The Histology of Lymphoid Organs

Cells that provide immune defenses are organized into

- Encapsulated lymphoid organs
  - Lymph nodes
  - Thymus
  - Spleen

- Non-encapsulated aggregates of cells
  - Diffuse non-encapsulated aggregates or nodules of cells = harbored in many areas underlying mucosal epithelia where bacterial infections tend to occur (i.e. GI tract)

- Individual free cells distributed in the blood, lymph fluid, or in intercellular spaces throughout the body

Lymphoid organs

- Primary = Bone marrow (B-cells) and Thymus (T-cells)
  - Where stem cells are involved in lymphopoiesis (differentiation of lymph cells from pluripotent progenitor cells)

- Secondary = areas where aggregates of lymphocytes are found in close proximity to APC and can also furnish an adaptive immune response (seeded with cells from primary tissues, lymphoid cells proliferate and differentiated in response to environmental conditions)

LYMPH NODES

- Small organs found in many areas of the body (found singly or in clusters)
- Serve as non-specific filters of debris, microorganisms, etc.
- Are a key site for antigen presentation in adaptive immunity
- Small interstitial spaces in tissues lead to small lymphatic vessels that are lined by a thin squamous endothelium → several of which connect to al lymph node via the afferent lymphatic vessel → lymphocytes enter the node in the subcapsular space → lymph fluid (with lymphocytes) leaves the node via the efferent lymphatic vessel
- Anatomy
- Connective tissue capsule with a subcapsular space below
  - Outer capsule is connected to short connective tissue trabeculae that extend into and partially subdivide the cortex
  - Lymph node also a series of reticular fibers that can seen with certain stains
- Outer Cortex
  - High in the cortex = lymphoid follicles
    - Some show large germinal centers, these are regions of active cell proliferation and apoptosis
    - These are mostly made up of B-cells and dividing activated B-cells and MO
- Loosely defined Paracortical region
  - This region is comprised mostly of T-cells (but also contains some B-cells)

NOTE: There is no real sharp demarcation line between any regions of the lymph node

- Medulla
  - Region of loosely arranged cords of cells (B-cells, T-cells, and plasma cells)
  - Between the cords, lymphatic fluid slowly moves en route to the efferent lymphatic vessel, where lymphocytes leave the node → eventually reach the thoracic duct

- Blood supply
  - Each lymph node = blood supply that enters via a small artery and leaves via a small vein at the hilus
  - The artery braches a lot to supply essentially the entire node with oxygen and nutrients
  - In lymph nodes, the vessels are lined by special endothelium = high endothelial venule = sites for recognition of diapedesis of lymphocytes from the blood into the lymphatic space of the node
• Endothelial cells of these venules = docking receptors (i.e. selectins) that function in initiating passage through the endothelium
• Unusual, as they are rounded and protrude into the lumen of the vessel (very unlike typical squamous endothelial cells of most venules)

**THYMUS**

• Where thymocytic precursor cells undergo all the processes that result in release of immunocompetent T-lymphocytes, including
  o Proliferation
  o Differentiation
  o Selection of these cells
• Provides a microenvironment for both (+) and (-) selection of thymocytes occurs = complex process (trained to not destroy self)
• Total lymphocyte mass of the thymus = lessens throughout childhood and by puberty, thymus involution (shrinking of an organ) is particularly apparent, with fat cells and connective tissue replacing many areas that were previously occupied by developing thymocytes
• General structure
  o Bi-lobed
  o Ensheathed by a connective tissue capsule from which connective tissue septa (trabeculae) partially divide the organ into series of pseudolobes
  o Cortex = darker staining with a more densely packed set of developing thymocytes with dark nuclei
  o More mature thymocytes precursors = less densely packed in the medulla
- Medulla = varying numbers of circulating bodies = Hassal’s corpuscles = comprised of concentric layers or reticular cells (it is thought that these cells produce thymic stromal lymphoprotein important in suppressing autoimmune events

NOTE: It is the relative densities of thymocytes/unit area that define the cortex and medulla

  o Cells just below capsule = blast cells that divide and give rise to other immature thymocytes (many mitotic figures are seen here)
  o A small % of circulating T-cells may return to the thymus and are found in the medulla

- Population of other cells are also found in the thymus = epithelioreticular cells (aka. stromal cells), which include
  - Epithelial-like cell
  - Dendritic cells
  - MO
  o These cells provide a matrix and generally envelop the developing thymocytes as large infolds as the thymocytes mature from the cortex of the thymus toward the medulla
  o There is EXTENSIVE interaction of these cells with developing thymocytes, both in the cortex and medulla (in the medulla, these cells form a greater percentage of the cross-sectional area and can be more readily identified)
  o Stromal cells = important in the (+) and (-) selection events at thymocytes mature
    - They also secrete various cytokines and unique thymic hormones important to thymocyte maturation
    - Majority of thymocytes = eliminated by (-) selection process

- Thymus = NO reticular fibers (there is NO bulk flow of fluid through it) as the stromal cells provide support

- At the end of the selection process, mature thymocytes in the medullary region, leave the thymus via lymphatics and blood vessels and are distributed throughout the body

- Blood flow through the thymus

  Vessels enter and leave through the outer capsule and run through connective tissue septa. The large vessels through larger trabeculae, which branch into smaller vessels that run within smaller connective tissue septa of the organ. Mature thymocytes can enter the blood via vessels that resemble the high endothelial venules of the lymph node.
Small arteries enter the thymus through the outer capsule and penetrate into the thymus and bifurcate within the connective tissue septa between the lobules.

- Endothelial cells = tight junctions that are surrounded by a region of connective tissue that is then ensheathed in endothelioreticular cells = these layers (but mostly the endothelioreticular cells) = blood-thymus barrier.

- Therefore, maturing thymocytes are not exposed to just any molecules that might be circulating in the blood:
  - The stromal cells provide a microenvironment that protects them from exposure to foreign antigens as well as providing the conditions for their maturation and selection.

**Spleen**

- **Blood Flow**
  - Spleen = major lymphoid organ that serves multiple purposes including its role in adaptive immunity.
  - Has an open blood circulation through porous splenic sinuses (very different than a lymph node or the thymus).
  - **Splenic artery** (blood to spleen) → **central arterioles** (run deeper into pulp of spleen, they become lined with discontinuous endothelial cells with gaps so large, that platelets, RBCs, and leukocytes can leave the vessels and enter the sinuses that have loosely packed arrangement of cells (primarily various leukocytes).
  - **Splenic vein** (drains blood)
  - Bulk of the lymphoid tissue = arranged as a sheath around the central arterioles = PeriArteriolar Lymphoid Sheath (PALS).
Germinal centers are arranged within these lymphoid sheaths
Blood flows through loosely-arranged channels/sinuses that constitute collectively the red pulp (the more organized lymphoid tissue = white pulp)
Like the lymph node = has a network of loosely-arranged reticular fibers that extend through it (primarily in the red pulp)

- Contains a large number of MO involved in
  - Removing senescent red cells and platelets
  - Recycling iron
  - Remove debris and potentially bacteria they encounter (as do the MO in the liver)
  - Found in both the red and white pulp

**MUCOSAL-ASSOCIATED LYMPHOID TISSUE (MALT)**
- Digestive tract and respiratory system = prime target for bacterial infection, therefore a large portion of the mass of your total lymphoid system = associated with mucosal protection
  - Form = unencapsulated collections of lymphoid cells and their associated support cells and MO
    - Tonsils (palatine, lingual, pharyngeal (adenoids))
    - Esophageal nodules
    - Appendix
    - Bronchial nodules
    - Large number of aggregations in the intestine (usually increasing in size and abundance along length of intestine until the colon), there are very abundant multiple groups of nodules, both in the mucosa and submucosa = Peyer’s Patches
  - Within the MALT a full repertoire of immune responses can occur
    - M-cells = found in the small intestine and respiratory tract, they are special surface epithelial cells that deliver antigen to underlying lymphoid
    - Lymphocytes within MALT can enter the lymph and general circulation and populate other regions of the body
  - Antibodies (IgA particularly) are secreted across mucosal epithelia via unique receptors (also secreted into bile)
    - Therefore, activated B-cells exposed to a specific antigen in the lymphoid MALT follicle can enter the lymph → undergo mitotic expansion in mesenteric lymph nodes → flow to the thoracic duct → enter the blood → pass into the underlying connective tissue along any region of the entire intestine where they complete maturation to = antibody secreting plasma cells
      - Therefore, a specific IgA may be moved across the mucosal layer of the intestine along its entire length after an adaptive immune response in one area
M-cells take antigens from outside a mucosal epithelial layer and deliver them to underlying lymphoid tissue beneath. In this way, foreign antigens in the lumen of the gut, or inhaled in airways can elicit an adaptive immune response.