Secondary Lymphoid Organs (SLO) Are Distributed Throughout the Body and Share Some Anatomical Features
The immune response occur within the SLO

- Lymph nodes and the spleen are the most highly organized of the secondary lymphoid organs and are compartmentalized from the rest of the body by a fibrous capsule.
- A some- what less organized system of secondary lymphoid tissue, collectively referred to as mucosa-associated lymphoid tissue (MALT), is found associated with the linings of multiple organ systems, including the gastrointestinal (GI) and respiratory tracts.
- MALT includes
- 1- tonsils,
- 2- Peyer's patches lymphoid follicles within the lamina propria (in the small intestine), GALT gut associated lymphoid tissue
- 3- and the appendix, as well as the mucous membranes lining the upper air ways NALT nasal associated lymphoid tissue, bronchi BALT bronchus associated lymphoid tissue, and genitourinary tract

SIXTH LECTURE

- The outermost layer, the **cortex**, contains lymphocytes (mostly B cells), macrophages, and follicular dendritic cells arranged in **follicles**.
- Beneath the cortex is the **paracortex**, which is populated largely by T lymphocytes and also contains dendritic cells that migrated from tissues to the node.
- The **medulla** is the innermost layer, and the site where lymphocytes exit (*egress*) the lymph node through the outgoing (*efferent*) lymphatics. It is more sparsely populated with lymphoid lineage cells, which include plasma cells that are actively secreting antibody molecules.

The Lymph Node Is a Highly Specialized Secondary Lymphoid Organ

Lymph nodes

- are the most specialized SLOs.
- They are encapsulated, bean-shaped structures that include networks of stromal cells packed with lymphocytes, macrophages, and dendritic cells. Connected to both blood vessels and lymphatic vessels, lymph nodes are the first organized lymphoid structure to encounter antigens that enter the tissue spaces.
- Structurally, a lymph node can be divided into three roughly concentric regions: the cortex, the paracortex, and the medulla, each of which supports a distinct microenvironment .

T Cells in the Lymph Node

- It takes every naïve T lymphocyte about 16 to 24 hours to browse all the MHC-peptide combinations presented by the antigen-presenting cells in a single lymph node.
- Once naïve T cells enter the lymph node, they browse MHC-peptide antigen complexes on the surfaces of the dendritic cells present in the paracortex.

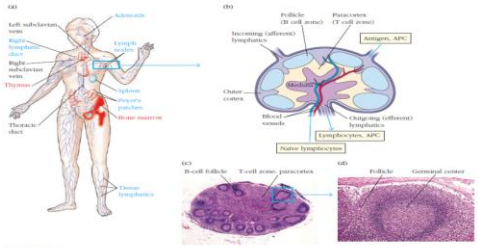


FIGURE 2–8 Structure of a lymph node. The microenvironments of the lymph node support distinct cell activities. (a) The lymph nodes are dispersed throughout the body and are connected by lymphatic vessels as well as blood vessels (not shown). (b) A drawing of the major features of a lymph node shows the major vessels that serve the organ: incoming (afferent) and outgoing (efferent) lymphatic vessels, and the arteries and veins. It also depicts the three major tissue layers: the outer cortex, the paracortex, and the innermost region, the medulla. Macrophages and dendritic cells, which trap antigen, are present in the cortex and paracortex. T cells are concentrated in the paracortex. B cells are primarily in the cortex, within follicles and germinal centers. The medulla is populated largely by antibody-producing plasma cells and is the site where cells exit via the efferent lymphatics. Naïve lymphocytes circulating in the blood enter the node via high-endothelial venules (HEV) via a process called extravasation (see Advances Box 14-2). Antigen and some leukocytes, including antigen-presenting cells, enter via afferent lymphatic vessels. All cells exit via efferent lymphatic vessels. (c) This stained tissue section shows the cortex with a number of oxoid follicles, which is surrounded by the T-cell-rich paracortex. (d) A stained lymph node section showing a follicle that includes a germinal center (otherwise referred to as a secondary follicle). [(a–b): Dr. Gladden Willis/Getty Images; (c–d): Image Source/Alamy]

B Cells in the Lymph Node

- The lymph node is also the site where B cells are activated and differentiate into high-affinity antibody-secreting plasma cells. B cell activation requires both antigen engagement by the B-cell receptor (BCR) and direct contact with an activated CD4_ TH cell. Both events are facilitated by the anatomy of the lymph node.
- Like T cells, B cells circulate through the blood and lymph and visit the lymph nodes on a daily basis, entering via the HEV. They respond to specific signals and chemokines that draw them not to the paracortex but to the lymph node follicle, they ultimately depend upon follicular dendritic cells (FDCs) for guidance . FDCs are centrally important in maintaining follicular and germinal center structure and "presenting" antigen to differentiating B cells.

- T cells that browse the lymph node but do not bind MHC-peptide combinations exit not via the blood, but via the *efferent lymphatics* in the medulla of the lymph node .
- T cells whose TCRs do bind to an MHC-peptide complex on an antigen-presenting cell that they encounter in the lymph node will stop migrating and take up residence in the node for several days. Here it will proliferate and, depending on cues from the antigen-presenting cell itself, its progeny will differentiate into effector cells with a variety of functions. CD8_ T cells gain the ability to kill target cells.

- CD4_ T cells can differentiate into several different kinds of effector cells, including those that can further activate macrophages,CD8_ T cells, and B cells.

- Some activated B cells differentiate directly into an antibody-producing cell (plasma cell) but others re-enter the follicle to establish a germinal center.
- A follicle that develops a germinal center is sometimes referred to as a **secondary follicle**;
- a follicle without a germinal center is sometimes referred to as a **primary follicle** .

The Generation of Memory T and B Cells in the Lymph Node

The interactions between TH cells and APCs, and between activated TH cells and activated B cells, results not only in the proliferation of antigen-specific lymphocytes and their functional differentiation, but also in the generation of memory T and B cells. Memory T and B cells can take up residence in secondary lymphoid tissues or can exit the lymph node and travel to and among tissues that first encountered the pathogen.

Memory T cells that reside in secondary lymphoid organs are referred to as ***central memory cells*** and are distinct in phenotype and functional potential from ***effector memory*** **T cells** that circulate among tissues

- B cells differ from T cells in that their receptors can recognize free antigen. A B cell will typically meet its antigen in the follicle. If its BCR binds to antigen, the B cell becomes partially activated and engulfs and processes that antigen. As mentioned above, B cells, in fact, are specialized antigen-presenting cells that present processed peptide-MHC complexes on their surface to CD4_ TH cells.
- Recent data show that B cells that have successfully engaged and move to the T-cell-rich paracortex, where they increase their chances of encountering an activated CD4_ TH cell that will recognize the MHC-antigen complex they present.
- When they successfully engage this TH cell, they maintain contact for a number of hours, becoming fully activated and receiving signals that induce B cell proliferation.

- The spleen is surrounded by a capsule from which a number of projections (**trabeculae**)
- Two main microenvironmental compartments can be distinguished in splenic tissue: the **red pulp** and **white pulp**, which are separated by a specialized region called the **marginal zone**

- The splenic red pulp consists of a network of sinusoids populated by red blood cells, macrophages, and some lymphocytes.
- 1- It is the site where old and defective red blood cells are destroyed and removed; many of the macrophages within the red pulp contain engulfed red blood cells or iron-containing pigments from degraded hemoglobin.
- 2- It is also the site where pathogens first gain access to the lymphoid-rich regions of the spleen, known as the white pulp.
- The splenic white pulp surrounds the branches of the splenic artery, and consists of the **periarteriolar lymphoid sheath (PALS)** populated by T lymphocytes as well as B-cell follicles. As in lymph nodes, germinal centers are generated within these follicles during an immune response

The Spleen Organizes the Immune Response Against Blood-Borne Pathogens

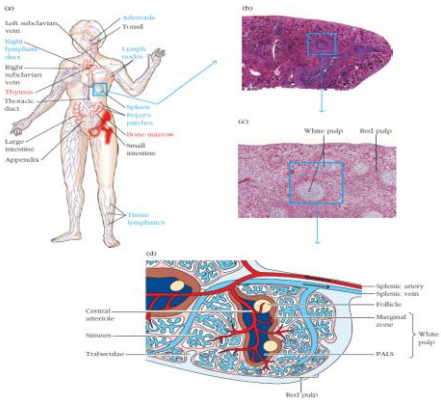
- The **spleen**, situated high in the left side of the abdominal cavity, is a large, ovoid secondary lymphoid organ that plays a major role in mounting immune responses to antigens in the bloodstream (Figure 2-10).
- Whereas lymph nodes are specialized for encounters between lymphocytes and antigen drained from local tissues, the spleen specializes infiltering blood and trapping blood-borne antigens; thus, it is particularly important in the response to systemic infections.
- Unlike the lymph nodes, the spleen is not supplied by lymphatic vessels. Instead, blood-borne antigens and lymphocytes are carried into the spleen through the **splenic artery** and out via the **splenic vein**.
- Experiments with radioactively labeled lymphocytes show that more recirculating lymphocytes pass daily through the spleen than through all the lymph nodes combined.

- The events that initiate the adaptive immune response in the spleen are analogous to those that occur in the lymph node.
- Briefly, circulating naïve B cells encounter antigen in the follicles, and circulating naïve CD8_ and CD4_ T cells meet antigen as MHC-peptide complexes on the surface of dendritic cells in the T-cell zone (PALS). Once activated, CD4_ TH cells then provide help to B cells and CD8_ T cells that have also encountered antigen. Some activated B cells, together with some TH cells, migrate back into follicles and generate germinal centers.

- The marginal zone, which borders the white pulp, is populated by unique and specialized macrophages and B cells, which are the first line of defense against certain blood-borne pathogens.
- Blood-borne antigens and lymphocytes
- 1- enter the spleen through the splenic artery, and interact first with cells at the marginal zone.
- 2- In the marginal zone, antigen is trapped and processed by dendritic cells,
- 3- which travel to the PALS.
- 4- Specialized, resident *marginal zone B cells* also bind antigen via complement receptors and convey it to the follicles.
- Migrating B and T lymphocytes in the blood enter sinuses in the marginal zone and migrate to the follicles and the PALS, respectively.

MALT Organizes the Response to Antigen That Enters Mucosal Tissues

- Lymph nodes and the spleen are not the only organs that develop secondary lymphoid microenvironments. T- and B-cell zones and lymphoid follicles are also found in mucosal membranes that line the digestive, respiratory, and urogenital systems, as well as in the skin.
- Mucosal membranes have a combined surface area of about 400 m2 (nearly the size of a basketball court) and are the major sites of entry for most pathogens. These vulnerable membrane surfaces are defended by a group of organized lymphoid tissues known collectively as **mucosa-associated lymphoid tissue (MALT)**.
- Lymphoid tissue associated with different mucosal areas is sometimes given more specific names; for instance, the respiratory epithelium is referred to as **bronchus-associated lymphoid tissue (BALT)** or **nasal-associated lymphoid tissue (NALT)**, and that associated with the intestinal epithelium is referred to as **gut-associated lymphoid tissue (GALT)**.



- Like lymphoid follicles in other sites, those that compose Peyer's patches can develop into secondary follicles with germinal centers. The overall functional importance of MALT in the body's defense is underscored by its large population of antibody-producing plasma cells, whose number exceeds that of plasma cells in the spleen, lymph nodes, and bone marrow combined.
- In the digestive tract, specialized **M cells** transport antigen across the epithelium (Figure 2-12). The structure of M cells is striking: they are flattened epithelial cells lacking the microvilli that characterize the rest of the mucosal epithelium. They have a deep invagination, or pocket, in the basolateral plasma membrane, which is filled with a cluster of B cells, T cells, and macrophages.

- The structure of GALT is well described and ranges from loose, barely organized clusters of lymphoid cells in the lamina propria of intestinal villi to well-organized structures such as the tonsils and adenoids (Waldeyer's tonsil ring), the appendix, and Peyer's patches, which are found within the intestinal lining and contain well-defined follicles and T-cell zones.
- The outer mucosal epithelial layer contains **intraepithelial lymphocytes (IELs)**, many of which are T cells.
- The **lamina propria**, which lies under the epithelial layer, contains large numbers of B cells, plasma cells, activatedT cells, and macrophages in loose clusters.
- Microscopy has revealed more than 15,000 lymphoid follicles within the intestinal lamina propria of a healthy child. **Peyer's patches**, nodules of 30 to 40 lymphoid follicles, extend into the muscle layers that are just below the lamina propria.

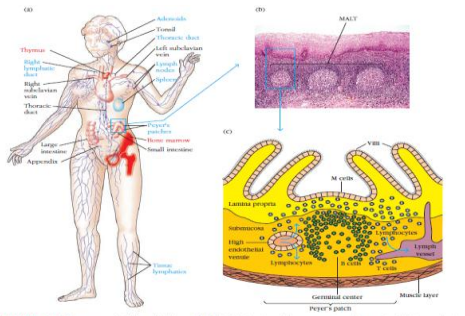


FIGURE 2-11 **Mucosa-associated lymphoid tissue (MALT).** (a) The Peyer's patch is a representative of the extensive MALT system that is found in the intestine. (b) A stained tissue cross-section of Peyer's patch lymphoid nodules in the intestinal submucosa is schematically diagrammed in (c). The intestinal lamina propria contains loose clusters of lymphoid cells and diffuse follicles. [2-11b Dr. Gladden Willis/Visuals Unlimited.]

Antigen transported across the mucous membrane by M cells ultimately leads to the activation of B cells that differentiate and then secrete IgA. This class of antibody is concentrated in secretions (e.g., milk) and is an important tool used by the body to combat many types of infection at mucosal sites.

The Skin Is an Innate Immune Barrier and Also Includes Lymphoid Tissue

- The epidermal (outer) layer of the skin is composed largely of specialized epithelial cells called keratinocytes. These cells secrete a number of cytokines that may function to induce a local inflammatory reaction. Scattered among the epithelial-cell matrix of the epidermis are Langerhans cells, skin-resident dendritic cells that internalize antigen by phagocytosis or endocytosis.
- The epidermis also contains **intraepidermal lymphocytes**, which are predominantly T cells; some immunologists believe that they play a role in combating infections that enter through the skin, a function for which they are well positioned.
- The underlying dermal layer of the skin also contains scattered lymphocytes, dendritic cells, monocytes, macrophages, and may even include hematopoietic stem cells.

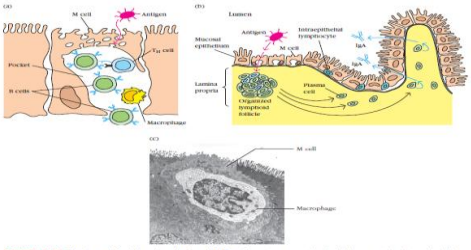


FIGURE 2-12 Structure of M cells and production of IgA at inductive sites. (a) M cells, situated in mucous membranes, endocytose antigen from the lumen of the digestive, respiratory, and urogenital tracts. The antigen is transported across the cell and released into the large basolateral pocket. (b) Antigen transported across the epithelial layer by M cells at an inductive site activates B cells in the underlying lymphoid follicles. The activated B cells differentiate into IgA producing plasma cells, which migrate along the lamina propria, the layer under the mucosa. The outer mucosal epithelial layer contains intraepithelial lymphocytes, of which many are T cells. (c) A stained section of mucosal lymphoid tissue (the Peyer's patch of the intestine) shows small, darkly stained intraepithelial lymphocytes encased by M cells, whose nuclei are labeled. Lymphocytes are also present in the lamina propria. [1-13c: Kucharzik, T., Lugering, N., Schmid, K.W., Schmidt, M.A., Stoll, R. Domschke, W. Human intestinal M cells exhibit enterocyte-like intermediate filaments. Gut 1998, 42: 54-52. doi: 10.1136/gut.42.1.54.]

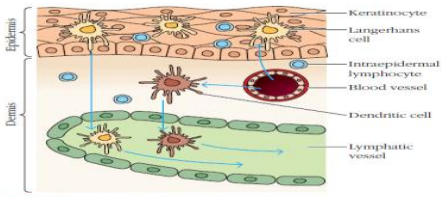


FIGURE 2-13 The distribution of immune cells in the skin. Langerhans cells reside in the outer layer, the epidermis. They travel to lymph nodes via the lymphatic vessels in the dermis, a layer of connective tissue below the epidermis. Dendritic cells also reside in the dermis and also can travel via the lymphatic vessels to lymph nodes when activated. White blood cells, including monocytes and lymphocytes travel to both layers of the skin via blood vessels, extravasating in the dermis, as shown.