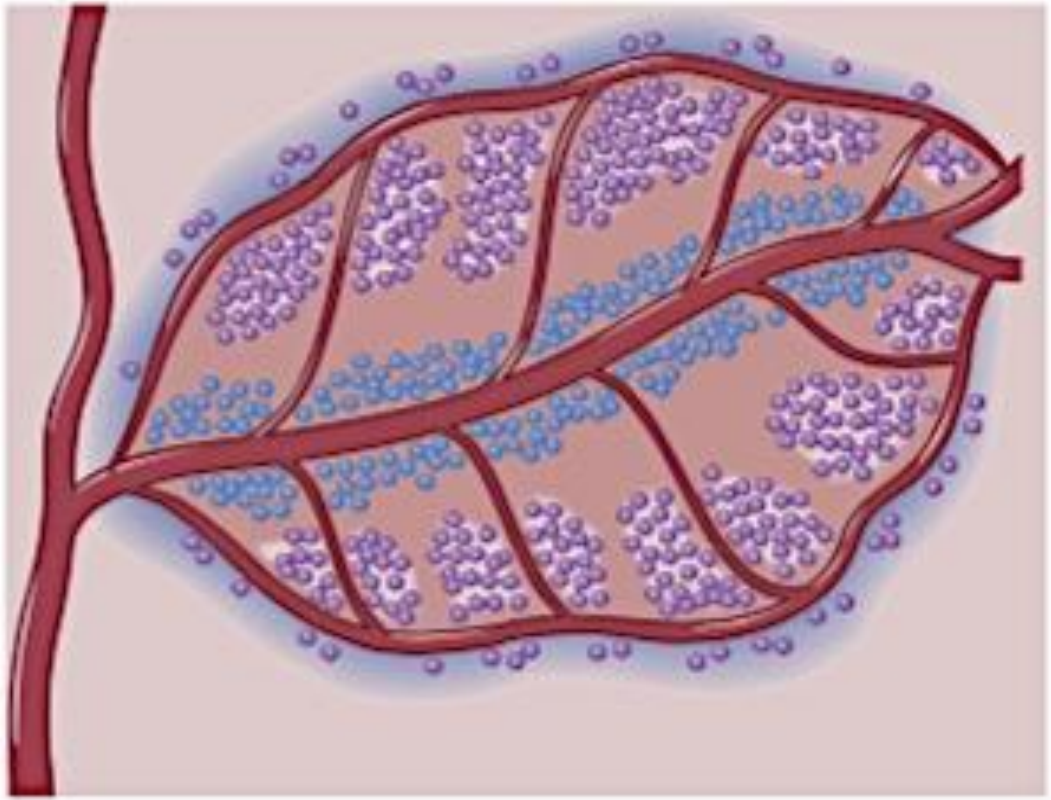
Introduction to the Immune System



Faculty of medicine

Arab American University

Ch.1

Basic immunology 6th ed.

Main lecture points

- **What is immunity and immune response?**
- **What is the importance of the immune system in health and disease?**
- **What types of immune responses that protect individuals from infections?**
- **What are the important characteristics of immunity, and what mechanisms are responsible for these characteristics?**
- **What are the main cells involved in immunity and how each cell can be activated?**

What is immunology?

- **Immune** (Latin- “immunus”)
  - To be free, exempt
  - People survived ravages of epidemic diseases when faced with the same disease again

- **Immunity**: The state of protection from infectious disease and resistance to pathogens, noninfectious substances including harmless environmental molecules, tumors and allergy.

Role of the immune system	Implications
Defense against infections	Deficient immunity results in increased susceptibility to infections; exemplified by AIDS Vaccination boosts immune defenses and protects against infections
Defense against tumors	Potential for immunotherapy of cancer
The immune system can injure cells and induce pathologic inflammation	Immune responses are the cause of allergic, autoimmune, and other inflammatory diseases
The immune system recognizes and responds to tissue grafts and newly introduced proteins	Immune responses are barriers to transplantation and gene therapy

FIGURE 1-1 Importance of the immune system in health and disease. This table summarizes some of the physiologic functions of the immune system and its role in disease. *AIDS*, Acquired immunodeficiency syndrome.

Immunology definitions

- **Antigen (Ag):** any substance (usually foreign) that binds specifically to a component of adaptive immunity.
- **Immunogen:** any substance capable of eliciting an immune response**.**
- **Antibody (Ab):** Secreted immunoglobulin from plasma cell
- **Immunoglobulin (Ig):** an antibody or a heavy or light polypeptide chain that is a part of an antibody molecule.
- **Vaccination:** deliberate induction of protective immunity to a pathogen
- **Immunization:** the ability to resist infection

- **Allergen**: noninfectious antigens that induce hypersensitivity reactions, most commonly IgE-mediated type I reactions.

- **Adaptive Immunity**: host defenses that are mediated by T & B cells following exposure to Ag.

- **Innate immunity**: nonspecific host defenses that exist prior to exposure to Ag.

- **Epitope (antigenic determinant)**: the portion of Ag that is recognized and bound by an Ab or T cell receptor.

- **Pathogen**: a disease causing organism.

Types of Immunity

❑ Innate immunity:

- ❖ **First line of defense for the body(epithelial barrier , mucosa)**
- ❖ **natural immunity or native immunity**
- ❖ **Provides immediate protection against microbial invasion.**
- ❖ **Uses nonspecific cells such as phagocytes and innate lymphoid cells, and several plasma proteins, such as the complement system.**
- ❖ **Required to initiate adaptive immune responses against the infectious agents.**

❑ Adaptive immunity:

- ➢ **Specific immunity or acquired immunity.**
- ➢ **Includes antigen recognition molecules and specific sets of lymphocytes.**
- ➢ **Uses cells and molecules of the innate immune system to eliminate microbes.**

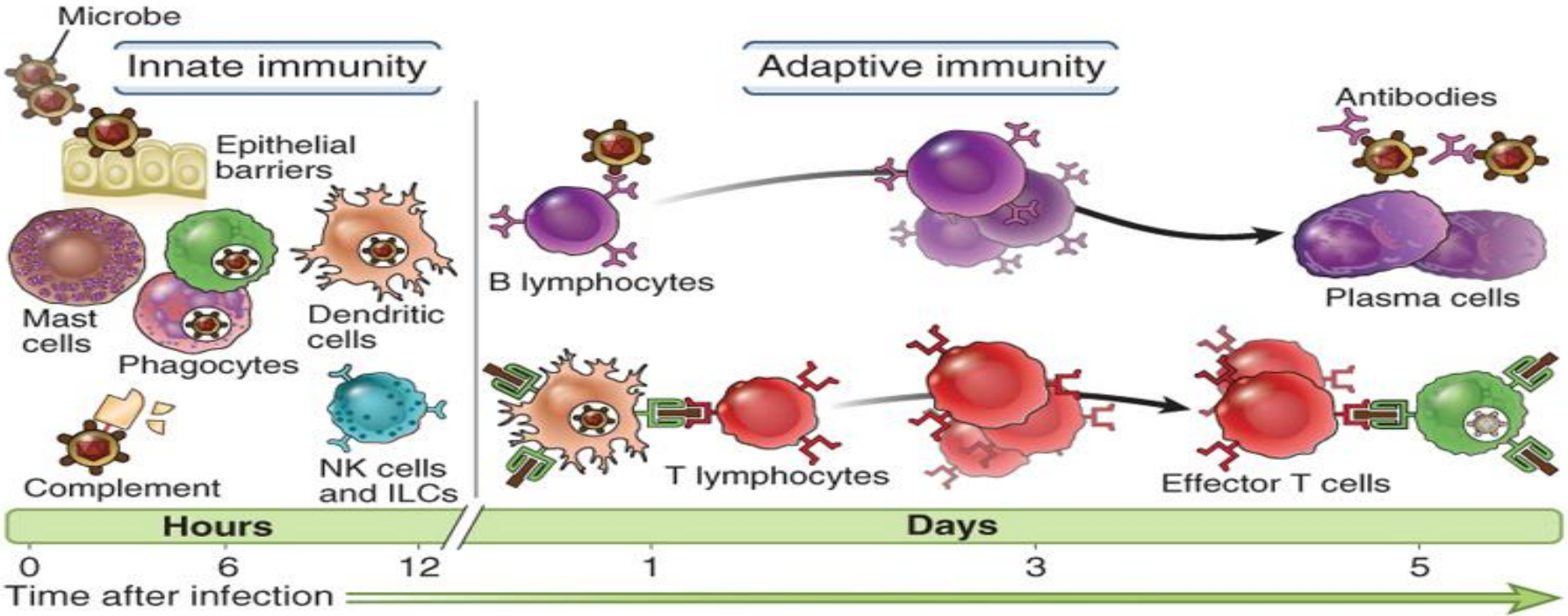


FIGURE 1-3 Principal mechanisms of innate and adaptive immunity. The mechanisms of innate immunity provide the initial defense against infections. Some mechanisms (e.g., epithelial barriers) prevent infections, and other mechanisms (e.g., phagocytes, natural killer [NK] cells and other innate lymphoid cells [ILCs], the complement system) eliminate microbes. Adaptive immune responses develop later and are mediated by lymphocytes and their products. Antibodies block infections and eliminate microbes, and T lymphocytes eradicate intracellular microbes. The kinetics of the innate and adaptive immune responses are approximations and may vary in different infections.

Antigen & Antigen Recognition

❑Antigen:

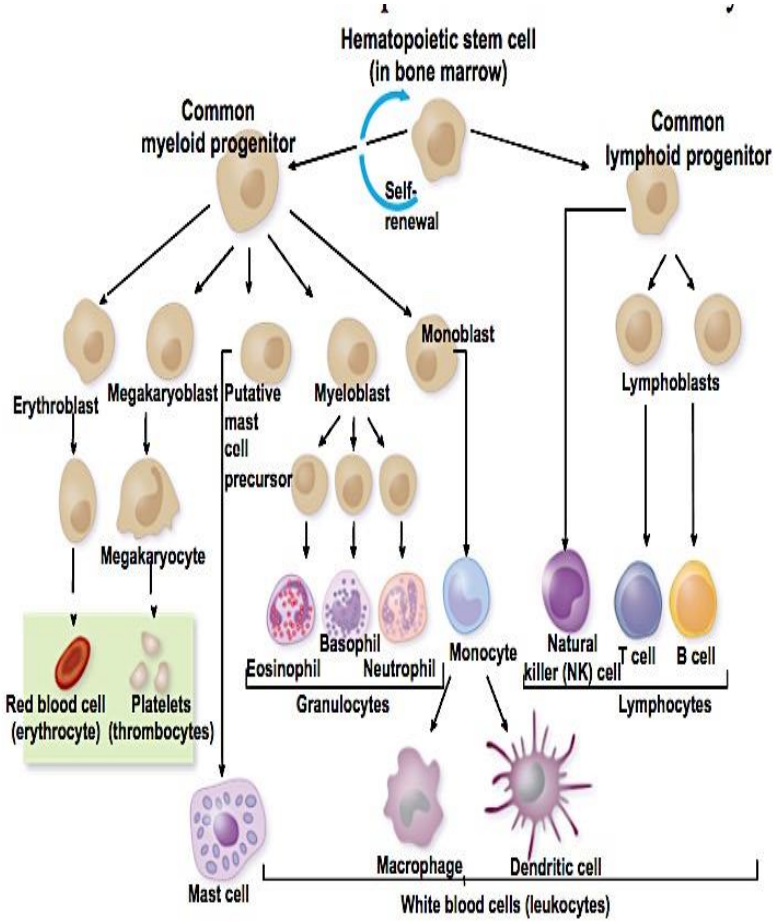
- ❖**Any molecule that is specifically recognized by lymphocytes or antibodies.**

❑Antigen receptors or antigen recognition molecules:

- ❖ **Antibodies (B-cell antigen receptors).**
- ❖**T-cell antigen receptors.**
- ❖**Protein products of a genetic region (major histocompatibility complex (MHC).**

Cells of the immune system

- **Lymphoid cells:**
  - Include B and T cells.
  - Circulate through lymphoid organs and non-lymphoid tissues.
  - They recognize foreign antigens and carry out adaptive immune responses.
- **Myeloid cells:**
  - Tissue-resident **dendritic cells, macrophages, and mast cells** serve as sentinels to detect the presence of microbes in tissues and initiate immune responses.
  - **Macrophages act as** sentinels, destroys microbes, and in tissue repair.



Types of Adaptive Immunity

❑ Humoral immunity

- ❖ **Antibodies enter the circulation, extracellular tissue fluids, lumens of mucosal organs such as the gastrointestinal and respiratory tracts.**
- ❖ B cells and antibodies are able to recognize many different types of molecules, including proteins, carbohydrates, nucleic acids, and lipids.
- ❖ preventing microbs from invading tissue cells
- ❖ neutralizing toxins made by the microbes.
- ➢ **extracellular microbes**; antibodies can enhance the uptake of these microbes into phagocytes

❑ Cell-mediated immunity

- ❖ **Most T cells recognize only peptide fragments of protein antigens presented on cell surfaces.**
- ❖ It is especially import ant to defend against intracellular organisms
- ❖ **Some of t cell Kill any type of host cells (including non-phagocytic cells) that harbor infectious microbes in the cytoplasm or nucleus.**
- ❖ **Defend against extracellular microbes by recruiting large numbers of phagocytes to sites of infection.**

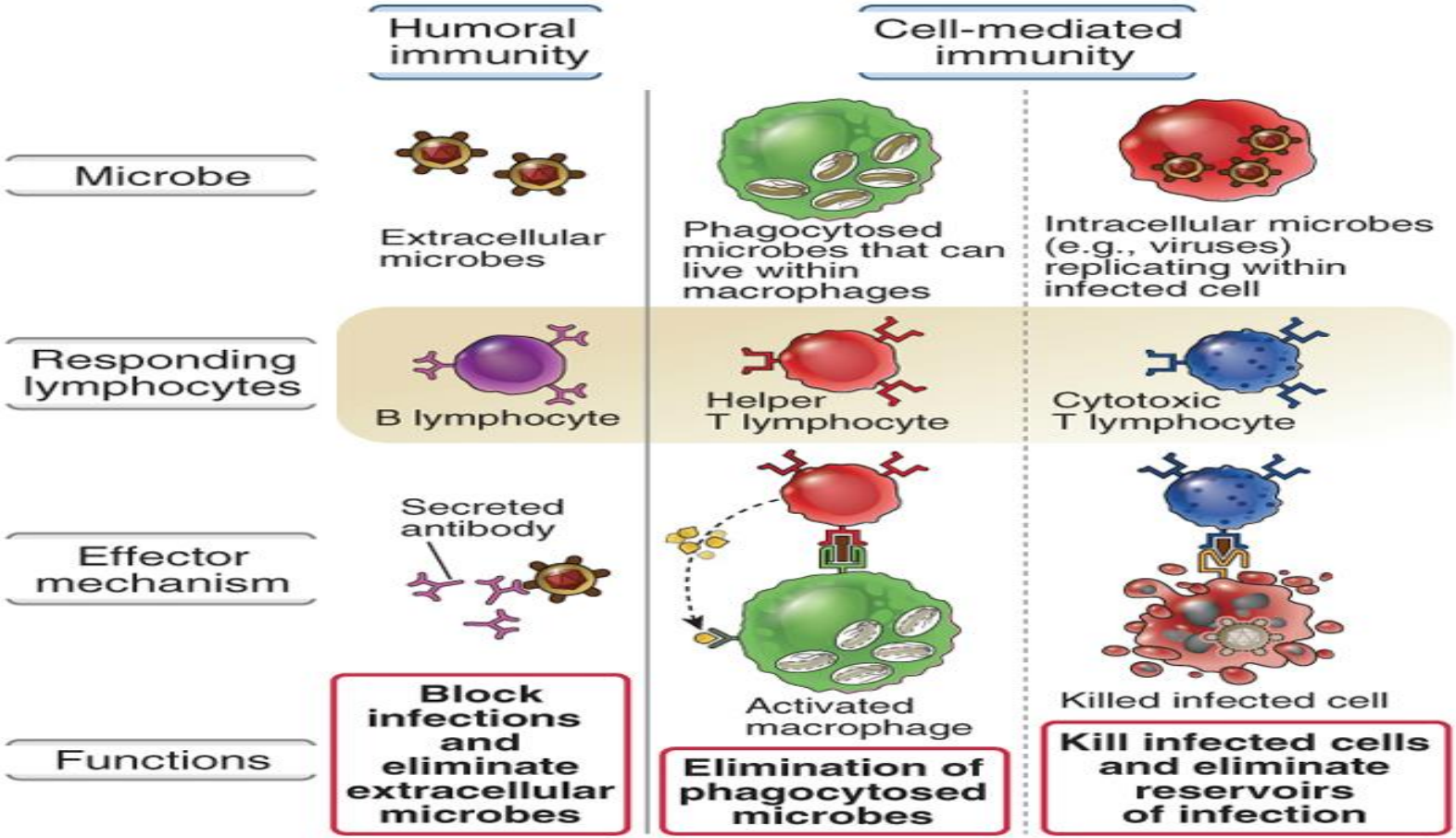


FIGURE 1-4 Types of adaptive immunity. In humoral immunity, B lymphocytes secrete antibodies that eliminate extracellular microbes. In cell-mediated immunity, different types of T lymphocytes recruit and activate phagocytes to destroy ingested microbes and kill infected cells.

Types of Adaptive Immunity

- **Active immunity:**
  - **Formed after exposure to the antigens.**
  - **Natural :following infection.**
  - **Artificial: by vaccination.**
- **Passive immunity:**
  - **Receiving antibodies or cells (e.g., lymphocytes) from another individual already immune to an infection.**
  - **Receiving protective antibodies synthesized using modern bioengineering techniques.**
  - **Natural : from mother across placenta or by breast feeding.**
  - **Artificial : treating some immunodeficiency diseases , snakebites , antibodies and T cells designed to recognize tumors** for passive immunotherapy of cancers..

Properties of Adaptive Immunity

- **Specificity and Diversity:**
- **The specificity capable of distinguishing millions of different antigens or portions of antigens, a feature**
- **T he diversity of the lymphocyte repertoire, which enables the immune system to respond to a vast number and variety of antigens,**
- **Clonal selection hypothesis:**
- **A clone refers to a population of lymphocytes with identical antigen receptors and therefore specificities;**
- **Total population of B and T lymphocytes consists of many different clones.**
- **Clones of lymphocytes specific for different antigens develop before an encounter with these antigens.**
- **Each antigen elicits an immune response by selecting and activating the lymphocytes of a specific clone.**

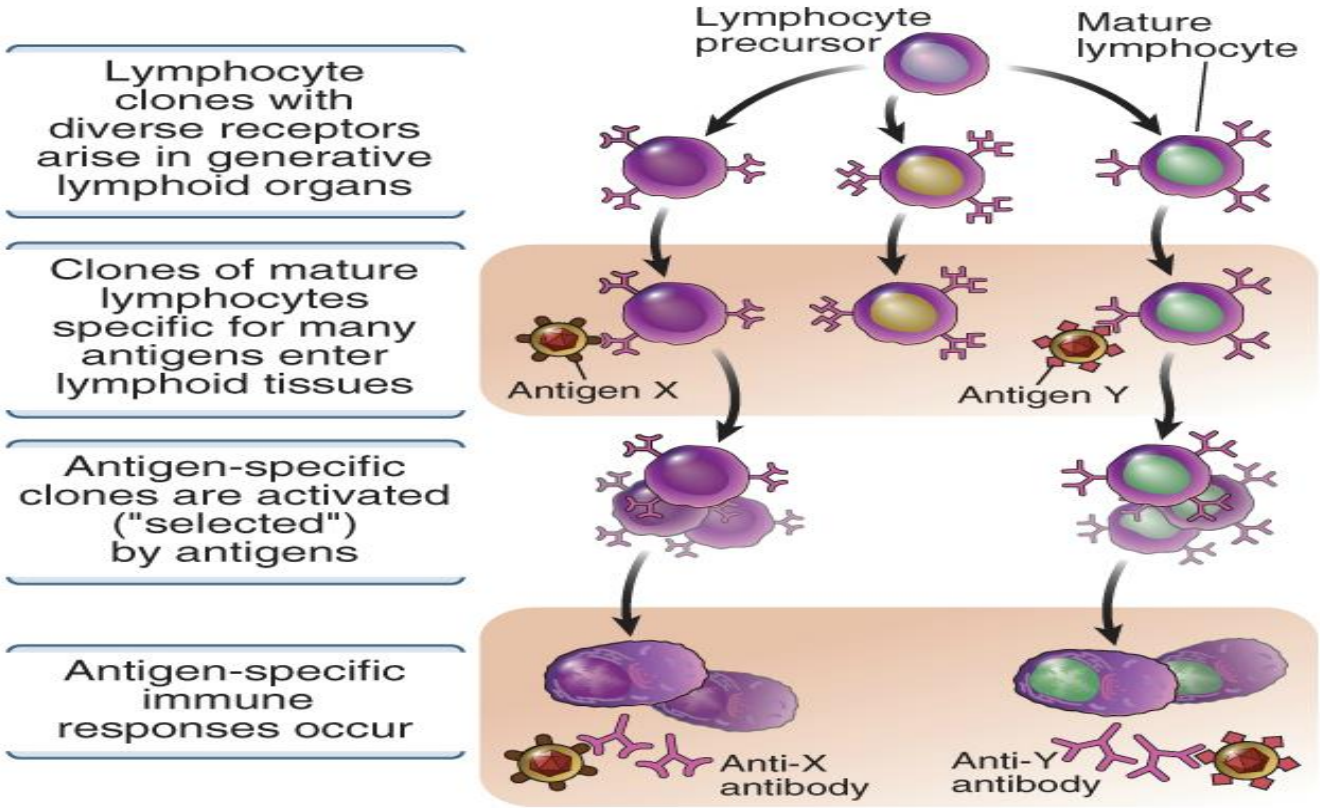
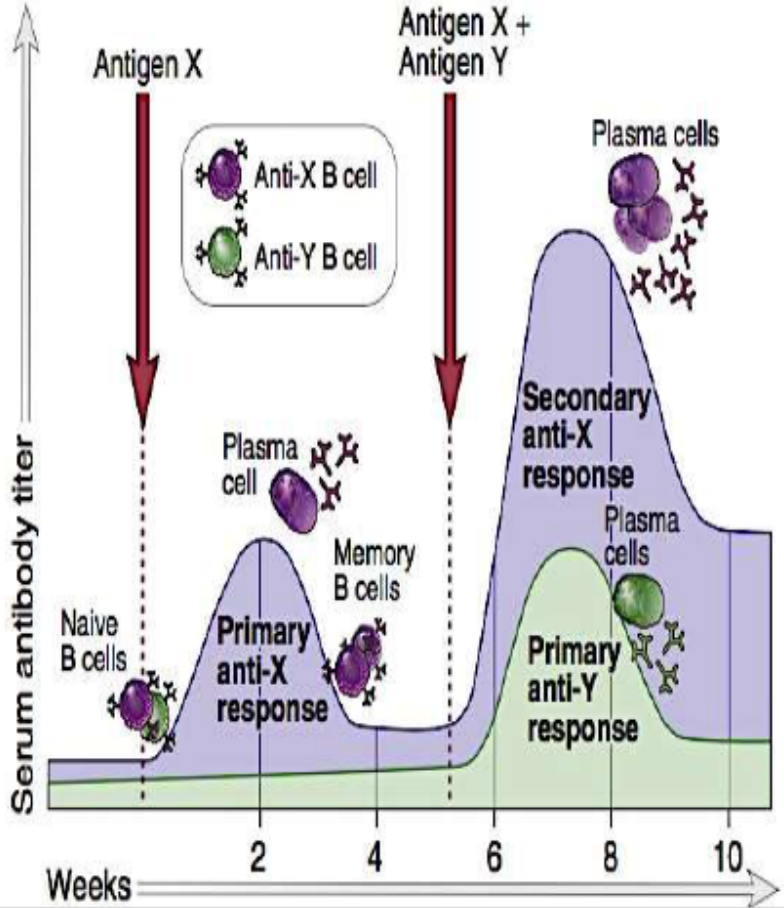


FIGURE 1-6 Clonal selection. Mature lymphocytes with receptors for many antigens develop before encountering these antigens. A clone refers to a population of lymphocytes with identical antigen receptors and therefore specificities; all of these cells are presumably derived from one precursor cell. Each antigen (e.g., X and Y) selects a preexisting clone of specific lymphocytes and stimulates the proliferation and differentiation of that clone. The diagram shows only B lymphocytes giving rise to antibody-secreting cells, but the same principle applies to T lymphocytes. The antigens shown are surface molecules of microbes, but clonal selection also is true for extracellular soluble and intracellular antigens.

Properties of Adaptive Immunity

❑Immunologic memory:

- ➢The immune system remembers every encounter with antigen.
- ➢ Repeated exposure to the same antigen mounts faster, larger and more effective responses.
- ➢Optimizes the ability of the immune system to combat persistent and recurrent infections.
- ➢Depending on memory, vaccines confer long-lasting protection against infections.



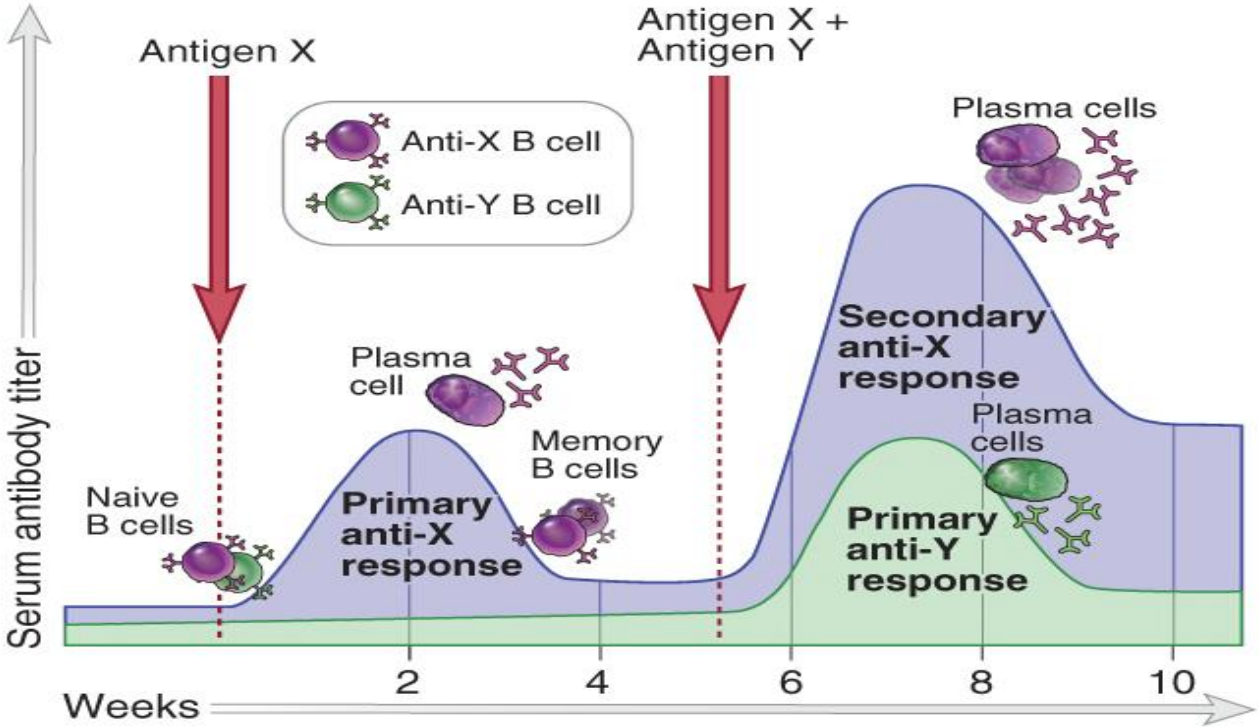


FIGURE 1-7 Primary and secondary immune responses. Antigens X and Y induce the production of different antibodies (a reflection of specificity). The secondary response to antigen X is more rapid and larger than the primary response (illustrating memory) and is different from the primary response to antigen Y (again reflecting specificity). Antibody levels decline with time after each immunization. The level of antibody produced is shown as arbitrary values and varies with the type of antigen exposure. Only B cells are shown, but the same features are seen with T cell responses to antigens. The time after immunization may be 1 to 3 weeks for a primary response and 2 to 7 days for a secondary response, but the kinetics vary, depending on the antigen and the nature of immunization.

Other Features of Adaptive Immunity

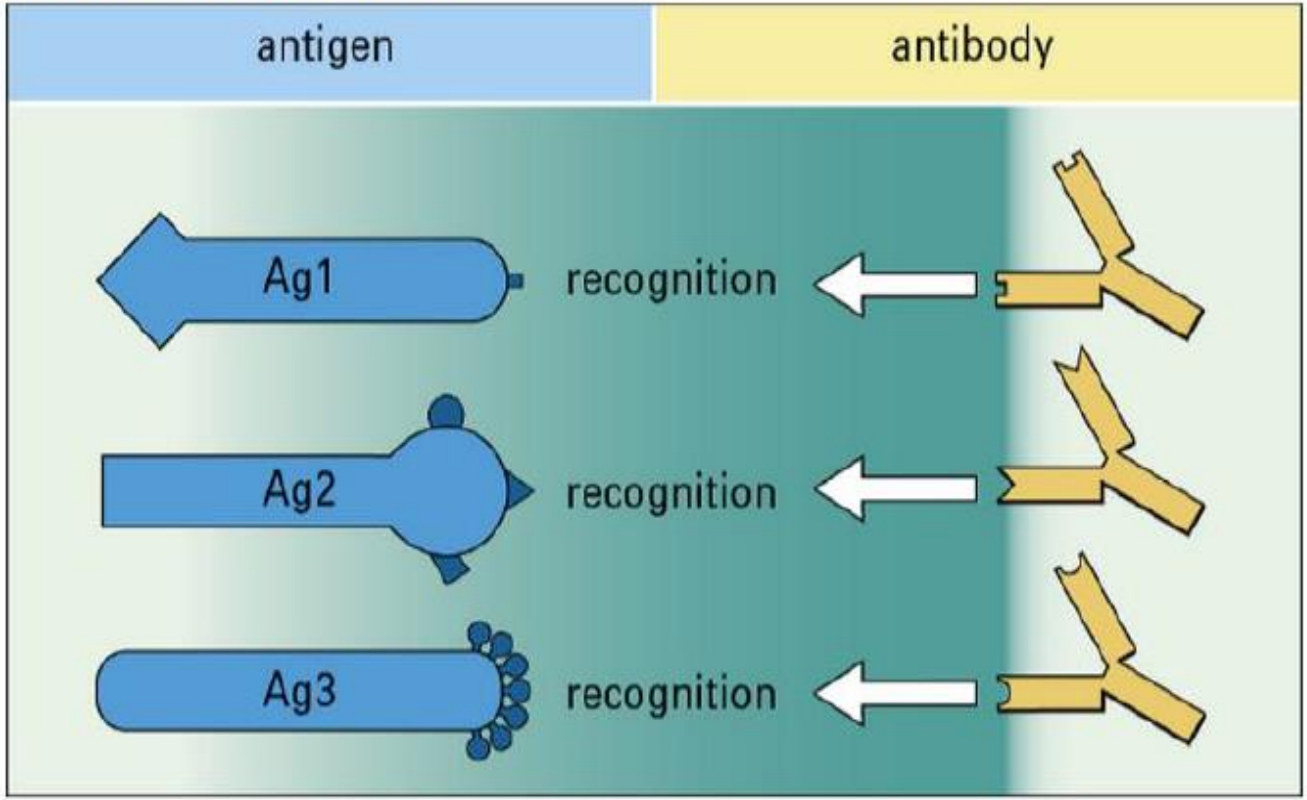
- **Self-limited :**
  - **Declines as the infection is eliminated.**
  - **Allows the system to return to a resting state (homeostasis).**
  - **Prepared the system to respond to another infection.**

- **Immunological tolerance:**
  - **Does not react against self antigens.**

Feature	Functional significance
Specificity	Ensures that distinct antigens elicit specific responses
Diversity	Enables immune system to respond to a large variety of antigens
Memory	Leads to enhanced responses to repeated exposures to the same antigens
Clonal expansion	Increases number of antigen-specific lymphocytes from a small number of naive lymphocytes
Specialization	Generates responses that are optimal for defense against different types of microbes
Contraction and homeostasis	Allows immune system to respond to newly encountered antigens
Nonreactivity to self	Prevents injury to the host during responses to foreign antigens

FIGURE 1-5 Properties of adaptive immune responses. This table summarizes the important properties of adaptive immune responses and how each feature contributes to host defense against microbes.

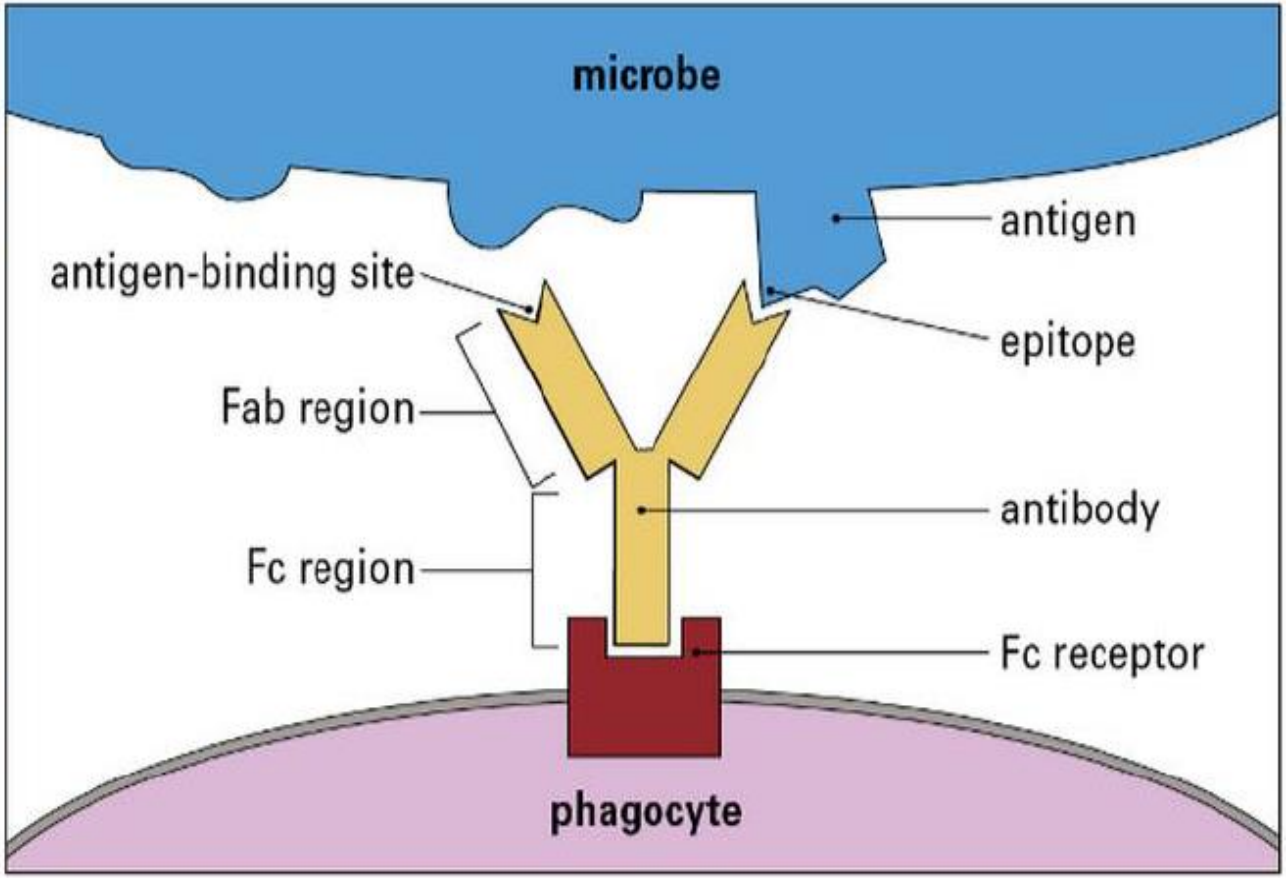
ANTIGEN RECOGNITION



Antibodies recognize molecular shapes (epitopes) on the surface of antigens. Each antigen (Ag1, Ag2, Ag3) may have several epitopes recognized by different antibodies. Some antigens have repeated epitopes (Ag3).

ANTIBODY ACTS AS AN ADAPTER THAT LINKS A MICROBE TO A PHAGOCYTE

The antibody binds to a region of an antigen (an epitope) on the microbe surface, using one of its antigen-binding sites. These sites are in the Fab regions of the antibody. The stem of the antibody, the Fc region, can attach to receptors on the surface of the phagocytes.



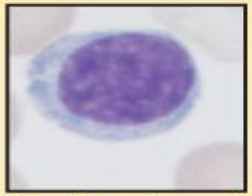
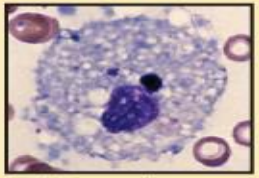
Cell type	Principal function(s)
Lymphocytes: B lymphocytes; T lymphocytes  *Blood lymphocyte*	Specific recognition of antigens • B lymphocytes: mediators of humoral immunity • T lymphocytes: mediators of cell-mediated immunity
Antigen-presenting cells: dendritic cells; macrophages; B cells; follicular dendritic cells  *Dendritic cell*	Capture of antigens for display to lymphocytes: • Dendritic cells: initiation of T cell responses • Macrophages: effector phase of cell-mediated immunity • Follicular dendritic cells: display of antigens to B lymphocytes in humoral immune responses
Effector cells: T lymphocytes; macrophages; granulocytes  *Macrophage*	Elimination of antigens: • T lymphocytes: activation of phagocytes, killing infected cells • Macrophages: phagocytosis and killing of microbes • Granulocytes: killing microbes

FIGURE 1-8 Principal cells of the immune system. The major cell types involved in immune responses and the key functions of these cells. Micrographs illustrate the morphology of some cells of each type.

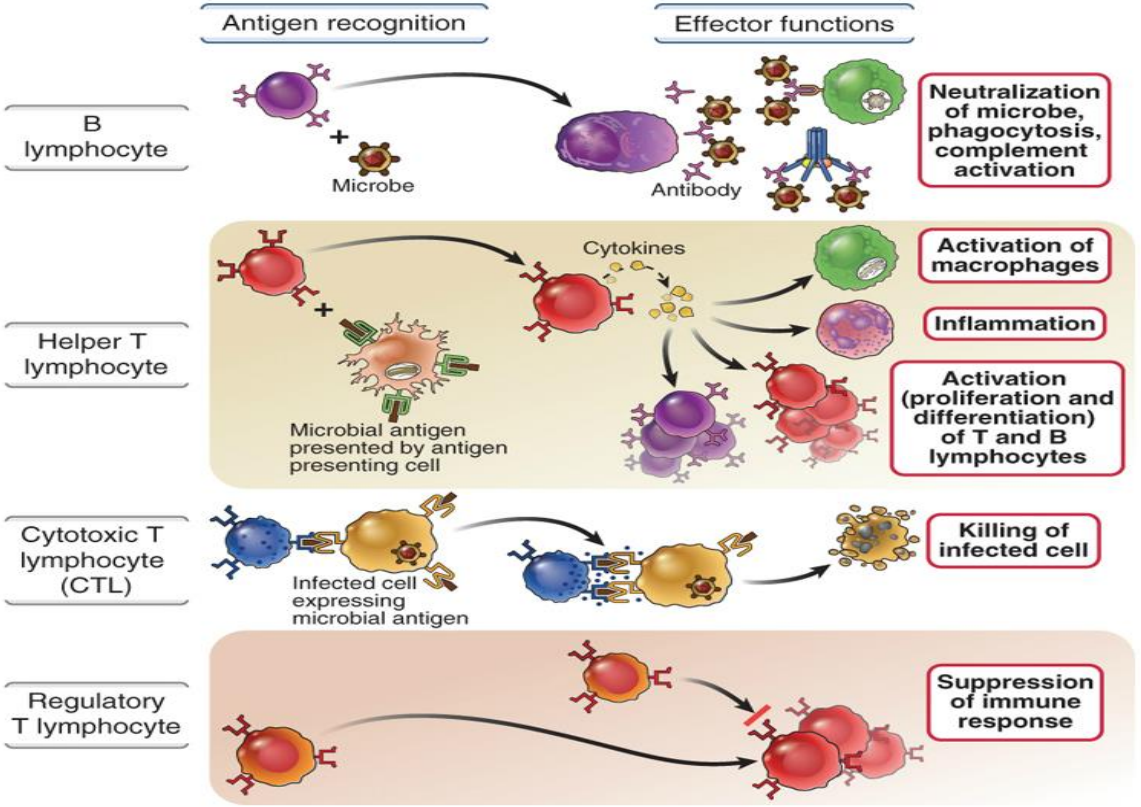


FIGURE 1-9 Classes of lymphocytes. Different classes of lymphocytes in the adaptive immune system recognize distinct types of antigens and differentiate into effector cells whose function is to eliminate the antigens. B lymphocytes recognize soluble or cell surface antigens and differentiate into antibody-secreting cells. Helper T lymphocytes recognize antigens on the surfaces of antigen-presenting cells and secrete cytokines, which stimulate different mechanisms of immunity and inflammation. Cytotoxic T lymphocytes recognize antigens in infected cells and kill these cells. (Note that T lymphocytes recognize peptides that are displayed by MHC molecules, discussed in Chapter 3.) Regulatory T cells limit the activation of other lymphocytes, especially of T cells, and prevent autoimmunity.

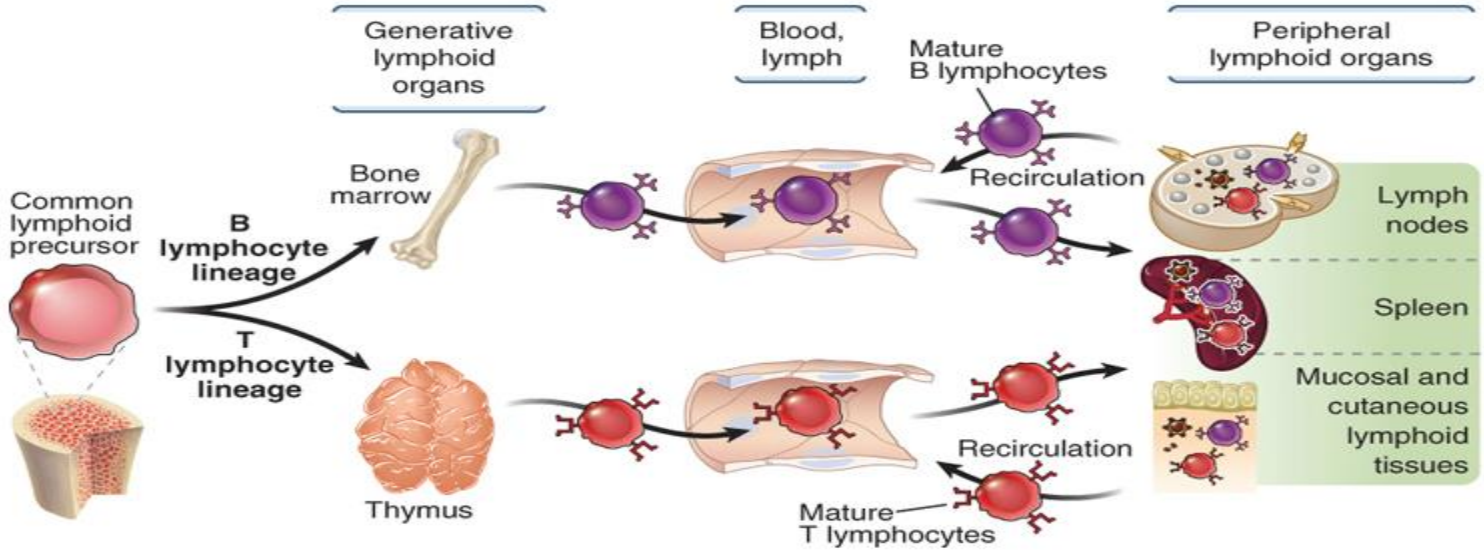


FIGURE 1-10 Maturation of lymphocytes. Lymphocytes develop from precursors in the generative lymphoid organs (bone marrow and thymus). Mature lymphocytes enter the peripheral lymphoid organs, where they respond to foreign antigens and recirculate in the blood and lymph. Some immature B cells leave the bone marrow and complete their maturation in the spleen (not shown).

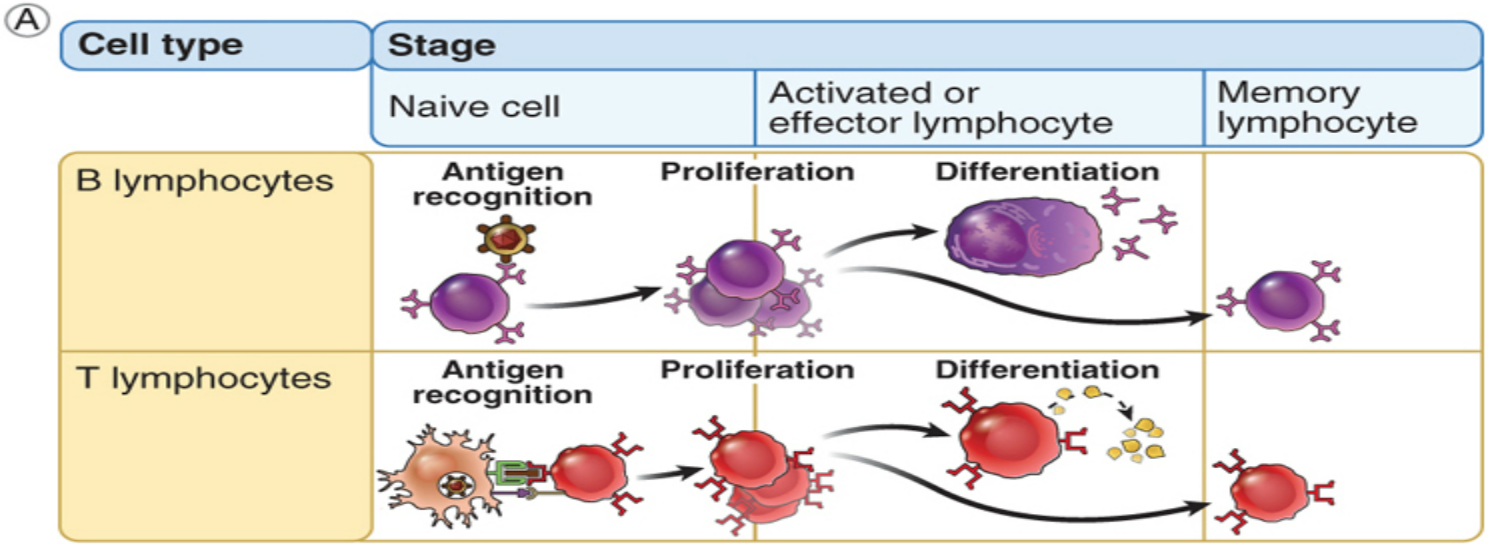


FIGURE 1-11A Stages in the life history of lymphocytes. A, Naive lymphocytes recognize foreign antigens to initiate adaptive immune responses. Naive lymphocytes need signals in addition to antigens to proliferate and differentiate into effector cells; these additional signals are not shown. Effector cells, which develop from naive cells, function to eliminate antigens. The effector cells of the B lymphocyte lineage are antibody-secreting plasma cells (some of which are long-lived). The effector cells of the CD4 T lymphocyte lineage produce cytokines. (The effector cells of the CD8 lineage are CTLs; these are not shown.) Other progeny of the antigen-stimulated lymphocytes differentiate into long-lived memory cells. **B,** The important characteristics of naive, effector, and memory cells in the B and T lymphocyte lineages are summarized. The generation and functions of effector cells, including changes in migration patterns and types of immunoglobulin produced, are described in later chapters.

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	Naive cell	Activated or effector lymphocyte	Memory lymphocyte
T lymphocytes			
Migration	Preferentially to peripheral lymph nodes	Preferentially to inflamed tissues	Heterogenous: one subset to lymph nodes, one subset to mucosa and inflamed tissues
Frequency of cells responsive to particular antigen	Very low	High	Low
Effector functions	None	Cytokine secretion; cytotoxic activity	None
B lymphocytes			
Membrane immunoglobulin (Ig) isotype	IgM and IgD	Frequently IgG, IgA, and IgE	Frequently IgG, IgA, and IgE
Affinity of Ig produced	Relatively low	Increases during immune response	Relatively high
Effector functions	None	Antibody secretion	None

FIGURE 1-11B Stages in the life history of lymphocytes. A, Naive lymphocytes recognize foreign antigens to initiate adaptive immune responses. Naive lymphocytes need signals in addition to antigens to proliferate and differentiate into effector cells; these additional signals are not shown. Effector cells, which develop from naive cells, function to eliminate antigens. The effector cells of the B lymphocyte lineage are antibody-secreting plasma cells (some of which are long-lived). The effector cells of the CD4 T lymphocyte lineage produce cytokines. (The effector cells of the CD8 lineage are CTLs; these are not shown.) Other progeny of the antigen-stimulated lymphocytes differentiate into long-lived memory cells. **B,** The important characteristics of naive, effector, and memory cells in the B and T lymphocyte lineages are summarized. The generation and functions of effector cells, including changes in migration patterns and types of immunoglobulin produced, are described in later chapters.

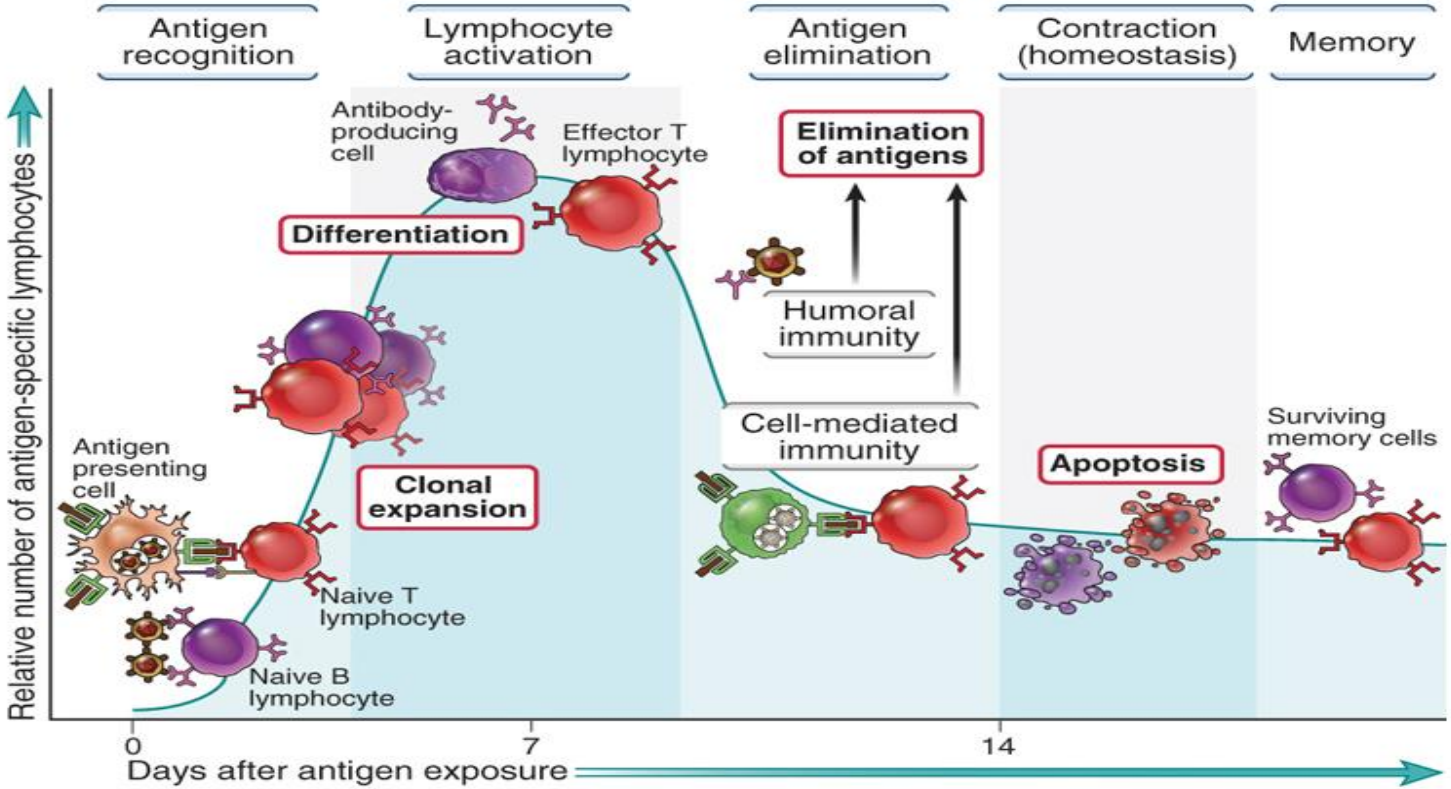


FIGURE 1-19 Phases of adaptive immune response. An adaptive immune response consists of distinct phases; the first three are recognition of antigen, activation of lymphocytes, and elimination of antigen (effector phase). The response declines as antigen-stimulated lymphocytes die by apoptosis, restoring the baseline steady state called homeostasis, and the antigen-specific cells that survive are responsible for memory. The duration of each phase may vary in different immune responses. These principles apply to both humoral immunity (mediated by B lymphocytes) and cell-mediated immunity (mediated by T lymphocytes).

Antigen-Presenting Cells

- **Specialized cells in the epithelium of skin , gastrointestinal, respiratory, and genitourinary tracts.**
- **Capture antigens, transport them to peripheral lymphoid tissues.**
- Present fragments of proteins for recognition by T- lymphocytes.

- **Include:**
- ✓ **Dendritic cells: present antigens and stimulate naïve T-cell to proliferate and differentiate into effector cells .**
- ✓ **Macrophages: present antigens to differentiated effector T-cells.**
- ✓ **B-cells: present antigens to differentiated effector T-cells.**
- **Follicular dendritic cell (FDC): resides in the germinal centers of lymphoid follicles in the peripheral lymphoid organs and displays antigens that stimulate the differentiation of B cells in the follicles.**

Peripheral (secondary) Lymphoid organ and tissues

The peripheral lymphoid organs and tissues

- consist of :
  - lymph nodes,
  - the spleen, and
  - mucosal and cotaneous immune systems

- organized in a way that **promotes** the development of adaptive immune responses.

Lymph nodes

- **Lymph nodes** are encapsulated nodular aggregates of lymphoid tissues located along lymphatic channels throughout the body

- Response to lymph-borne antigens

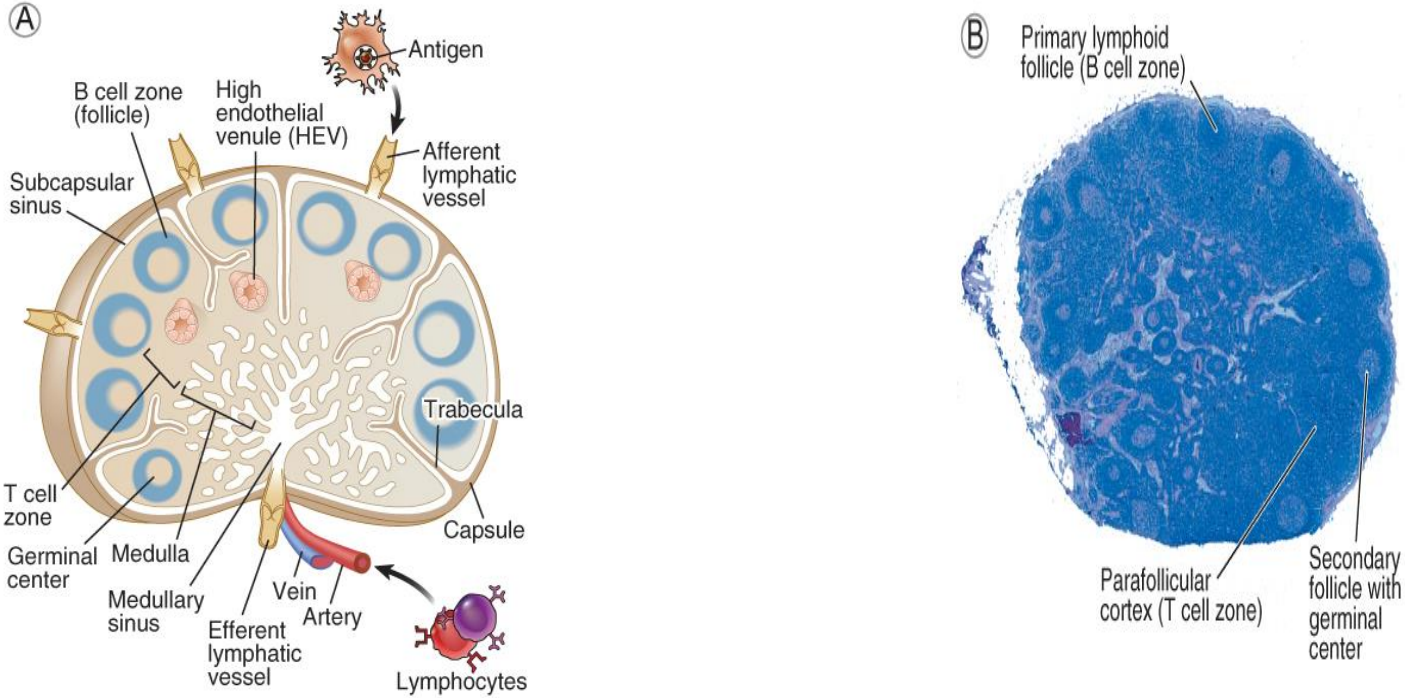
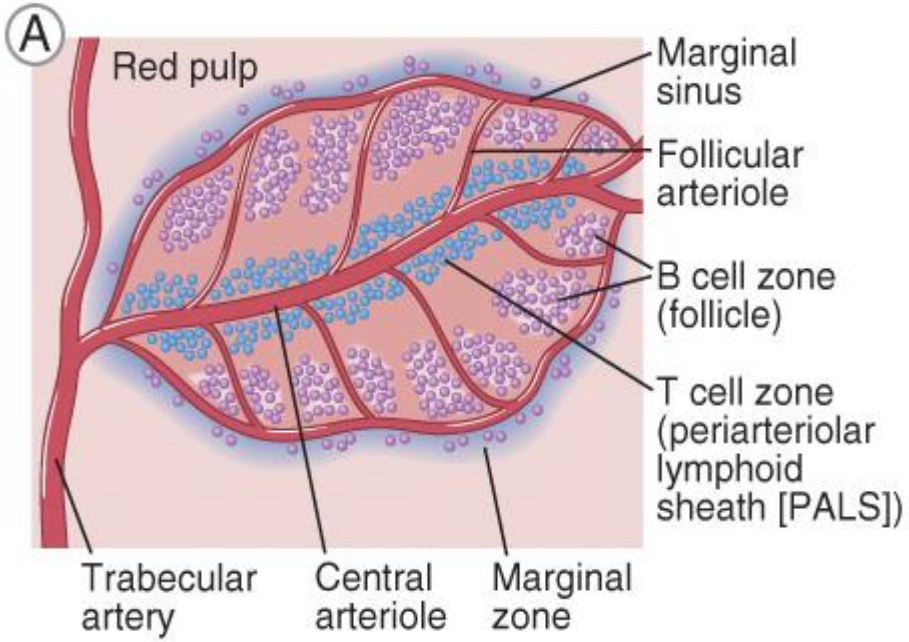


FIGURE 1-14B Morphology of lymph nodes. A, Schematic diagram shows the structural organization of a lymph node. **B,** Light micrograph shows a cross section of a lymph node with numerous follicles in the cortex, some of which contain lightly stained central areas (germinal centers).

Spleen

- ✓ The spleen is a highly vascularized abdominal organ that serves the same role in immune responses to blood-borne antigens.
- ✓ Blood-borne antigens are captured and concentrated by dendritic cells and macrophages in the spleen.
- ✓ The spleen contains abundant phagocytes that line the sinusoids, which ingest and destroy microbes in the blood. These macrophages also ingest and destroy old red blood cells.



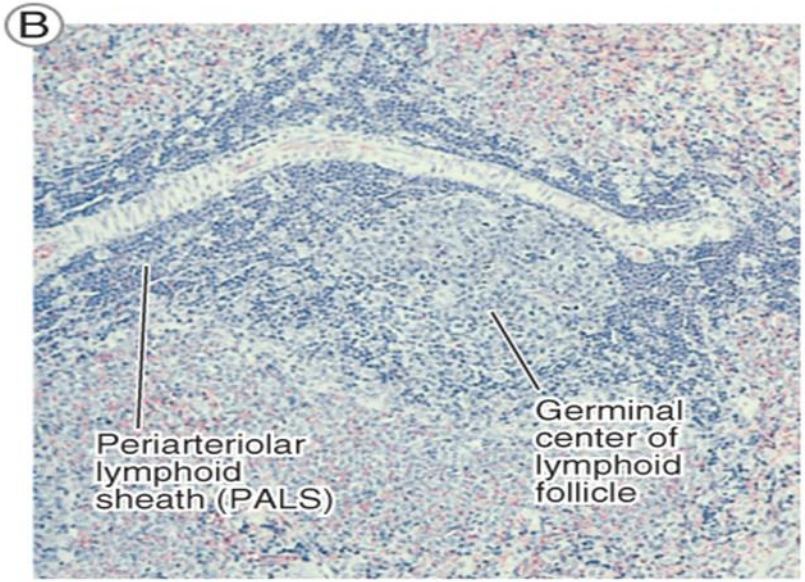


FIGURE 1-15B Morphology of the spleen. A, Schematic diagram shows a splenic arteriole surrounded by the periarteriolar lymphoid sheath (PALS) and attached follicle containing a prominent germinal center. The PALS and lymphoid follicles together constitute the white pulp. **B,** Light micrograph of a section of spleen shows an arteriole with the PALS and a follicle with a germinal center. These are surrounded by the red pulp, which is rich in vascular sinusoids.

cutaneous immune system and mucosal immune system:

- specialized collections of lymphoid tissues and APCs located in and under the epithelia of the skin and the gastrointestinal and respiratory tracts, respectively.

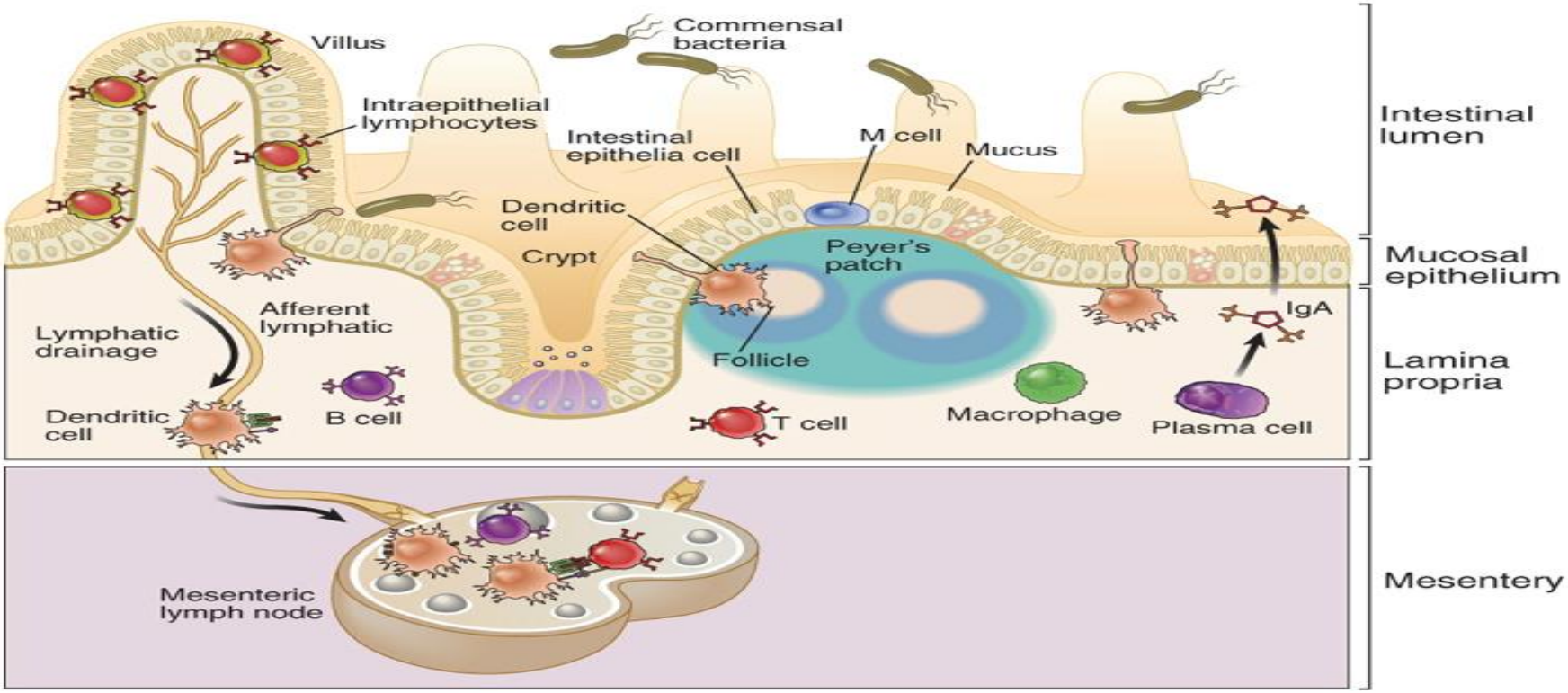


FIGURE 1-16 Mucosal immune system. Schematic diagram of the mucosal immune system uses the small bowel as an example. Many commensal bacteria are present in the lumen. The mucus-secreting epithelium provides an innate barrier to microbial invasion (discussed in Chapter 2). Specialized epithelial cells, such as M cells, promote the transport of antigens from the lumen into underlying tissues. Cells in the lamina propria, including dendritic cells, T lymphocytes, and macrophages, provide innate and adaptive immune defense against invading microbes; some of these cells are organized into specialized structures, such as Peyer's patches in the small intestine. Immunoglobulin A (IgA) is a type of antibody abundantly produced in mucosal tissues that is transported into the lumen, where it binds and neutralizes microbes.

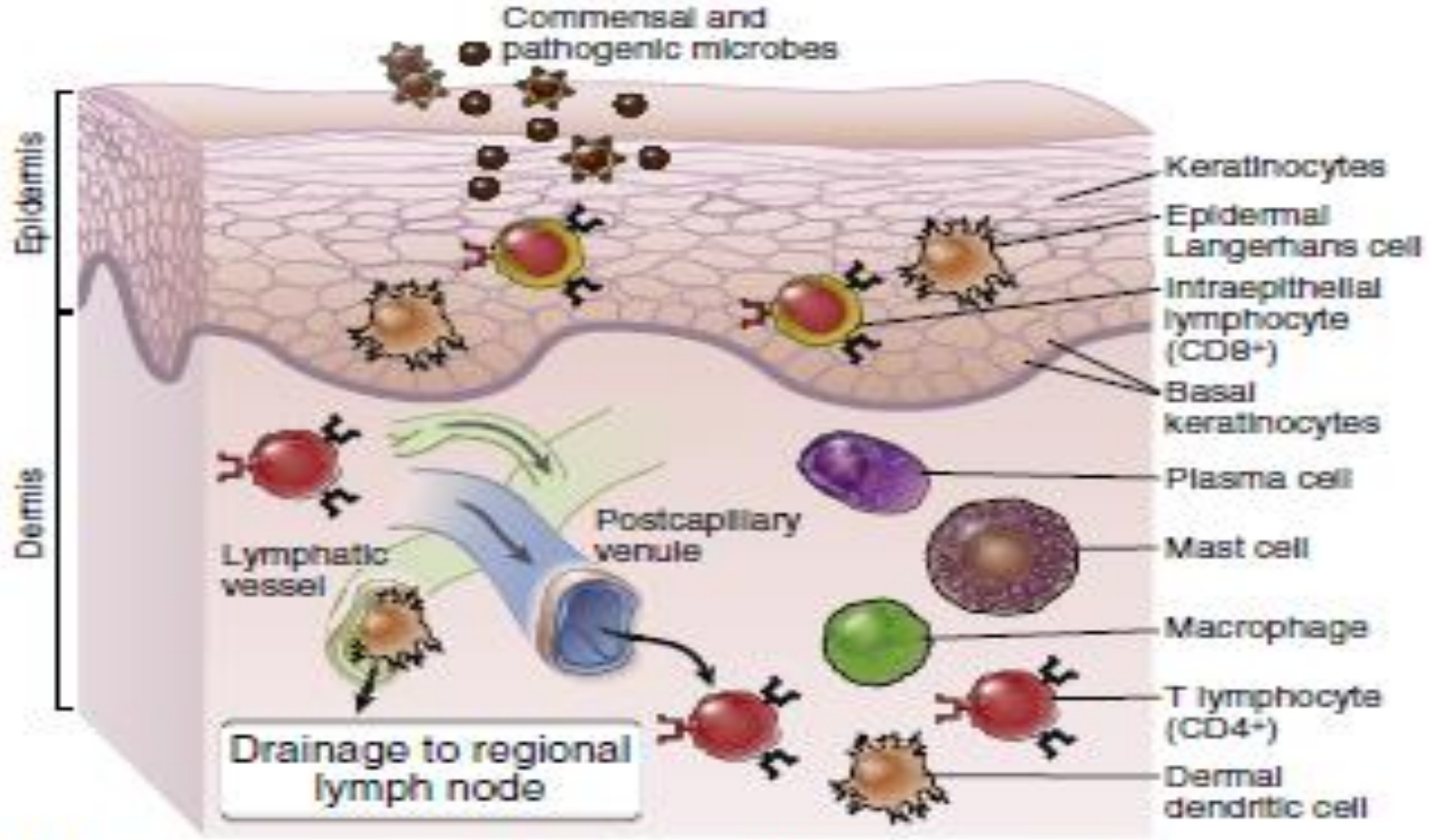


Fig. 1.17 Cutaneous immune system. The major components of the cutaneous immune system shown in this schematic diagram include keratinocytes, Langerhans cells, and intraepithelial lymphocytes, all located in the epidermis, and T lymphocytes, dendritic cells, and macrophages, located in the dermis.

Segregation of T and B lymphocytes in Different Regions of Peripheral Lymphoid Organs

- In **lymph nodes**, the B cells are concentrated in discrete structures, called **follicles**, located around the periphery, or cortex, of each node.
- **germinal center**: central lightly staining region in follicles.
  - Has a role in the production of highly effective antibodies
- The T lymphocytes are concentrated outside but adjacent to the follicles, in the **paracortex**.
- The **follicles** contain the FDCs that are involved in the activation of B cells, and the **paracortex** contains dendritic cells that present antigens to T lymphocytes.
- In the **spleen**, T lymphocytes are concentrated in periarteriolar lymphoid sheaths surrounding small arterioles, and B cells reside in the follicles.

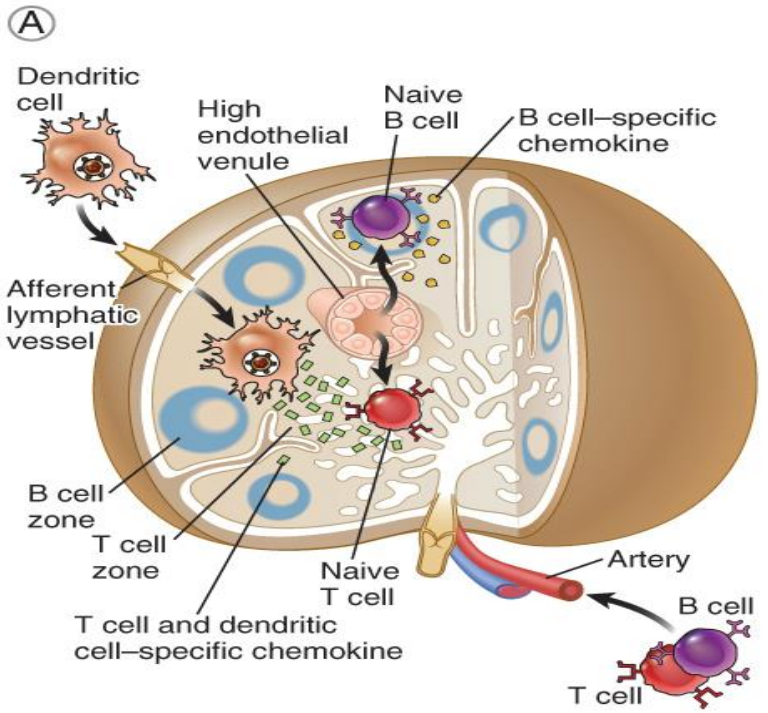


FIGURE 1-17A Segregation of T and B lymphocytes in different regions of peripheral lymphoid organs. A, Schematic diagram illustrates the path by which naive T and B lymphocytes migrate to different areas of a lymph node. Naive B and T lymphocytes enter through a high endothelial venule (HEV), shown in cross section, and are drawn to different areas of the node by chemokines that are produced in these areas and bind selectively to either cell type. Also shown is the migration of dendritic cells, which pick up antigens from epithelia, enter through afferent lymphatic vessels, and migrate to the T cell–rich areas of the node. **B,** In this histologic section of a lymph node, the B lymphocytes, located in the follicles, are stained green, and the T cells, in the parafollicular cortex, are stained red using immunofluorescence. In this technique, a section of the tissue is stained with antibodies specific for T or B cells coupled to fluorochromes that emit different colors when excited at the appropriate wavelengths. The anatomic segregation of T and B cells also occurs in the spleen (not shown).

Courtesy Drs. Kathryn Pape and Jennifer Walter, University of Minnesota Medical School, Minneapolis.

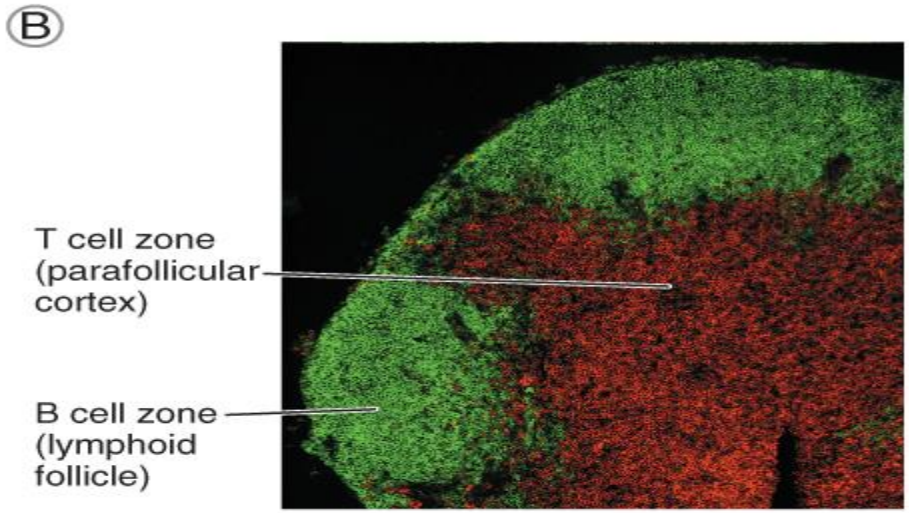


FIGURE 1-17B Segregation of T and B lymphocytes in different regions of peripheral lymphoid organs. A, Schematic diagram illustrates the path by which naive T and B lymphocytes migrate to different areas of a lymph node. Naive B and T lymphocytes enter through a high endothelial venule (HEV), shown in cross section, and are drawn to different areas of the node by chemokines that are produced in these areas and bind selectively to either cell type. Also shown is the migration of dendritic cells, which pick up antigens from epithelia, enter through afferent lymphatic vessels, and migrate to the T cell–rich areas of the node. **B,** In this histologic section of a lymph node, the B lymphocytes, located in the follicles, are stained green, and the T cells, in the parafollicular cortex, are stained red using immunofluorescence. In this technique, a section of the tissue is stained with antibodies specific for T or B cells coupled to fluorochromes that emit different colors when excited at the appropriate wavelengths. The anatomic segregation of T and B cells also occurs in the spleen (not shown).

Courtesy Drs. Kathryn Pape and Jennifer Walter, University of Minnesota Medical School, Minneapolis.

Immune cells Interaction

- Lymphocyte are kept apart from each other until it is useful for them to interact, after exposure to an antigen.
- Antigen activated B cells and T cells migrate toward each other and meet at the edge of follicles.
- Helper T cells interact with and help B cells to differentiate into antibody producing cells.
- Many of effector T cells exit the node through efferent lymphatic vessels and leave the spleen through veins and end up in the circulation where they can go to distant sites of infection.
- Some activated T cells remain in the lymphoid organ and migrate into lymphoid follicles, where they help B cells to make high-affinity antibodies.

Lymphocyte Recirculation and Migration into Tissues

- **High endothelial venules (HEVs) is not present in spleen.**
- Plasma cells do not need to migrate to sites of infection; instead, they secrete antibodies, and the antibodies enter the blood.
- **Antibodies enter the blood bind pathogens or toxins in the blood, or in tissues into which the antibodies enter.**
- Migration of effector lymphocytes to sites of infection is most relevant for T cells because effector T cells have to locate and eliminate microbes at these sites.

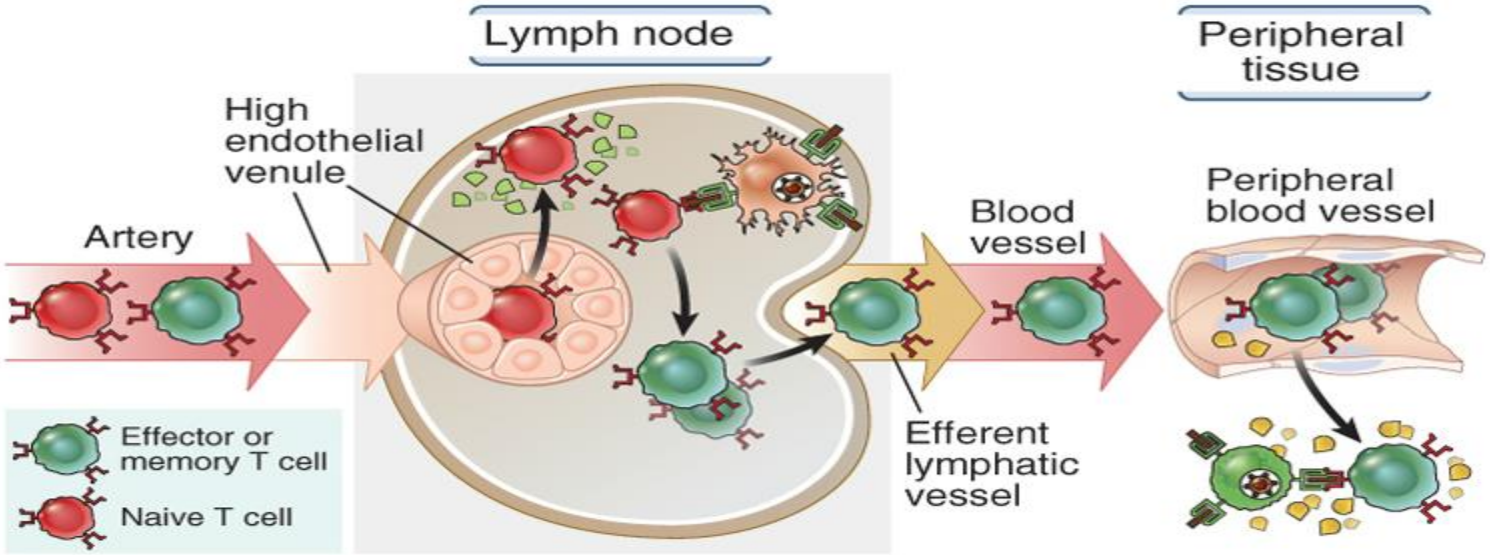
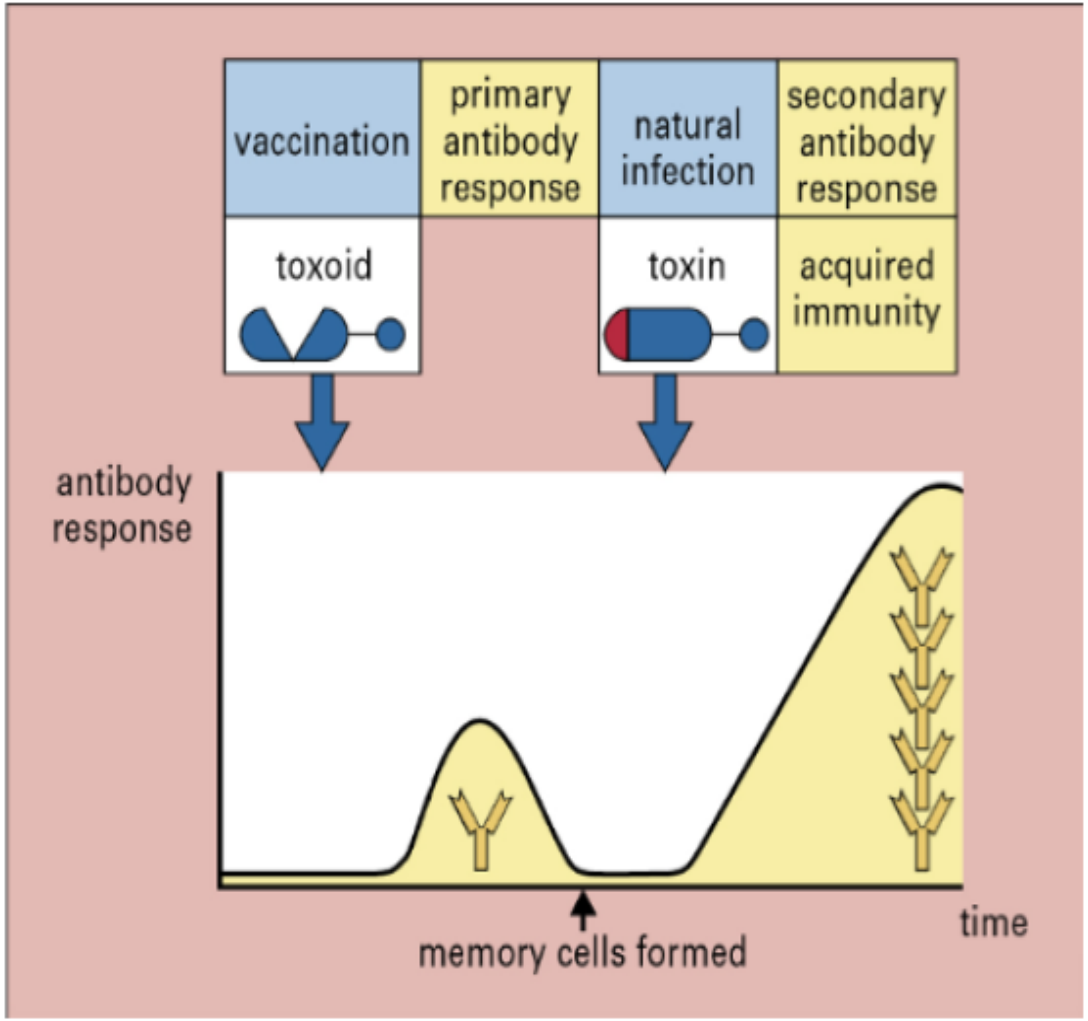


FIGURE 1-18 Migration of T lymphocytes. Naive T lymphocytes migrate from the blood through high endothelial venules into the T cell zones of lymph nodes, where the cells are activated by antigens. Activated T cells exit the nodes, enter the bloodstream, and migrate preferentially to peripheral tissues at sites of infection and inflammation. The adhesion molecules involved in the attachment of T cells to endothelial cells are described in Chapters 5 and 6.

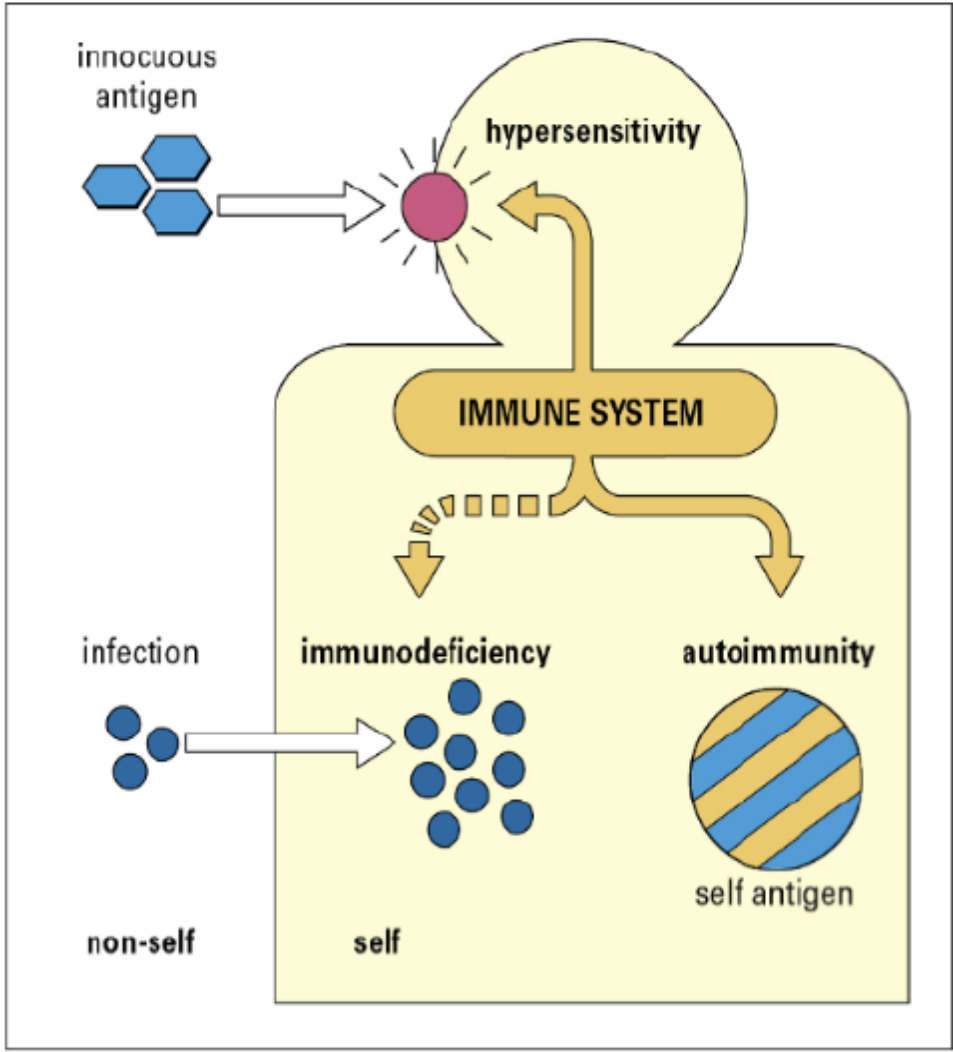
VACCINATION

Chemical modification of tetanus toxin produces a toxoid, which has lost its toxicity but retains many of its epitopes. A primary antibody response to these epitopes is produced following vaccination with the toxoid. If a natural infection occurs, the toxin re-stimulates memory B cells, which produce a faster and more intense secondary response against that epitope, so neutralizing the toxin.



IMMUNOPATHOLOGY

The three principal ways in which the immune system can fail result in hypersensitivity (an overactive immune response to an antigen), immunodeficiency (an ineffective immune response to an infection), and autoimmunity (the immune system reacts against the body's own tissues).



Thank you