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Lec (4)

Biotechnology

Immunology

Cells and Organs

Introduction

In contrast to the morphologically distinct cells of the innate immune system, lymphocytes of the adaptive immune systemgenerally 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 bythe 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 andfunction. Also, cells of the adaptive immune response undergo “basic training” in specialized training centers (thymus or bonemarrow), “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 circulatorysystem.

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 thesurfaces of its cells, receptors that recognize structures on potentially invasive organisms (see Chapter 5). The adaptiveimmune system, on the other hand, utilizes somatically generated epitope-specific T cell and B cell receptors (TCRs andBCRs). These receptors are created anew and randomly within each individual T and B lymphocyte by gene recombinationprior to antigen encounter (more about this in Chapter 8). No two individuals, even identical twins, have identical adaptiveimmune systems. Lymphocytes are usually defined by where they undergo “basic training”: in the thymus (thymus-derivedlymphocytes or T cells, and natural killer T or NKT cells) or in the bone marrow (B lymphocytes or B cells). They are alsodefined by the type of receptors they display on their cell surfaces: TCR (T cells and NKT cells), BCR or immunoglobulins (Bcells), 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 asorchestrating 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 fromnonself. Although most thymocytes fail the screening process and are eliminated, those that pass scrutiny and survive areable to further differentiate and mature to become thymus-derived lymphocytes or T cells and enter the circulation. Thedevelopmental pathways for T cells are discussed in greater detail in Chapter 9. Although T cells show a wide diversity inadaptive immune function (see Chapters 8,9,10,11,12,13,14,15,16,17,18,19), all can be identified by the presence of theCD3 (cluster of differentiation–3) molecule that is associated with the TCR on the T cell surface. Two other CD molecules arealso 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 onthe 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 knownas 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 cytotoxicT (Tc) and suppressor T (Ts) cells. Tc cells identify body cells that are infected with intracellular organisms, such asviruses and intracellular bacteria, and eliminate the cells harboring these organisms. Ts cells function to downregulateand thus control adaptive immune responses.

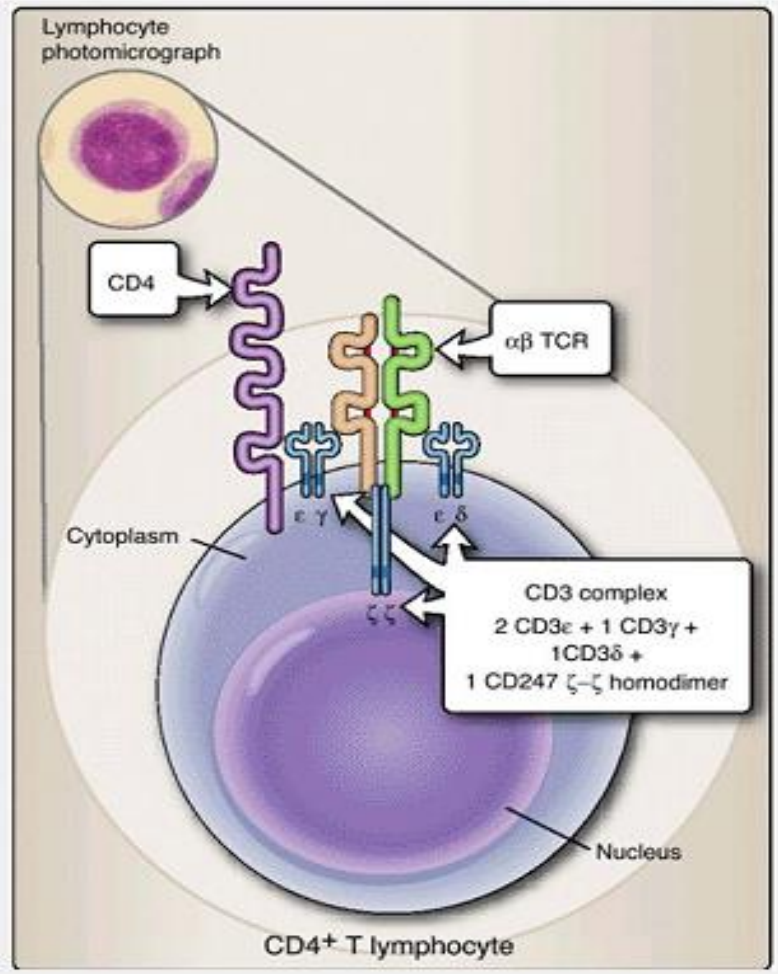

Figure 7.1 Comprising approximately two thirds of all T lymphocytes, CD4+ T cellsare the workhorses of the adaptive immune system. They display T cell receptors(TCRs), associated CD3 signalling complex molecules, and CD4 molecules on theircell surfaces.

B. Bone marrow-derived cells

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

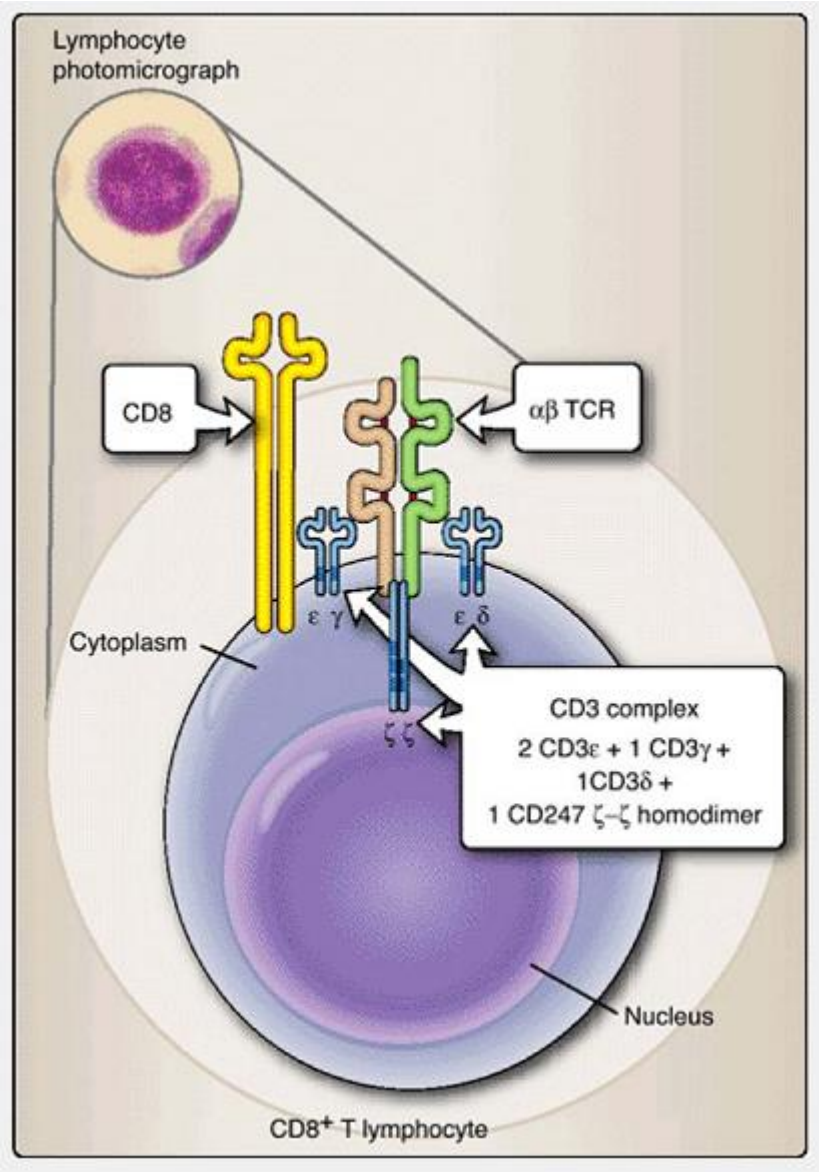

Figure 7.2 Approximately one third of the T cells found in peripheral blood, CD8+ T cellsdisplay T cell receptors (TCRs), associated CD3 molecules, and CD8 dimers on their cellsurfaces.

1. B cells arise from pluripotent hematopoietic stem cells in the bone marrow. They do not migrate to the thymus butdevelop within the bone marrow. B cells arise from two distinct lineages: B-1 and B-2 cells. So named because theyare the first to develop embryologically, B-1 cells are a self-renewing population that dominate the plural and peritonealcavities. In contrast, conventional or B-2 cells arise during and after the neonatal period, are continuously replacedfrom 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 isthe extreme diversity among B cells, each producing a single form of immunoglobulin, that generates the overalldiversity 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. Theycease touse immunoglobulin as a membrane receptor and instead secrete it into the fluids around the cells. Plasma cells, withincreased size and metabolic activity, are factories that produce large quantities of immunoglobulin during their shortlifespan 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).

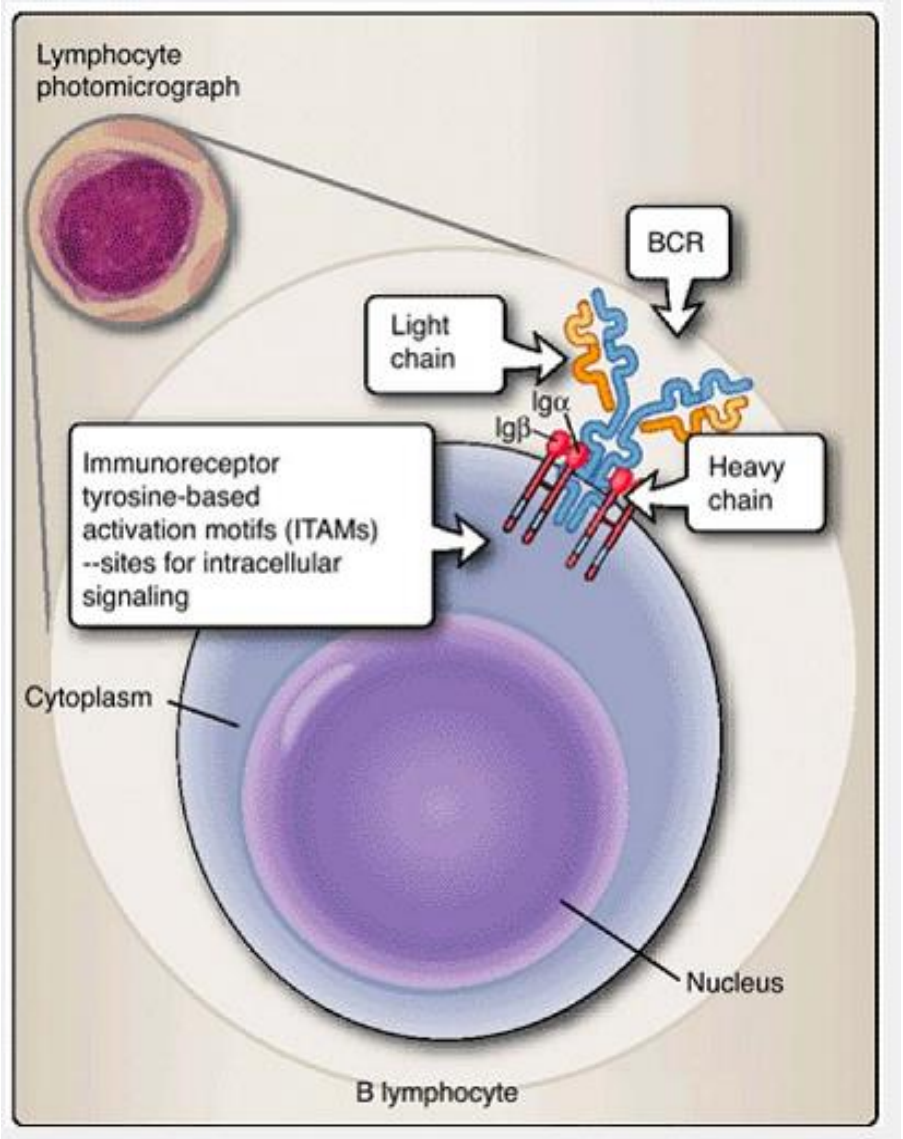

Figure 7.3 Bone-marrow derived lymphocytes or B cells synthesize immunoglobulin molecules that are found both within and displayed on their cell surface. On the surface they function as the B cell epitope-specific receptor (BCR). BCR-associated Igα and Igβ molecules signal the cell when an epitope is bound by the BCR.

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 tumorcells without prior sensitization (see Chapters 4 and 5). Their granular appearance is due to the presence of cytoplasmicgranules that can be released to damage the membranes of the cells they attack. NK cells develop within the bone marrowand lack TCR produced by rearrangement of TCR genes (see Chapter 8). However, they do bear another set of receptorscalled killer activation receptors (KARs) and killer inhibition receptors (KIRs) that allow them to recognize host cells that mightneed to be destroyed (Fig. 7.5, left). In addition, a unique subset of T cells, designated NKT because they share somefunctional characteristicswith NK cells, develop within the thymus and express a rearranged TCR of extremely limited repertoire (Fig. 7.5, right). Unlikeconventional T cells, NKT cells respond to lipids, glycolipids, or hydrophobic peptides presented by a specialized, nonclassicalMHC class I molecule, CD1d, and secrete large amounts of cytokines, especially interleukin-4 (IL-4).

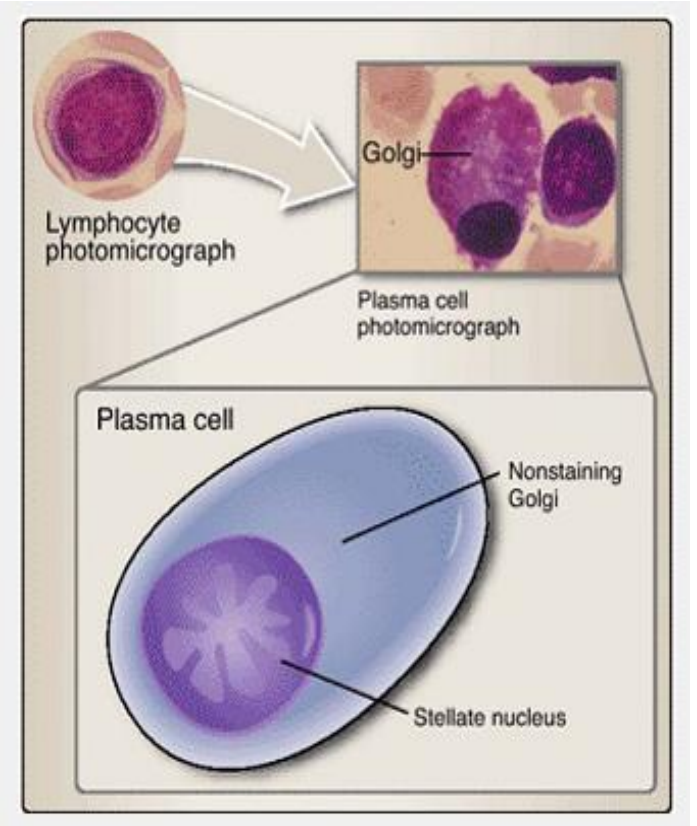

Figure 7.4 Plasma cells are terminally differentiated B cells that both synthesize andsecrete immunoglobulin. Anatomically distinguishable from lymphocytes, their cytoplasmreflects increased ribosomes and endoplasmic reticulum. Immunoglobulin molecules areassembled within their (nonstaining) Golgi prior to export to the fluids surrounding the cell.

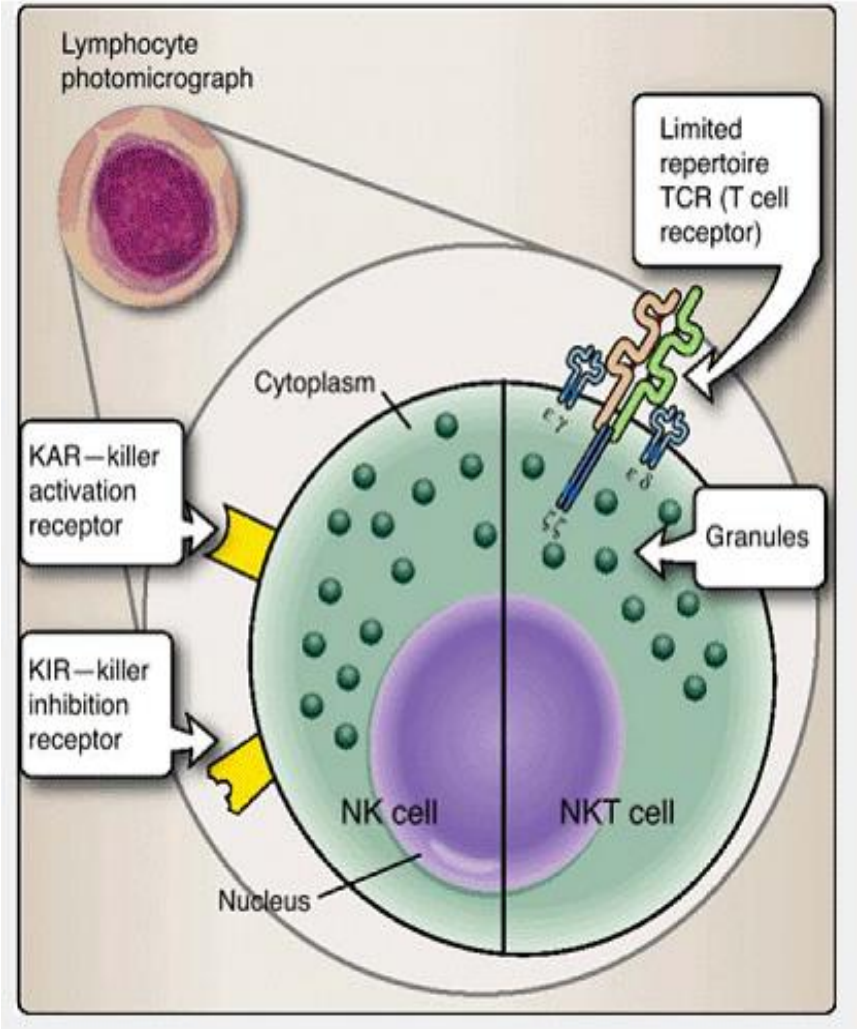

Figure 7.5 Natural killer (NK) and natural killer T (NKT) cells bridge both adaptive andinnate immune systems. NK cells are characteristically large granular lymphocytes thatexpress neither TCRs nor BCRs and bear receptors for stress molecules (killer activationreceptors or KARs) and for MHC class I molecules (killer inhibition receptors or KIRs).
Unlike NK cells, NKT cells express low levels of TCRs with extremely limited repertoires.

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 asprimary or secondary. Lymphocytes develop within the primary organs: thymus and bone marrow. The secondary lymphoidorgans (e.g., spleen, lymph nodes, lymphoid accumulations) trap and concentrate immunogens and provide sites where largenumbers of circulating immune cells can make contact with each another. Specific immune reactions are initiated with theinteractions 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 lymphocytesoriginate within the bone marrow, those destined to become T cells are sent at an early age to the thymus for “advancededucation” in distinguishing self from nonself. Other lymphocytic lineage cells are “home schooled” and remain within the bonemarrow, destined to become B cells. Stromal cells within the thymus and bone marrow closely regulate the development of Tand 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 lifeand progressively involutes following puberty. Stem cells of bone marrow origin called prothymocytes that arecommitted to the T cell lineage migrate via the circulation to the thymic cortex. In this new environment, they are calledcortical 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" positiveselection cease to express both CD4 and CD8 to become single positive (SP) CD4+ or CD8+ cells. SP thymocytesmove into the medulla, where they encounter antigen-presenting cells. At this stage, termed negative selection, thosethat show strong interaction with MHC or pMHC are fated to die by programmed cell death (apoptosis). Tremendousnumbers of thymocytes are processed by the thymus, but fewer than 5% of the thymocytes successfully complete thisprocess. We will revisitthe processes of positive and negative selection in greater detail in Chapter 9.

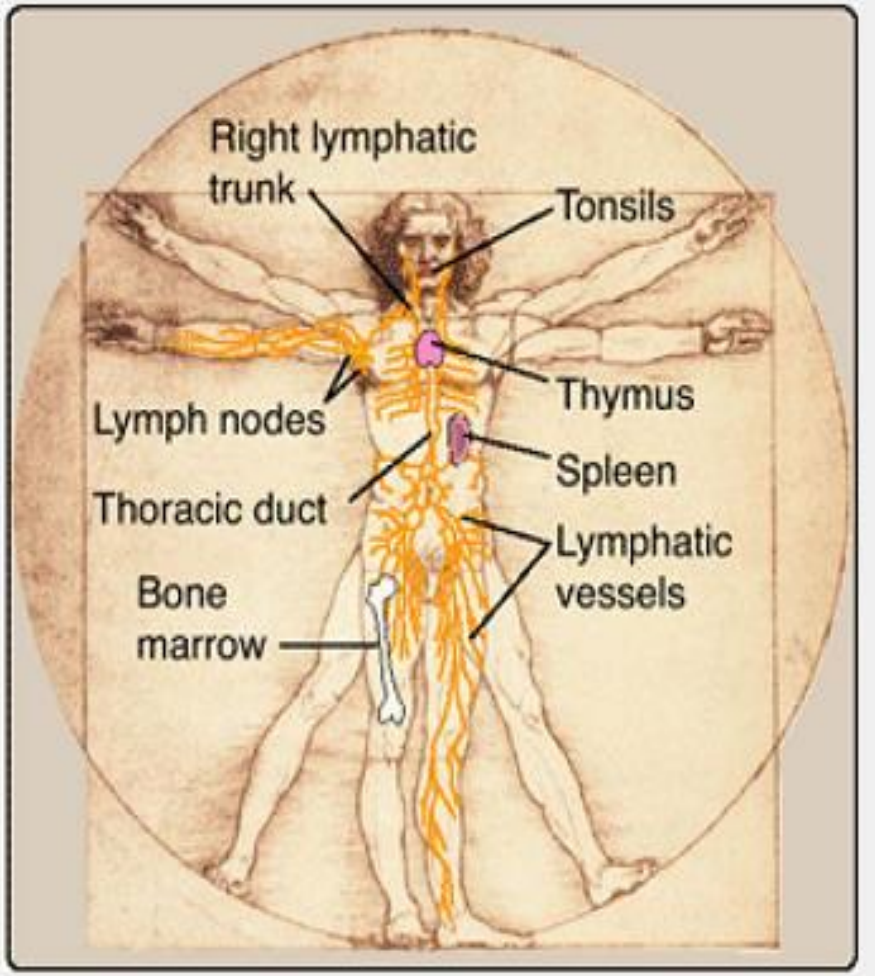

Figure 7.6 Lymphatics, lymphoid organs, and tissues. The lymphatics serve as adrainage system to remove cellular debris and microbes from the body's tissues tothe lymph nodes. Lymphatic trunk vessels join to form the thoracic duct, whichreturns fluid (lymph) to the cardiovascular circulation.

B. Secondary lymphoid tissues and organs

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

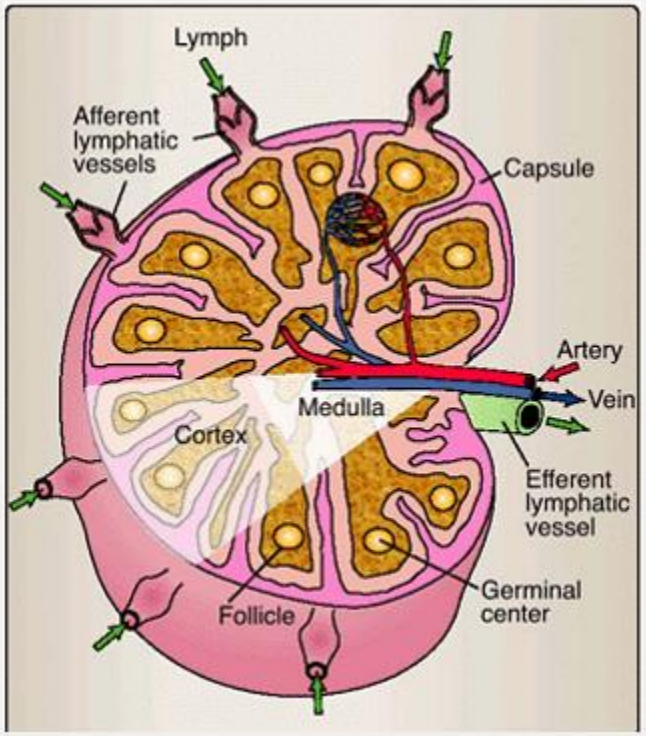

Figure 7.8 Circulation of lymph through a lymph node. Afferent lymphatic vessels enterthe cortical portion of the lymph node. Leukocyte- and debris-rich lymph percolatesthrough the body of the lymph node where it encounters phagocytic cells (macrophagesand dendritic cells) that remove dead and dying cells, cellular debris, and microorganismsfrom the lymph. The "scrubbed" lymph exits the lymph node via an efferent lymphaticvessel. The vessels of the cardiovascular system transport leukocytes to and from thelymph node.

1. Spleen: The largest lymphoid organ, the spleen clears particulate matter from the blood and concentrates blood-borneantigens and microbes. In addition to B and T lymphocytes and other leukocytes, the spleen contains large numbers ofplasma cells secreting immunoglobulins into the circulation. It is histologically divided into the lymphocyte-rich whitepulp 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 leukocyteaccumulations occurring periodically throughout the lymphatic circulatory system (see Fig. 7.6). They function as filtersto purify lymph, the fluid and cellular content of the lymphatic circulatory system, and provide sites for mingling oflymphocytes, monocytes, and dendritic cells for initiation of immune responses. Anatomically, a lymph node is dividedinto the cortex and medulla (Fig. 7.8). The reticulum or framework of the organ is composed of phagocytes andspecialized 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 sometimescalled the thymus-independent area and contains mostly B cells. When an immune response takes place, the folliclesdevelop a central area, with large proliferating cells, termed a germinal center. The deep cortex is the T cell–richarea. Circulating cells enter the outer cortical area through blood or lymphatic vessels and then filter down through thedeep 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 facilitateinteraction among circulating leukocytes include tonsils in the nasopharynx and Peyer's patches in the submucosalsurfaces of the small intestine (Fig. 7.10). These secondary lymphoid tissues defend the mucosasurfaces and are located at potential portals of microbial entry. Peyer's patches function similarly to lymph nodes andthe spleen, with cells entering at the cortical end, promoting the intermingling of antigen-presenting cells, B cells, and Tcells and the exit of cells at the medullary end.

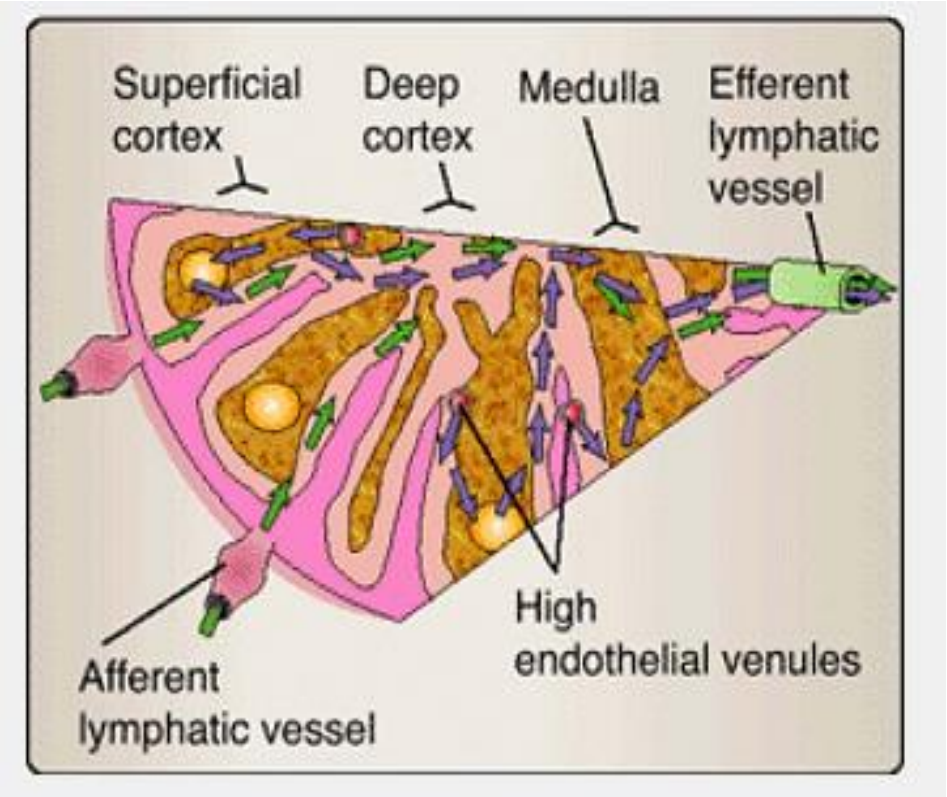

Figure 7.9 Section from lymph node in Figure 7.8 (see white triangle). Specialized highendothelium vessels provide a portal for leukocyte entry into the lymph node from thecardiovascular system. B cell–rich areas (superficial cortex and germinal centers) areanatomic sites of immunoglobulin production. The deep cortex and medullary regions aresites for T cell homing and activation.

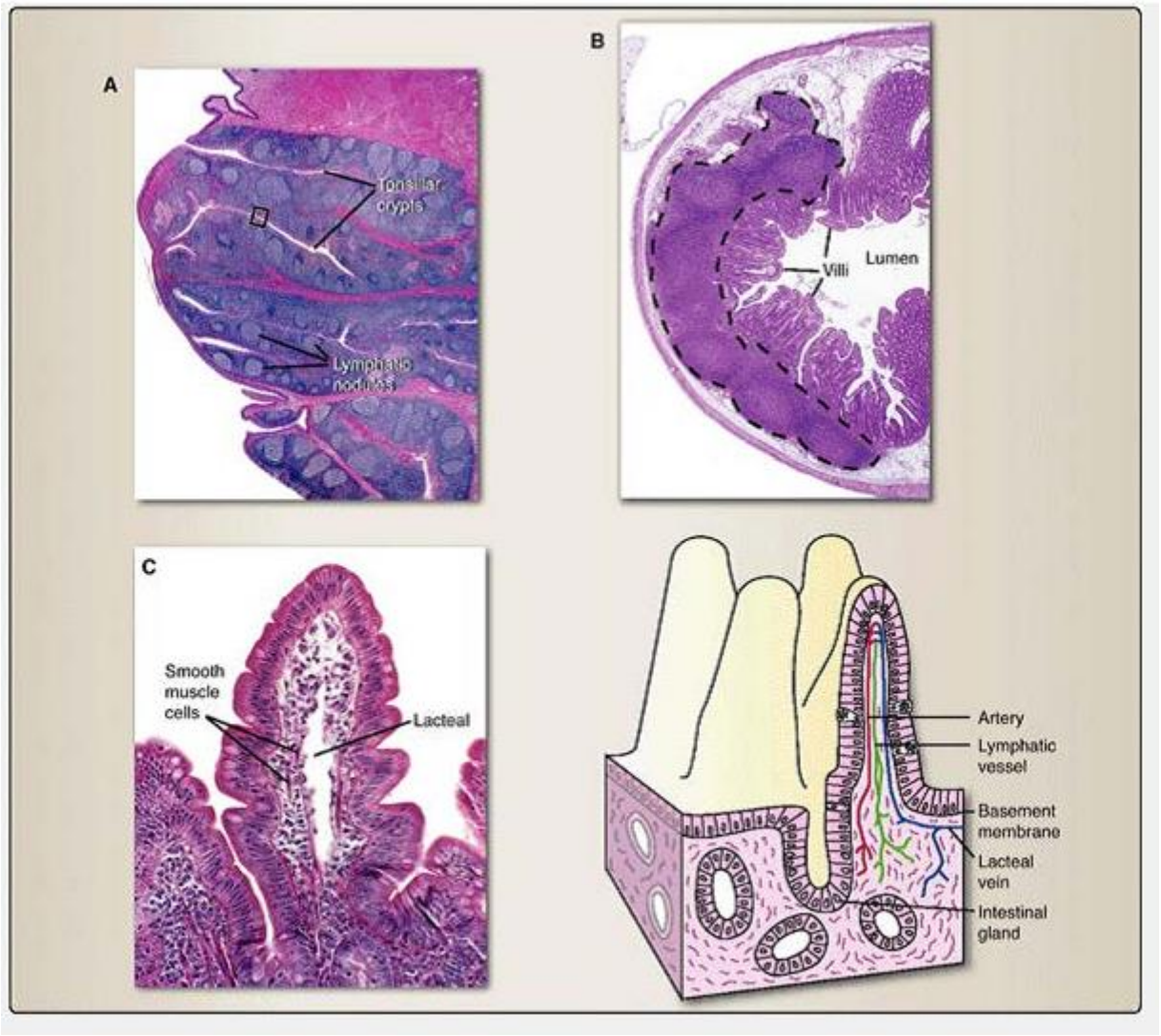

Figure 7.10 Mucosa-associated lymphoid tissues are anatomically placed at strategicareas of potential microbial entry. A. Tonsils are located as a defensive ring around thenasopharynx at the portal of entry for both the respiratory and gastrointestinal systems. B.Peyer's patches are lymphoid accumulations lying underneath the villi of the small bowel(within the area delineated by the dotted line). C. Intestinal villi contain intraepitheliallymphocytes, interstitial leukocytes, and draining lymphatics (lacteals) that serve to bothsample the intestinal environment and defend the bowel from microbial invasion.

C. Lymphatic circulatory system

Leukocytes and their products use two circulatory systems. One, the cardiovascular system, is responsible for the circulationof blood(both its soluble and cellular components) throughout the body. The other system, the lymphatic circulatory system (see Fig.7.6), is an extensive capillary network that collects lymph, a watery clear fluid containing leukocytes and cellular debris, fromvarious organs and tissues. Lymphatic vessels within small intestine villi, designated lacteals, contain a milk-white fluid, chyle,produced by digestion. The lymphatic capillaries drain into large lymphatic vessels that drain into lymph nodes for filtration.Ultimately, the lymphatic trunk vessels join to form the thoracic duct that conveys lymph into the subclavian artery.

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 displayedon 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 oneepitope.
•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 thesmall 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.