I. OVERVIEW

In contrast to the morphologically distinct cells of the innate immune system, lymphocytes of the adaptive immune system generally look alike except for size, ranging from small (4 to 7 µm) to medium (7 to 11 µm) to large (11 to 15 µm). Lymphocytes may be broadly categorized by the antigen-specific receptors they generate through gene rearrangement and by the organs in which they develop. These cells may be likened to the soldiers of the adaptive immune system. Like soldiers, they often display combinations of additional surface molecules that serve essentially as molecular “badges” of rank and function. Also, cells of the adaptive immune response undergo “basic training” in specialized training centers (thymus or bone marrow), “bivouac” in specialized areas (spleen, lymph nodes, and lymphocyte accumulations), may be “promoted” (differentiation), and are transported from one anatomic site to another via the bloodstream or in their own lymphatic circulatory system.

II. LYMPHOCYTES

The immune system must be able to distinguish its own molecules, cells, and organs (self) from those of foreign origin (nonself). The innate immune system does this by expressing germline-encoded pattern recognition receptors (PRRs) on the surfaces of its cells, receptors that recognize structures on potentially invasive organisms (see Chapter 5). The adaptive immune system, on the other hand, utilizes somatically generated epitope-specific T cell and B cell receptors (TCRs and BCRs). These receptors are created anew and randomly within each individual T and B lymphocyte by gene recombination prior to antigen encounter (more about this in Chapter 8). No two individuals, even identical twins, have identical adaptive immune systems. Lymphocytes are usually defined by where they undergo “basic training”: in the thymus (thymus-derived lymphocytes or T cells, and natural killer T or NKT cells) or in the bone marrow (B lymphocytes or B cells). They are also defined by the type of receptors they display on their cell surfaces: TCR (T cells and NKT cells), BCR or immunoglobulins (B cells), or neither (natural killer or NK cells).

A. Thymus-derived cells

T cells are the key players in most adaptive immune responses. They participate directly in immune responses as well as orchestrating and regulating the activities of other cells. T cells arise from hematopoietic stems cells in the bone marrow. Immature T cells called prothymocytes
migrate to the thymus, where, as thymocytes, they develop TCRs and are screened for their ability to distinguish self from nonself. Although most thymocytes fail the screening process and are eliminated, those that pass scrutiny and survive are able to further differentiate and mature to become thymus-derived lymphocytes or T cells and enter the circulation. The developmental pathways for T cells are discussed in greater detail in Chapter 9. Although T cells show a wide diversity in adaptive immune function (see Chapters 8–19), all can be identified by the presence of the CD3 (cluster of differentiation–3) molecule that is associated with the TCR on the T cell surface. Two other CD molecules are also used to identify CD3+ T cell subsets, CD4+ and CD8+, and to readily distinguish their potential immune function.

1. **CD4+ T cells**: These cells account for approximately two thirds of mature CD3+ T cells. CD4 molecules displayed on the surfaces of these T cells recognize a nonpeptide-binding portion of MHC class II molecules (Fig. 7.1). As a result, CD4+ T cells, also known

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**Figure 7.1**

Comprising approximately two thirds of all T lymphocytes, CD4+ T cells are the workhorses of the adaptive immune system. They display T cell receptors (TCRs), associated CD3 signalling complex molecules, and CD4 molecules on their cell surfaces.
as helper T (Th) cells, are “restricted” to the recognition of pMHC class II complexes.

2. **CD8⁺ T cells** account for approximately one third of all mature CD3⁺ T cells. CD8 molecules displayed on the surfaces of these T cells recognize the nonpeptide-binding portion of MHC class I molecules. As a result, CD8⁺ T cells are “restricted” to the recognition of pMHC I complexes (Fig. 7.2). Functionally, CD8⁺ T cells are also known as **cytotoxic T (Tc)** and **suppressor T (Ts) cells**. Tc cells identify body cells that are infected with intracellular organisms, such as viruses and intracellular bacteria, and eliminate the cells harboring these organisms. Ts cells function to downregulate and thus control adaptive immune responses.

**B. Bone marrow-derived cells**

Not all lymphocytes of bone marrow origin are destined for thymic education. Certain cells of lymphoid lineage remain and develop within the bone marrow and are the precursors of immunoglobulin-producing
lymphocytes. These bone marrow–derived lymphocytes, also known as B lymphocytes or B cells, synthesize immunoglobulin and display it on their surfaces, where it functions as their BCR. Plasma cells are derived from differentiated, mature B cells and both synthesize and secrete immunoglobulin.

1. **B cells** arise from pluripotent hematopoietic stem cells in the bone marrow. They do not migrate to the thymus but develop within the bone marrow. B cells arise from two distinct lineages: B-1 and B-2 cells. So named because they are the first to develop embryologically, B-1 cells are a self-renewing population that dominate the plural and peritoneal cavities. In contrast, conventional or B-2 cells arise during and after the neonatal period, are continuously replaced from the bone marrow, and are widely distributed throughout the lymphoid organs and tissues. Each B cell is specific, that is, it produces immunoglobulin of only one antibody specificity that recognizes only one epitope. Like T cells, it is the extreme diversity among B cells, each producing a single form of immunoglobulin, that generates the overall diversity of the immunoglobulin (or antibody) response (Fig. 7.3).

2. **Plasma cells** derive from terminally differentiated B cells and are immunoglobulin-producing and -secreting cells. They cease to

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**Figure 7.3**

Bone-marrow derived lymphocytes or B cells synthesize immunoglobulin molecules that are found both within and displayed on their cell surface. On the surface they function as the B cell epitope-specific receptor (BCR). BCR-associated Igα and Igβ molecules signal the cell when an epitope is bound by the BCR.
use immunoglobulin as a membrane receptor and instead secrete it into the fluids around the cells. Plasma cells, with increased size and metabolic activity, are factories that produce large quantities of immunoglobulin during their short lifespan of less than 30 days. They are characterized by basophilic cytoplasm, a nucleus that has a stellate (starlike) pattern within it, and nonstaining Golgi (Fig. 7.4).

C. Natural killer cells

Approximately 5% to 10% of peripheral blood lymphocytes lack both T cell (CD3) and B cell (surface immunoglobulin) markers. These cells are known as natural killer (NK) cells to reflect their ability to kill certain virally infected cells and tumor cells without prior sensitization (see Chapters 4 and 5). Their granular appearance is due to the presence of cytoplasmic granules that can be released to damage the membranes of the cells they attack. NK cells develop within the bone marrow and lack TCR produced by rearrangement of TCR genes (see Chapter 8). However, they do bear another set of receptors called killer activation receptors (KARs) and killer inhibition receptors (KIRs) that allow them to recognize host cells that might need to be destroyed (Fig. 7.5, left). In addition, a unique subset of T cells, designated NKT because they share some functional characteristics...
with NK cells, develop within the thymus and express a rearranged TCR of extremely limited repertoire (Fig. 7.5, right). Unlike conventional T cells, NKT cells respond to lipids, glycolipids, or hydrophobic peptides presented by a specialized, nonclassical MHC class I molecule, CD1d, and secrete large amounts of cytokines, especially interleukin-4 (IL-4).

III. LYMPHOID TISSUES AND ORGANS

Leukocytes may be found in the body distributed as single cells in the tissues and circulation, as lymphoid accumulations (e.g., Peyer’s patches), or within lymphoid organs (e.g., thymus, spleen, lymph nodes) (Fig. 7.6). Lymphoid organs are classified as primary or secondary. Lymphocytes develop within the primary organs: thymus and bone marrow. The secondary lymphoid organs (e.g., spleen, lymph nodes, lymphoid accumulations) trap and concentrate immunogens and provide sites where large numbers of circulating immune cells can make contact with each another. Specific immune reactions are initiated with the interactions that occur in secondary lymphoid organs.

A. Primary organs

The primary lymphoid organs, the thymus and bone marrow, serve as lymphocyte educational centers. While all lymphocytes originate within the bone marrow, those destined to become T cells are sent at an early age to the thymus for “advanced education” in distinguishing self from nonself. Other lymphocytic lineage cells are “home schooled” and remain within the bone marrow, destined to become B cells. Stromal cells within the thymus and bone marrow closely regulate the development of T and B lymphocytes. Developmental details of B and T cells are described in upcoming chapters.

1. Thymus: The bilobed thymus is the first lymphoid organ to develop. It increases in size during fetal and neonatal life and progressively involutes following puberty. Stem cells of bone marrow origin called prothymocytes that are committed to the T cell lineage migrate via the circulation to the thymic cortex. In this new environment, they are called cortical thymocytes (see Fig. 8.4) and acquire a nascent TCR, as well as CD4 and CD8 surface molecules.

One of the first tests that these so-called double positive (DP, because they express both CD4 and CD8 molecules) thymocytes encounter, called positive selection, is the recognition of MHC class I (by CD8) or MHC class II (by CD4) (Fig. 7.7). Failure to do so appropriately means the demise of the DP thymocyte. Thymocytes that “pass” positive selection cease to express both CD4 and CD8 to become single positive (SP) CD4+ or CD8+ cells. SP thymocytes move into the medulla, where they encounter antigen-presenting cells. At this stage, termed negative selection, those that show strong interaction with MHC or pMHC are fated to die by programmed cell death (apoptosis). Tremendous numbers of thymocytes are processed by the thymus, but fewer than 5% of the thymocytes successfully complete this process. We will revisit

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**Figure 7.6**

Lymphatics, lymphoid organs, and tissues. The lymphatics serve as a drainage system to remove cellular debris and microbes from the body’s tissues to the lymph nodes. Lymphatic trunk vessels join to form the thoracic duct, which returns fluid (lymph) to the cardiovascular circulation.
the processes of positive and negative selection in greater detail in Chapter 9.

2. Bone marrow: Lymphocytic lineage cells fated to become immunoglobulin-producing lymphocytes undergo their early stages of differentiation within the bone marrow. They develop their BCRs by DNA rearrangement, express auxiliary molecules such as Igα and Igβ, and begin to display IgM on their surfaces prior to leaving the bone marrow. As with T cells in the thymus, interactions with stromal cells of the bone marrow serve to carefully regulate the development of B cells. While still within the bone marrow, the randomly generated BCRs of some B cells may recognize and bind molecules in their local environment. By definition, these B cells would be self-reactive. At this early stage of development, the binding of BCRs triggers the cells bearing
them to undergo apoptotic death. This mechanism removes self-reactive cells. The developmental pathways of B cells are discussed in greater detail in Chapter 9.

B. Secondary lymphoid tissues and organs

Cellular interactions are critical for the development of adaptive immune responses. The secondary lymphoid tissues function as filtration devices removing foreign matter, dead cells, and protein aggregates from the circulation. Blood vessels and lymphatic vessels that facilitate movement of lymphocytes, monocytes, and dendritic cells into and out of these organs richly supply secondary lymphoid tissues. Specialized regions of the vasculature, called high endothelial venules, permit the movement of cells between the blood and the tissues or organs through which they are passing. The leukocyte-rich nature of the secondary lymphoid tissues facilitates cellular interaction, providing leukocytes an environment in which they can “compare notes,” exchange regulatory signals, undergo further development, and proliferate before reentering the circulation. The major secondary lymphoid organs are the spleen and lymph nodes. The tonsils and Peyer’s patches also act as secondary lymphoid accumulations.

1. Spleen: The largest lymphoid organ, the spleen clears particulate matter from the blood and concentrates blood-borne antigens and microbes. In addition to B and T lymphocytes and other leukocytes, the spleen contains large numbers of plasma cells secreting immunoglobulins into the circulation. It is histologically divided into the lymphocyte-rich white pulp and erythrocyte-rich red pulp. The white pulp surrounds small arterioles.

2. Lymph nodes: Small round or oval-shaped peripheral or secondary lymphoid organs, lymph nodes are leukocyte accumulations occurring periodically throughout the lymphatic circulatory system (see Fig. 7.6). They function as filters to purify lymph, the fluid and cellular content of the lymphatic circulatory system, and provide sites for mingling of lymphocytes, monocytes, and dendritic cells for initiation of immune responses. Anatomically, a lymph node is divided into the cortex and medulla (Fig. 7.8). The reticulum or framework of the organ is composed of phagocytes and specialized kinds of reticular or dendritic cells. Lymphocytes are distributed mainly in two areas of the cortex (Fig. 7.9). The superficial cortex is closely packed with clusters of lymphocytes forming nodules or follicles. It is sometimes called the thymus-independent area and contains mostly B cells. When an immune response takes place, the follicles develop a central area, with large proliferating cells, termed a germinal center. The deep cortex is the T cell–rich area. Circulating cells enter the outer cortical area through blood or lymphatic vessels and then filter down through the deep cortex and into the medulla before leaving the lymph node and moving on.

3. Mucosa-associated lymphoid tissues: In addition to the spleen and lymph nodes, other sites that facilitate interaction among circulating leukocytes include tonsils in the nasopharynx and Peyer’s patches in the submucosal surfaces of the small intestine (Fig. 7.10). These secondary lymphoid tissues defend the mucosa.
surfaces and are located at potential portals of microbial entry. Peyer’s patches function similarly to lymph nodes and the spleen, with cells entering at the cortical end, promoting the intermingling of antigen-presenting cells, B cells, and T cells and the exit of cells at the medullary end.

C. Lymphatic circulatory system

Leukocytes and their products use two circulatory systems. One, the cardiovascular system, is responsible for the circulation of blood
CD4+ T cells account for approximately two thirds of mature CD3+ T cells. CD4 molecules displayed on the surfaces of these T cells recognize a nonpeptide-binding portion of MHC class II molecules.

CD8+ T cells account for approximately one third of all mature CD3+ T cells. CD8 molecules displayed on the cell surfaces of these T cells recognize the nonpeptide-binding portion of MHC class I molecules.

B cells form two distinct lineages: B-1 and B-2 cells. B-1 cells develop before B-2 cells. Each B cell is specific; that is, it produces immunoglobulin of only one antibody specificity that recognizes only one epitope.

Plasma cells derive from terminally differentiated B cells and are immunoglobulin-producing and secreting cells.

Approximately 5% to 10% of peripheral blood lymphocytes lack T cell (CD3) and B cell (surface immunoglobulin) markers. These cells are known as natural killer (NK) cells to reflect their ability to kill certain tumor cells without prior sensitization.

Lymphoid organs are classified as primary or secondary. Lymphocytes develop within the primary organs: the thymus and bone marrow. The secondary lymphoid organs (e.g., spleen, lymph nodes, lymphoid accumulations) trap and concentrate immunogens and provide sites where large numbers of circulating immune cells can make contact with each another. The largest lymphoid organ, the spleen, clears particulate matter from the blood and concentrates blood-borne antigens and microbes.

In addition to the spleen and lymph nodes, other sites that facilitate interaction among circulating leukocytes include tonsils in the nasopharynx and Peyer’s patches in the submucosal surfaces of the small intestine.

Lymph nodes are located along lymphatic vessels that contain lymph, a watery mixture containing cellular debris and leukocytes. The lymph nodes act as filters to remove cellular debris and microorganisms from the lymph prior to its return to the cardiovascular circulatory system.

Chapter Summary

- CD4+ T cells account for approximately two thirds of mature CD3+ T cells. CD4 molecules displayed on the surfaces of these T cells recognize a nonpeptide-binding portion of MHC class II molecules.
- CD8+ T cells account for approximately one third of all mature CD3+ T cells. CD8 molecules displayed on the cell surfaces of these T cells recognize the nonpeptide-binding portion of MHC class I molecules.
- B cells form two distinct lineages: B-1 and B-2 cells. B-1 cells develop before B-2 cells. Each B cell is specific; that is, it produces immunoglobulin of only one antibody specificity that recognizes only one epitope.
- Plasma cells derive from terminally differentiated B cells and are immunoglobulin-producing and secreting cells.
- Approximately 5% to 10% of peripheral blood lymphocytes lack T cell (CD3) and B cell (surface immunoglobulin) markers. These cells are known as natural killer (NK) cells to reflect their ability to kill certain tumor cells without prior sensitization.
- Lymphoid organs are classified as primary or secondary. Lymphocytes develop within the primary organs: the thymus and bone marrow. The secondary lymphoid organs (e.g., spleen, lymph nodes, lymphoid accumulations) trap and concentrate immunogens and provide sites where large numbers of circulating immune cells can make contact with each another. The largest lymphoid organ, the spleen, clears particulate matter from the blood and concentrates blood-borne antigens and microbes.
- In addition to the spleen and lymph nodes, other sites that facilitate interaction among circulating leukocytes include tonsils in the nasopharynx and Peyer’s patches in the submucosal surfaces of the small intestine.
- Lymph nodes are located along lymphatic vessels that contain lymph, a watery mixture containing cellular debris and leukocytes. The lymph nodes act as filters to remove cellular debris and microorganisms from the lymph prior to its return to the cardiovascular circulatory system.
Study Questions

7.1 T cell receptors, when coexpressed with CD8 molecules, are restricted to recognizing and binding peptide fragments associated with
A. CD3 molecules.
B. CD4 molecules.
C. MHC class I molecules.
D. MHC class II molecules.
E. MHC class III molecules.

The correct answer is C. CD8+ T cells are restricted to the recognition of pMHC I complexes. CD3 molecules are associated with the TCR on the T cell surface and are found on both mature CD4+ and CD8+ T cells. CD4+ T cells are restricted to the recognition of pMHC class II complexes. MHC class III molecules include complement components C4, Bf, and C2 and are not involved in T cell recognition.

7.2 B lymphocytes synthesize and express immunoglobulin
A. containing multiple epitope specificities.
B. in cytoplasmic phagosomes.
C. in membrane complexes also containing CD3.
D. on their cell membrane surface.
E. only after leaving the bone marrow.

The correct answer is D. B cells synthesize and express immunoglobulin on their cell surfaces. Immunoglobulins within an individual B cell contain specificity for one epitope, not several. Cytoplasmic phagosomes are involved in degradation of unwanted materials. Membrane complexes also containing CD3 are T cell receptors (TCR) on the surfaces of T cells. B cells express surface IgM before leaving the bone marrow.

7.3 The primary lymphoid organs are those in which
A. adaptive immune responses are usually initiated.
B. filtration devices remove foreign matter.
C. large numbers of circulating leukocytes make contact with one another.
D. lymphocytes undergo their initial differentiation.
E. pattern recognition receptors bind antigens.

The correct answer is D. Primary lymphoid organs are sites where lymphocytes undergo their initial differentiation. Adaptive immune responses are initiated by mature lymphocytes that have migrated out of primary lymphoid organs. Secondary lymphoid organs contain filtration devices to remove foreign materials. Circulating leukocytes are found within blood and lymph and secondary lymphoid organs but not within primary lymphoid organs. Pattern recognition receptors (PRRs) are expressed by cells of the innate immune system (see Chapter 5).

7.4 The thymus is the site of initial differentiation for
A. B cells.
B. erythrocytes.
C. hematopoietic stem cells.
D. NK cells.
E. T cells.

The correct answer is E. The thymus is the site of initial differentiation of T cells. Erythrocytes develop from erythroid precursors in the bone marrow. Hematopoietic stem cells differentiate along any one of several lineages within the bone marrow. Natural killer (NK) cells develop within the bone marrow and lack rearranged TCR.

7.5 Lymph nodes have two main regions: the
A. cortex and medulla.
B. lymph and cortex.
C. reticulum and cortex.
D. lymph and medulla.
E. reticulum and medulla.

The correct answer is A. Lymph nodes are divided into the cortex and the medulla. Lymph is the watery fluid of the lymphatic circulatory system that contains leukocytes and cellular debris from various organs and tissues. Reticulum refers to the framework of a lymph node that is composed of phagocytes and specialized kinds of reticular or dendritic cells.

7.6 Which of the following molecules is expressed on the surface of mature CD4+ cells?
A. B cell receptor
B. CD1d
C. CD3
D. CD8
E. CD19

The correct answer is C. Mature T cells (both CD4+ and CD8+) express CD3, a molecular complex associated with the TCR. CD4+ cells are T cells with T helper function and do not express B cell receptors. CD1d is a specialized, nonclassical MHC class I molecule on NKT cells. CD8 is a molecule expressed by T cytotoxic and suppressor cells. CD19 is expressed on B cells.
7.7 Positive selection refers to
A. the ability of single positive cells to bind both MHC class I and II.
B. cortical thymocytes’ acquisition of TCR.
C. migration of stem cells to the thymus to become T cells.
D. programmed cell death of single positive T cells.
E. recognition of MHC by CD4+CD8+ thymocytes.

7.8 Which of the following is a primary lymphoid organ?
A. bone marrow
B. lymph node
C. Peyer’s patch
D. spleen
E. tonsil

7.9 The white pulp of the spleen is enriched in
A. erythrocytes carrying hemoglobin.
B. CD4+CD8+ T cells binding to MHC.
C. natural killer cells recognizing targets.
D. plasma cells secreting immunoglobin.
E. precursor cells developing into mature B cells.