

Chapter 10

Lymphatic System

10.1. General Comments

The primary functions of lymphoid organs are protective or immunologic in nature. They are the source of immunocompetent cells which are capable of neutralizing antigens to which the body has been exposed. The actions of the lymphatic system also include the actions of lymphocytes, plasma cells, and a variety of macrophages. These cells and their precursors form the primary cellular populations of lymphoid organs. As a result, these cells are often referred to as Lymphoid Cells. Many, however, use the term lymphoid cell **only** for the lymphocytes and plasma cells, not for the macrophages. The term "lymphatic system" includes not only the cells within distinct lymphoid organs but also the widely distributed cells found in circulation and in the loose connective tissues as well as those in certain epithelial tissues. The term "immune system" includes the lymphoid cells, accessory cells (such as macrophages) and their secretory products.

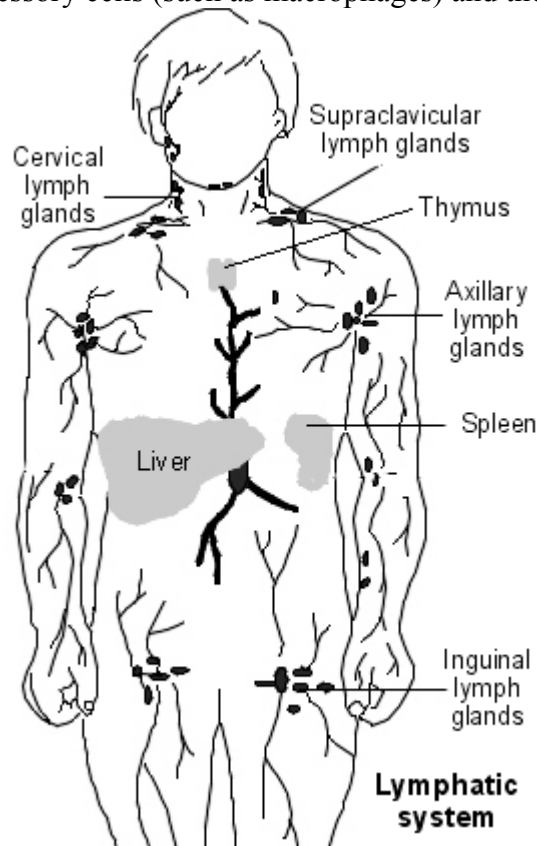


Fig.10.1. Lymphatic System

10.2. Developmental Overview

The origin of the stem cells for the lymphoid organs can be traced to mesenchyme. These stem cells are the hemocytoblasts. Soon after their development the vasculature will have become confluent and these multipotent cells will migrate to temporary depots such as

the liver and spleen. There they will proliferate and differentiate along the various leucocyte lines. Later, bone marrow becomes the predominant source of these stem cells. Red marrow maintains this capability throughout our lifetime. Late in fetal development many stem cells will migrate from the bone marrow into the Primary/Central Lymphoid Organs. Within the primary lymphoid organs special epithelially derived cells will induce the immigrant stem cells to proliferate and differentiate into immunocompetent stem cells. There are two primary lymphoid organs (among endothermic vertebrates):

a] Thymus - this is the site of T cell maturation.

b] Bursa of Fabricius/Bursa Equivalent - this is the site of B cell maturation.

It's actual location in higher mammals is still undetermined but may be Peyer's patches, liver, red marrow, lymph nodes, or any combination. Shortly after birth cells from the primary lymphoid organs migrate into the Secondary/Peripheral Lymphoid Organs. The secondary lymphoid organs are the: tonsils, lymph nodes, spleen, and GALT (gut associated lymphatic tissue). In the secondary lymphoid organs the T and B cells set up populations in fairly distinct zones ready for the immune response.

10.3. The Two Types of Immunity

Although morphologically similar, T and B lymphocytes are functionally dissimilar:

1) T cells are primarily involved in cell-mediated immunity.

2) B cells, and their derivatives the plasma cells, are involved in humoral immunity, also known as antibody mediated immunity.

10.3.1. Cell-Mediated Immunity

Activated T lymphocytes, called Effector T Cells, eliminate antigens either by attacking them directly or indirectly through the release of Lymphokines. Lymphokines are a class of chemical agents that will elicit a number of responses throughout the immune system. The effector T cells that produce lymphokines are called Helper T Cells. Those effector T cells that attack the antigen directly are called Cytotoxic/Killer T Cells. The primary distinguishing feature of cell-mediated immunity is that specifically sensitized lymphocytes seek out the antigen. Contact with the antigen is required to trigger the reaction. This causes cell-mediated immunity to be a localized reaction. Among the effector T cells are several varieties that can be distinguished from one another by unique cell surface molecules and by their specialized functions.

a] **Killer T Cells** - attack the antigen bearing agent directly. Some will have a specific affinity for destroying tumor cells. Some will have a specific affinity for fighting infections.

b] **Helper T Cells** - will secrete a variety of chemical agents, such as lymphokines, to enhance the immune response.

c] **Suppressor T Cells** - will secrete a variety of substances designed to suppress the immune response (after the infection is under control).

10.3.2. Humoral Immunity

Activated B cells and plasma cells secrete specific antibodies, in response to specific antigens, which will bind to those antigens forming inactive complexes. A distinguishing feature of humoral immunity is that contact between the lymphocyte and the antigen is not required to incapacitate or kill the antigen. Instead, following sensitization, specific antibodies are secreted by plasma cells and distributed throughout the fluids of the body. The antibodies will seek out the antigens. Antibodies belong to a class of plasma proteins

called Immunoglobulins. There are five distinct classes: IgG, IgA, IgM, IgE, and IgD. Although certain antigens will trigger either a humoral immunity response or a cell-mediated immunity response, in most cases both immune response must work cooperatively.

10.4. Lymphoid Tissue

The term "lymphoid tissue" refers to the parenchyma of lymphoid organs and of the loose connective tissues throughout the body in which lymphoid cells make up a large portion of the population. The connective tissue framework of these regions will generally consist of a reticular meshwork. The reticular meshwork consists of fine reticular fibers and reticular cells. Lymphoid tissue is usually described in terms of the relative densities of its lymphoid cell aggregates:

1) Diffuse Lymphatic Tissue - refers to a relatively loose aggregate of lymphoid cells.

2) Nodular Lymphatic Tissue - refers to a denser, more organized tissue. A Nodule usually consists of a dense, spherical aggregate of lymphocytes with a paler staining center surrounded by a darker staining corona.

10.5. Comparison of the Stroma and Parenchyma Between Primary and Secondary Lymphoid Organs

a) Stroma - the supporting framework of an organ. Typically the stroma is a connective tissue.

b) Parenchyma - the working tissue of an organ.

10.5.1. Primary Lymphoid Organs

In primary lymphoid organs the stroma lacks reticular fibers and the reticular cells are of epithelial origin. These reticular cells are nonphagocytic. They are stellate shaped. They are believed to have an inductive effect on incoming stem cells from the bone marrow. The parenchyma is a diffuse lymphoid tissue.

10.5.1. Secondary Lymphoid Organs

The stroma is rich in reticular fibers and the reticular cells are of mesenchymal origin. Most secondary lymphoid organ reticular cells are quite phagocytic but some are involved in reticular fiber synthesis and antigen trapping. The parenchyma is composed of both diffuse and nodular lymphoid tissue. Diffuse lymphoid tissue is predominantly occupied by T cells. Nodular lymphoid tissue is predominantly occupied by B cells.

10.6. The Primary Lymphoid Organs

10.6.1. The Thymus

The thymus is a bilobed mass located in the midline of the mediastinum, deep to the sternum. It attains its greatest relative weight and is at its most developed at about the time of birth. The thymus will begin to progressively degenerate with the onset of puberty. The thymus is the site of T cell maturation. T lymphocytes begin their development in the red marrow and will migrate into the thymus to mature.

a) The Stroma: The stroma of the thymus includes a thin connective tissue Capsule which surrounds the organ. Extensions of the capsule will run into the thymus dividing it up into partial lobules. These connective tissue extensions are called Septa. To further partition the thymus smaller septa will radiate off of larger septa. The stellate shaped

epithelial-reticular cells will form an delicate inner framework. Though lacking the support of reticular fibers these reticular cells are very branched and will connect to one another by desmosomes. The reticular cells of the thymus are of epithelial origin. In particular, they develop from the endoderm. They reflect their epithelial origins in their secretory nature. They produce a variety of peptide hormones most of which regulate T cell development and maturation.

These reticular cells are not phagocytic.

b) The Parenchyma: The parenchyma within each lobule of the thymus is divided up into a Cortex and a Medulla. Since the lobules are incomplete the medulla is continuous between adjacent lobules. The cortex is composed primarily of aggregated lymphocytes called Thymocytes. However, the density of these aggregates is not as great as that seen in nodular lymphoid tissue so this is still considered to be diffuse lymphoid tissue. The medulla will be lighter staining due to having fewer lymphocytes. However, the medulla does have more epithelial-reticular cells than does the cortex. Scattered throughout the medulla are a third type of cell. These are concentrically arranged epithelial cells called Thymic Corpuscles. Their function is unknown. The parenchyma will also include macrophages in large numbers and in lower numbers mast cells, plasma cells, and granulocytes.

c) The Vascular Supply of the Thymus: Vascularization of the thymus consists of small vessels that penetrate the capsule, ramify in the interlobular c.t./septa, and enter into the parenchyma between the cortex and medulla. Capillaries will extend into the cortex from the corticomedullary zone of the lobules and will extensively anastomize with one another. These capillaries will drain into postcapillary venules and small veins of the medulla. The postcapillary venules are the route by which lymphoid cells can migrate into or out of the thymus. The capillaries of the cortex, however, are impervious to cells and macromolecules which means that they form the Blood-ThymusBarrier. The blood-thymus barrier prevents antigens from entering the cortex. Those antigens which enter into the medulla are phagocytized before they can spread into the cortex.

d) Functional Aspects of the Thymus: The cortex of a newborn's thymus displays the extensive proliferation of lymphocytes. These proliferating cells are randomly arranged throughout the cortex. This extensive proliferation of lymphocytes is called Blastogenesis. Blastogenesis is driven by hormone-like inductive substances produced by the epithelial-reticular cells. Over ten factors have been identified including: thymosin, thymopoietin, and serum thymus factor. The thymus is the site of T lymphocyte maturation. At puberty the thymus begins to undergo a progressive degenerative process called Involution. Lymphocyte populations become greatly depleted and will largely be replaced by adipose tissue. The thymic corpuscles become greatly enlarged. The gradual, age related degeneration of the thymus is termed Age-Involution. In the mature individual immunocompetence has been established and so the thymus is less significant. T lymphocytes are generally long-lived cells which will migrate extensively between the blood and the secondary lymphoid organs.

e) The Bursa Equivalent: In birds the B lymphocytes migrate from the bone marrow to mature in the bursa of Fabricius. In mammals an equivalent to this primary avian lymphoid organ exists but it has not been identified as yet. Candidates range from the spleen or the lymph nodes to the GALT or the diffuse lymphoid microenvironments of certain epithelia.

10.7. The Secondary Lymphoid Organs

10.7.1. The Lymph Nodes

Lymph nodes are small, encapsulated organs located along lymphatic vessels through which lymph fluid flows. Lymph nodes serve to filter lymph and to add plasma cells to the lymph. They are located throughout the body but are most prominent in the axillary and inguinal areas.

a) The Stroma: The lymph node is covered by a connective tissue capsule. Extensions called Trabeculae radiate from the capsule into the parenchyma of the lymph node. The lymph node also has a Hilus. The hilus is an area of dense irregular connective tissue on the concave surface of the lymph node where lymph vessels exit the organ. These lymph vessels are called Efferent Lymphatics and are carrying lymph fluid away from the lymph node. Lymph is carried to the lymph node by Efferent Lymphatics which penetrate the capsule on the convex surface of the organ. The inner stroma is composed of a delicate meshwork of reticular fibers and reticular cells. These mesenchymal derived reticular cells are phagocytic and will also trap antigens.

b) The Parenchyma: The parenchyma of the lymph node is divided into a cortex and a medulla. The cortex is composed primarily of nodular lymphoid tissue. It forms prominent nodules called Lymph Nodules having prominent germinal centers. Surrounding the lymph nodules is a small amount of scattered diffuse lymphoid tissue called the Paracortical Region. The paracortical region is predominantly occupied by T cells while the lymph nodules are mainly composed of B cells. The medulla is composed of diffuse lymphoid tissue arranged into cord or strand-like structures called Medullary Strands/Cords. Typically macrophages are found in great numbers on around the medullary cords.

c) Lymphatic Sinuses: Lymph enters the lymph node via the afferent Lymphatics and passes through the organ, to the efferent lymphatics, by a system of sinuses. Lymph first enter into the Subcapsular/Marginal Sinuses located immediately below the capsule. It then percolates into the Cortical Sinuses. From the cortical sinuses it flows into the Medullary Sinuses. The medullary sinuses will drain into the efferent lymphatics at the hilus. Lymph will also flow through the diffuse lymphoid tissues of the lymph node but at a slower rate. The walls of the sinus are composed of a reticular fiber meshwork. The sinuses are also lined with two types of cells: macrophages and nonphagocytic endothelial cells. This lining is discontinuous.

d) Functional Aspects of the Lymph Node: Lymph borne antigens from the body's connective tissues are transported by lymph vessels to the lymph nodes where they will induce immune activity. During a peak humoral immune response plasma cells will be found in the medullary cords in large numbers. Typically the antigens will be phagocytized by phagocytic cells of the lymph node. Many lymphoid cells will enter the lymph node sinuses by way of the afferent lymphatics and will exit the lymph node by way of the efferent lymphatics. They will migrate to other lymphoid organs and to connective tissue spaces. Some cells, particularly memory cells, will recirculate back to the lymph nodes.

10.7.2. The Spleen

The spleen is the largest lymphoid organ. It is located in the left hypochondriac region of the abdominal cavity. The spleen is interposed in the systemic circulation and so serves to

filter blood. It also serves as a source of immunocompetent cells and even has some nonimmunological functions. In the fetus it serves as a hemopoietic organ. The spleen is a reservoir of blood. Along with filtering out antigens the spleen removes senescent blood cells.

a) The Stroma

The spleen is encapsulated by a thick capsule of dense irregular connective tissue. Peritoneum will cover the free surfaces of the spleen external to the capsule. This is the case for all of the organs in the abdominopelvic cavity. Trabeculae branch off of the capsule and extend into the spleen. Both the trabecular and capsular connective tissues will contain some elastic fibers and smooth muscle. This is to allow the spleen to expand to store blood and to contract to release this blood back into circulation. The hilus will allow for passage of the splenic artery and splenic vein. The inner stroma is composed of reticular fibers and reticulocytes.

b) The Parenchyma

The parenchyma of the spleen is composed of lymphoid tissue called the Splenic Pulp which is divided into the White Pulp and the Red Pulp. White pulp is composed of both diffuse and nodular lymphoid tissue. It is organized around the arteries of the parenchyma. Diffuse lymphoid tissue forms a sheath around the artery called the Periarterial Lymphocyte Sheath. Nodular lymphoid tissue surrounds this periarterial sheath. These nodules are called Splenic Nodules. Red pulp is composed of diffuse lymphoid tissue surrounding anastomizing venous sinuses. The lymphoid tissue of the red pulp is arranged into strands between the venous sinuses called Splenic Cords/Strands. Between the red and white pulp are poorly defined regions called Marginal Zones. Marginal zones receive much of the blood entering the spleen.

c) The Organization of the Spleen in Reference to the Vasculature

The splenic artery enters the spleen at the hilus and then branches. These branches are called Trabecular Arteries and they will travel with the trabeculae into the spleen. Central Arteries will branch off of the trabecular arteries, branching out of the trabeculae and into the parenchyma. The central arteries will have their outermost tunic, the tunica adventitia, be largely replaced by reticular fibers which are highly infiltrated with lymphocytes. This cuff of lymphocytes surrounding each central artery is the periarterial lymphocyte sheath. Surrounding the sheath will be a large nodule of nodular lymphatic tissue, the splenic nodule, with pronounced germinal centers. The central arteries branch into many smaller vessels which service the capillaries of the marginal zones. The central arteries finally terminate in the red pulp as highly branched small vessels called Penicilli. The cells lining the venous sinuses are discontinuous and so present little barrier to the movement of cells between the red pulp and the venous sinuses. These venous sinuses anastomize freely. The venous sinuses are drained by the Red Pulp Veins. The red pulp veins will drain into the Trabecular Veins which will travel with the trabeculae out of the parenchyma. The red pulp veins will drain into the splenic vein at the hilus.

d) Functional Aspects of the Spleen

The dense reticular meshwork in the marginal zones and in the red pulp cords functions as an effective trap for antigens and for senescent blood cells. These regions contain large numbers of macrophages and phagocytic reticular cells for the removal of trapped cells and antigens. The cells lining the venous sinuses are nonphagocytic. As an effector organ

in immunity, the spleen has much in common with the lymph nodes. The diffuse lymphoid tissue of the spleen is predominantly populated by T lymphocytes. The nodular lymphoid tissue of the spleen is predominantly populated by B lymphocytes.

10.7. 3. Gut Associated Lymphatic Tissue (GALT)

The lamina propria of the digestive tube and of the respiratory tract is often considered to be a lymphoid tissue since it is rich in lymphoid cells and has a reticular stroma. Most of the plasma cells of this area secrete the antibody class IgA which is very effective in preventing bacterial and viral invasion. At different portions of the digestive tube the lamina propria is greatly enlarged by the presence of more highly organized lymphoid tissue. These tissue expansions form the: tonsils, Peyer's patches, appendix, and solitary lymph nodules scattered throughout the entire tract but most numerous in the colon. Like a typical secondary lymphoid organ the organs of GALT also are composed of both diffuse and nodular lymphoid tissue. Their cellular proliferation is antigen driven particularly by ingested antigens. Immunocompetent cells will recirculate through postcapillary venules in diffuse lymphoid tissue. These organs maintain a close association with an epithelial tissue which is also highly infiltrated by lymphocytes. The epithelium associated with nodules of GALT, called GALT Nodules/GALT Follicles, is histologically distinct from the surrounding epithelium and is called Follicular Epithelium. Follicular epithelium is specialized so as to allow for the enhanced take up of luminal particles and microorganisms. This is accomplished by a localized decrease in the epithelial barrier. This will stimulate the response of the underlying lymphocytes and macrophages.

a) The Tonsils

The tonsils form a ring of lymphatic tissue around the entrance into the throat. The tonsils consist of two paired structures, the Palatine and Lingual Tonsils, and a singular Pharyngeal Tonsil. The tonsils are overall quite similar with only slight differences between them. The lymphoid tissue of tonsils will contain nodules having unusually large germinal centers surrounded by diffuse lymphoid tissue. In many ways it looks much like the cortex of a lymph node. The tonsils will have a scanty capsule located deep in the lamina propria. The capsule will have short trabeculae radiating off from it. The inner stroma of the tonsil will be composed of reticular fibers and reticulocytes. The tonsils are closely associated with the overlying epithelium. The type of epithelium present depends on the tonsil. The pharyngeal tonsil is covered by pseudostratified ciliated columnar epithelium with goblet cells. The lingual and palatine tonsils are covered by stratified squamous, nonkeratinized, epithelium. The epithelium is highly infolded and forms deep Crypts. The trabeculae of the tonsil are orientated towards these crypts. A number of small glands are associated with this region. Their ducts will open into the bases of the crypts. Skeletal muscle is located immediately below these glands.

b) The Peyer's Patches

Peyer's patches are also known as aggregated nodules and are found in the ileum of the small intestine. The Peyer's patch will consist of between about 30 to 40 nodules. They are histologically similar to the tonsils. They are typically confined to the lamina propria. However, some of the larger Peyer's patches may extend into the surrounding tissue layers of the ileum. The largest ones will even bulge into the lumen, flattening the villi in this area. The nodules are interspersed with diffuse lymphoid tissue. The follicular

epithelium of Peyer's patches is highly specialized. These are areas where the villi are often absent. While most of the constituent cells of follicular epithelium are the (simple) columnar epithelial cells typical for the small intestine, there are some modified cells. These unique epithelial cells have cytoplasmic extensions forming bridges between them. This allows these cells to trap antigens from the intestinal lumen and to present them to the cells of the underlying lymph nodules. Macrophages and lymphocytes are often found in close association with these modified epithelial cells. Together they form structures called Intraepithelial Lymphoid Nests.

c) The Appendix

The appendix is a blind evagination of the cecum located near the ileocecal junction. The lamina propria of the appendix is composed entirely of lymphoid tissue similar histologically to the tonsils and Peyer's patches. In certain cases there are crypts associated with the appendix but they are often absent or poorly developed.

10.8. The Lymph Vessels

Lymph vessels serve as a drainage system for interstitial fluid, returning it to the blood stream. Interstitial fluid is a filtrate of plasma and leaks out of the capillaries into the interstitial spaces. It is not picked up by the postcapillary venules since it may now carry pathogenic agents which have entered the connective tissue spaces. During lymph circulation lymph is not only returned to the blood stream but also is cleansed of foreign invaders and augmented by antibodies and immunocompetent cells to deal with any invaders.

Lymph circulation begins with the Lymph Capillaries. Lymph capillaries are blind ended microscopic tubes which will drain the interstitial fluid from the interstitial spaces. The lymph capillary is composed of endothelium, a simple squamous epithelium, and Lymphatic Anchoring Filaments. The lymphatic anchoring filaments are extracellular filaments which terminate in the basal lamina of the endothelium. They give structural support to these thin vessels. The endothelial cells will slightly overlap forming Minivalves to prevent the back flow of lymph. Unlike blood capillaries, lymph capillaries are more variable in size and shape and usually have a larger luminal diameter. Also they branch and anastomize more extensively.

Lymph capillaries will drain into larger vessels which in turn will drain into larger lymph vessels called Lymphatics. Lymphatics are similar to veins except: They have larger lumens. They have simpler walls. The walls are composed of endothelium, a few smooth muscle cells, and a few bundles of collagen and elastic fibers. They have many more valves. Periodically along the lymphatics will be lymph nodes for the cleansing of the lymph and the addition of immunocompetent cells. The lymphatics will drain into larger vessels called Lymph Ducts.

The largest of the lymph ducts are the Right and Left Lymphatic Ducts. The left lymphatic duct is also known as the Thoracic Duct. It is much larger than is the right lymphatic duct since it drains a greater portion of the body. It drains lymph from all regions of the body inferior to the diaphragm and the left portion of the body superior to the diaphragm. The right lymphatic duct drains lymph from only the right portion of the body superior to the diaphragm. The right and left lymphatics will drain into the right and left subclavian veins respectively.

Structururally, the lumen is lined by endothelium. The next layer is a thicker component of smooth muscle than was found in lymphatics and also includes some elastic fibers.

The outer layer of the lymphatic duct is very similar to the outer layer of a vein, the tunica adventitia. It has a heavy connective tissue component and a longitudinal array of smooth muscle fibers. Lymph fluid is not pumped through the lymph vessels. Lymph fluid is moved through lymph circulation by contractions of surrounding skeletal muscles.