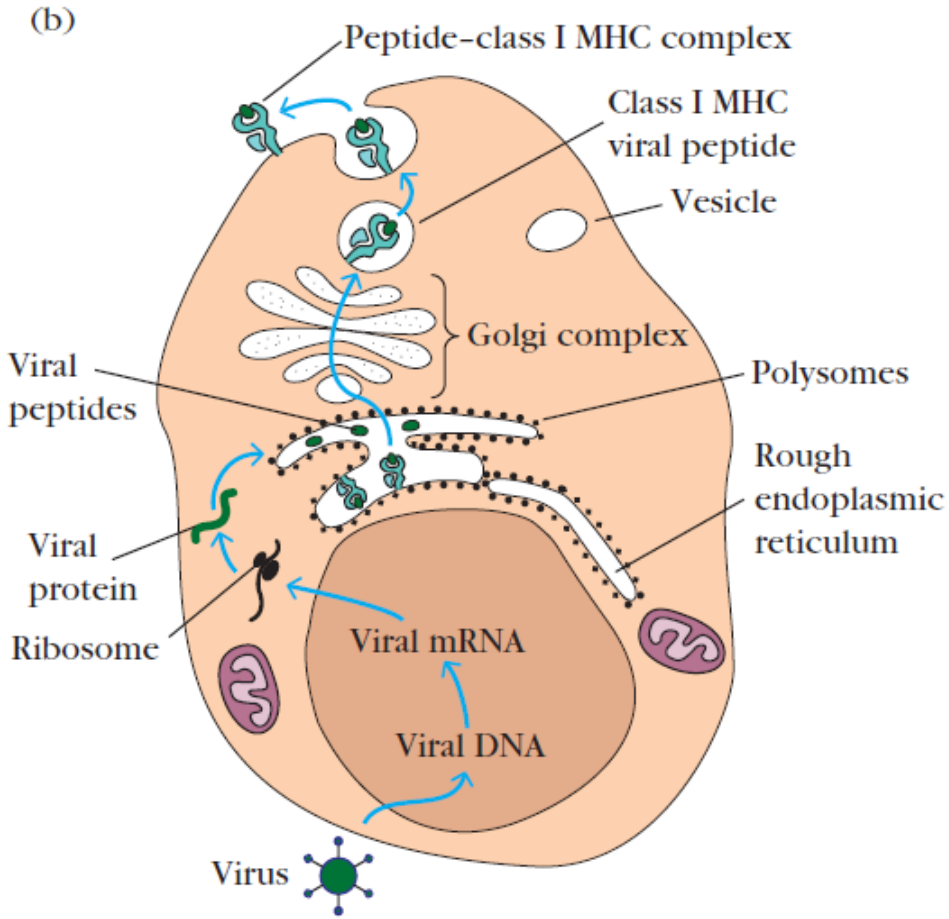
Each of these molecules plays a unique role in antigen recognition, ensuring that the immune system can recognize and respond to the different types of antigen that it encounters.

Processing and presentation of exogenous and endogenous antigens.

Exogenous antigen

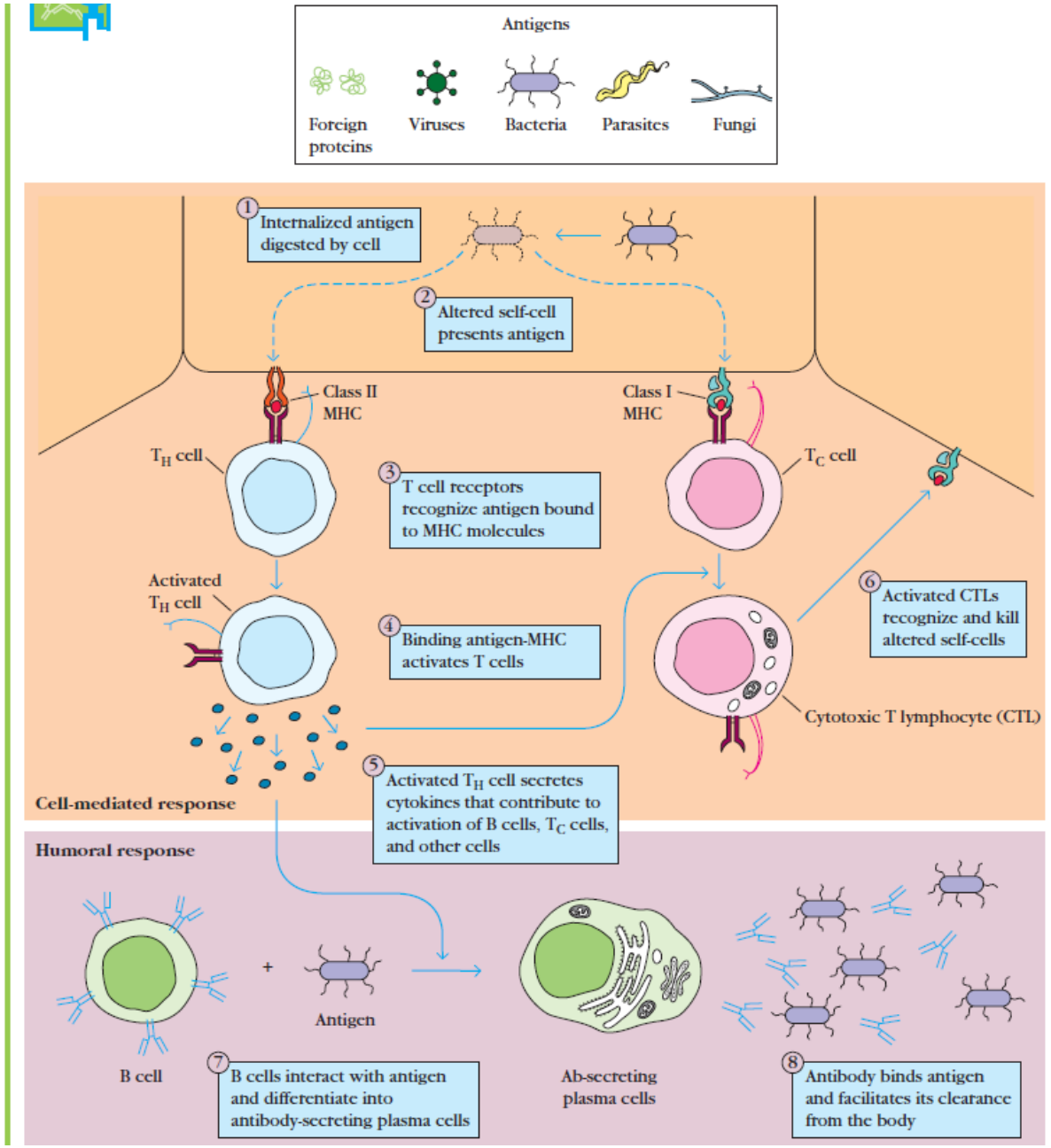


Endogenous antigen



Overview of the humoral and cell-mediated branches of the immune system.

- In the humoral response, B cells interact with antigen and then differentiate into antibody-secreting plasma cells.
- The secreted antibody binds to the antigen and facilitates its clearance from the body.
- In the cell-mediated response, various subpopulations of T cells recognize antigen presented on self-cells.
- TH cells respond to antigen by producing cytokines.
- TC cells respond to antigen by developing into cytotoxic T lymphocytes (CTLs), which mediate killing of altered self-cells (e.g., virus-infected cells).



Differences in the primary and secondary response to injected antigen

- When an animal is injected with an antigen, it produces a primary serum antibody response of low magnitude and short duration, peaking at about 10–17 days.
- A second immunization with the same antigen results in a secondary response that is greater in magnitude, peaks in less time (2–7 days), and lasts longer (months to years) than the primary response.

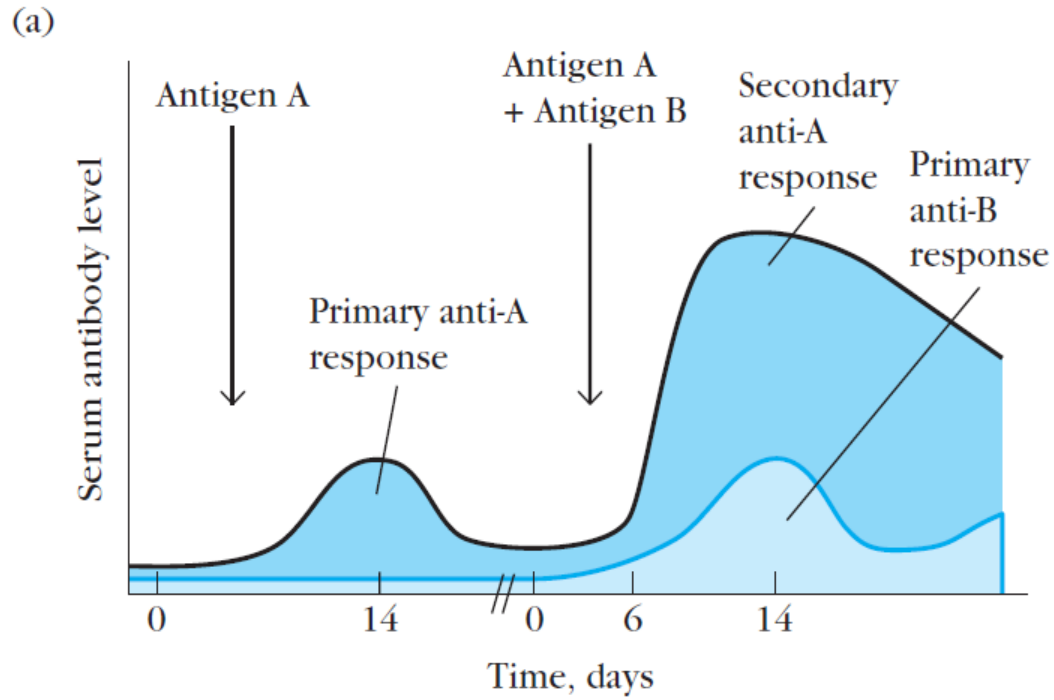


TABLE 1-3 Comparison of adaptive and innate immunity

	Innate	Adaptive
Response time	Hours	Days
Specificity	Limited and fixed	Highly diverse, improves during the course of immune response
Response to repeat infection	Identical to primary response	Much more rapid than primary response

Comparative Immunity

TABLE 1-4 Immunity in multicellular organisms

Taxonomic group	Innate immunity (nonspecific)	Adaptive immunity (specific)	Invasion-induced protective enzymes and enzyme cascades	Phagocytosis	Antimicrobial peptides	Pattern-recognition receptors	Graft rejection	T and B cells	Antibodies
Higher plants	+	–	+	–	+	+	–	–	–
Invertebrate animals									
Porifera (sponges)	+	–	?	+	?	?	+	–	–
Annelids (earthworms)	+	–	?	+	?	?	+	–	–
Arthropods (insects, crustaceans)	+	–	+	+	+	+	?	–	–
Vertebrate animals									
Elasmobranchs (cartilaginous fish; e.g., sharks, rays)	+	+	+	+	equivalent agents	+	+	+	+
Teleost fish and bony fish (e.g., salmon, tuna)	+	+	+	+	probable	+	+	+	+
Amphibians	+	+	+	+	+	+	+	+	+
Reptiles	+	+	+	+	?	+	+	+	+
Birds	+	+	+	+	?	+	+	+	+
Mammals	+	+	+	+	+	+	+	+	+

KEY: + = definitive demonstration; – = failure to demonstrate thus far; ? = presence or absence remains to be established.

Summary

- Immunity is the state of protection against foreign organisms or substances (antigens). Vertebrates have two types of immunity, innate and adaptive.
- Innate immunity is not specific to any one pathogen but rather constitutes a first line of defense, which includes anatomic, physiologic, endocytic and phagocytic, and inflammatory barriers.
- Innate and adaptive immunity operate in cooperative and interdependent ways.
- The activation of innate immune responses produces signals that stimulate and direct subsequent adaptive immune responses.
- Adaptive immune responses exhibit four immunologic attributes:specificity, diversity, memory, and self/nonself recognition.
- The high degree of specificity in adaptive immunity arises from the activities of molecules (antibodies and T-cell receptors) that recognize and bind specific antigens.

- Antibodies recognize and interact directly with antigen. T cell receptors recognize only antigen that is combined with either class I or class II MHC molecules.

- The two major subpopulations of T lymphocytes are the CD4 T helper (TH) cells and CD8 T cytotoxic (TC) cells. TH cells secrete cytokines that regulate immune response upon recognizing antigen combined with class II MHC. TC cells recognize antigen combined with class I MHC and give rise to cytotoxic T cells (CTLs), which display cytotoxic ability.

- Exogenous (extracellular) antigens are internalized and degraded by antigen-presenting cells (macrophages, B cells, and dendritic cells); the resulting antigenic peptides complexed with class II MHC molecules are then displayed on the cell surface.

- Endogenous (intracellular) antigens (e.g., viral and tumor proteins produced in altered self-cells) are degraded in the cytoplasm and then displayed with class I MHC molecules on the cell surface.

- The immune system produces both humoral and cell-mediated responses. The humoral response is best suited for elimination of exogenous antigens; the cell-mediated response, for elimination of endogenous antigens.

- While an adaptive immune system is found only in vertebrates, innate immunity has been demonstrated in organisms as different as insects, earthworms, and higher plants.

- Dysfunctions of the immune system include common maladies such as allergy or asthma. Loss of immune function leaves the host susceptible to infection; in autoimmunity, the immune system attacks host cells or tissues,