Lymphoid System Lecture Objectives

- Describe the function, components, and circulation of lymph.
- Describe the following features of lymphoid organs:
  - Function of each organ
  - Classification as primary or secondary
  - Histologic regions and structures that are characteristic of each organ
  - Location of B and T lymphocytes within each organ
  - Composition of the stroma

Lymphoid System Lecture Outline

- Introduction
- Primary lymphoid organs
  - Bone marrow
  - Thymus
- Secondary lymphoid organs
  - Lymph nodes
  - Spleen
  - MALT

Function of the Lymphoid System

- The main purpose of the lymphoid system is to detect and inactivate foreign substances, such as:
  - Invading microorganisms
  - Cells of transplanted organs
  - Foreign materials (like pollen)
  - Cancer cells
- Lymph also brings nutrients from blood vessels to cells and picks up waste products.

Lymph (Lymphatic Fluid)

- Formed when interstitial fluid seeps into lymphatic vessels. Also contains lymphocytes, proteins, and sometimes bacteria or metastatic tumor cells.
- Composition varies in different body regions. Usually lymph is clear, but lymph draining the gut (called “chyle”) is milky and contains a lot of triglycerides.
- Lymphatic vessels eventually merge together and empty into the blood circulation via the thoracic duct and right lymphatic duct.
Stroma of Lymphoid Organs

- The stroma of all lymphoid organs except the thymus is composed of reticulin fibers.
- The stroma of the thymus is composed of cell processes of epithelial reticular cells.

Cells of the Lymphoid System

- Lymphocytes
  - B lymphocytes
  - T lymphocytes
  - Natural killer (NK) cells
- All lymphocytes have surface receptors that recognize infected cells.

All lymphocytes look the same!*

- You can't reliably tell the type of lymphocyte by looking under a microscope.
- You have to use a technique called flow cytometry to look for markers (molecules) on the surface of the cells.
- B cells, T cells and NK cells have different markers on their cell surfaces.

* Pretty much. Sometimes T cells and NK cells are bigger and have little granules in the cytoplasm.

More Cells of the Lymphoid System

- Antigen-presenting cells:
  - Macrophages
  - Dendritic cells
- Other blood cells:
  - Mast cells
  - Neutrophils
  - Monocytes
  - Eosinophils
There are two main ways lymphocytes fight intruders (like bugs): humoral and cellular immunity.

**Humoral immunity**
- B cells turn into plasma cells, which make antibodies. Antibodies coat and eliminate bugs.

**Cellular immunity**
- T cells turn into cytotoxic T cells (which kill cells infected with bugs) and helper T cells (which help other cells do their jobs).

There are two primary lymphoid organs:
- **Bone marrow**
  - All lymphocytes arise in the bone marrow. B cells and NK cells mature in the bone marrow.
  - **Thymus**
    - T cells mature here.

**B lymphocytes and natural killer cells are formed and mature in bone marrow.** They then leave bone marrow, populate secondary lymphoid organs, and recirculate through blood, epithelia, and connective tissue.

**Immature T-cell precursors originate in the bone marrow.** They then leave bone marrow and travel through blood to the thymus. They finish maturing in the thymus and leave as CD4+ and CD8+ cells (this will make more sense next year!).

**Primary (Central) Lymphoid Organs**

**What do B cells do in primary and secondary lymphoid organs?**
- B lymphocytes and natural killer cells are formed and mature in bone marrow.
- They then leave bone marrow, populate secondary lymphoid organs, and recirculate through blood, epithelia, and connective tissue.

**What do T cells do in primary and secondary lymphoid organs?**
- Immature T-cell precursors originate in the bone marrow.
- They then leave bone marrow and travel through blood to the thymus.
- They finish maturing in the thymus and leave as CD4+ and CD8+ cells (this will make more sense next year!).
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Thymus

- Located in mediastinum
- Thymus consists of lobes, capsule, and septa. Septa incompletely divide the lobes into numerous lobules.
- Lobules have 2 regions:
  - Cortex is peripheral and darker staining.
  - Medulla is central and lighter staining.
Cells of the Thymus

T cells (thymocytes)
- T cells in the cortex are in various stages of differentiation.
- T cells in the medulla are mature.

Thymic epithelial reticular cells
- Present in both the cortex and medulla.
- Abundant cytoplasm, large lightly-staining nuclei and long cytoplasmic processes attached to processes of adjacent cells by desmosomes.
Hassel corpuscle (closely-packed, concentric reticular cells)

Thymus, high power: post-capillary venule

T Cells in the Cortex

• T cell precursors from the bone marrow enter the thymus in the subcapsular region.
• In the outer cortex, T cells undergo active proliferation.
• In the deeper cortex, T cells undergo "selection." If they can't bind well enough to cell receptors, or if they bind too well to "self" cells, they die.
• So: many T cells are produced, but most (97%) die.

T Cells in the Medulla

• The remaining T cells survive and migrate to the medulla.
• Cells in the medulla include mature T cells and epithelial reticular cells.
• Hassall's corpuscles are made of degenerating epithelial reticular cells and keratin filaments. Found only in medulla. Function unknown.

T Cells in the Blood

• Mature T cells leave the thymus and enter the blood.
• Arterioles and capillaries in cortex are surrounded by epithelial reticular cells with tight junctions, forming a blood-thymus barrier which excludes most circulating antigens.
• Thymus has no afferent lymphatics, and does not filter lymph like a lymph node does.

Development and Involution of the Thymus

• The thymus is well-developed before birth.
• The thymus is heaviest at puberty. After puberty, it involutes but never completely disappears.
• In old age, the thymus is composed mainly of connective tissue and fat, but it is still capable of producing lymphocytes.
The thymus in elderly people consists mostly of fat and connective tissue.

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Secondary (Peripheral) Lymphoid Organs

Secondary lymphoid organs trap antigens and initiate immune responses. Lymphoid cells can undergo further maturation here too. There are three secondary lymphoid organs:
- Lymph nodes
- Spleen
- Mucosa-associated lymphoid tissue (MALT)

Secondary (Peripheral) Lymphoid Organs

- Secondary lymphoid organs consist of lymphoid follicles and diffuse lymphoid tissue in different architectural arrangements.
- Main function: trap antigens and present them to circulating lymphocytes.
- Specific functions:
  - Lymph nodes: filter lymph
  - Spleen: filters blood
  - MALT: filters antigens that attempt to cross mucosal surfaces

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Lymph Node Architecture

- Outer cortex contains round structures called lymphoid follicles (composed of B cells)
- Paracortex (inner cortex) contains T cells and high endothelial venules
- Medulla composed of cords (containing B cells and macrophages) and sinuses (containing reticular fibers, lymph, circulating cells and antigens)

Lymph Node Follicles

- Primary (unstimulated) follicles are composed of small, dark, mature lymphocytes.
- Secondary (stimulated) follicles are composed of:
  - Germinal center: a lighter-staining central area containing larger lymphocytes
  - Mantle zone: around germinal center; contains small, dark lymphocytes
Secondary follicle with germinal center and mantle zone

B cells are in follicles; T cells are in interfollicular areas

Lymph node: medulla

Lymph node: medulla

Medullary cords contain B cells, plasma cells and macrophages

Medullary sinuses contain reticular fibers, lymph, circulating cells and antigens

Medullary cord with tons of plasma cells (arrows)

Medullary sinus with macrophages (1), reticular cells (2) and trabeculae (3)
**Lymph Node Stroma**

- The capsule and trabeculae consist of dense irregular connective tissue.
- The fine stroma consists of reticular connective tissue (fibroblasts and reticular fibers).

**Afferent and Efferent Lymphatic Vessels**

**Afferent lymphatic vessels**
- Penetrate the capsule of the lymph node on the convex side.
- Carry lymph (with antigen and cells) from sites of infection back to the lymph nodes.

**Efferent lymphatic vessels**
- Leave through the hilum.
- Carry lymph (with lymphocytes) from the lymph node and return them to the blood.

**The Hilum**

- The hilum is a depression in the concave surface of the lymph node.
- Arteries and nerves enter at the hilum.
- Veins and efferent lymphatics leave at the hilum.

**How does lymph flow through the node?**

- Afferent lymphatics bring lymph.
- Subcapsular sinus
- Intermediate sinus
- Medullary sinus
- Efferent lymphatics take it away
- Dump lymph into larger lymphatics, then into blood.
High Endothelial Venules

- High-endothelial venules (venules with tall endothelial cells) in paracortex allow lymphocytes in blood vessels to adhere to endothelial cells and migrate across the vessel wall to the lymphoid tissue.
- Lymphocytes move from blood circulation to lymphatic circulation via high-endothelial venules.

Flow of lymphocytes from blood to lymph in lymph node

- Lymphocytes enter the lymph node in arterial vessels in the hilum, travel through arterioles and capillaries to high-endothelial venules in paracortex.
- Lymphocytes squeeze between endothelial cells of high-endothelial venules and enter lymphatic circulation in the cortex of the lymph node.
- Lymphocytes leave the node via efferent lymphatic vessels in the hilum.

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Functions of the Spleen

- Immunologic filtration of blood (trapping of antigens)
- Activation and proliferation of lymphocytes
- Removal of old red cells, platelets and debris (by macrophages)
Structure of the Spleen

- The parenchyma of spleen is called splenic pulp and consists of white pulp and red pulp.
- No cortex or medulla are present.
- Stroma consists of capsule, trabeculae, and reticular connective tissue.
- Hilum contains nerves, arteries and veins.

White Pulp of the Spleen

White pulp consists of:
- Periarteriolar lymphatic sheaths (PALS)
  - Circular collections of T cells around arterioles
- Splenic follicles (nodules)
  - Just like secondary follicles in lymph nodes, except with one more layer: the marginal zone
  - Composed of B cells
  - Usually have arteriole at periphery
Spleen: cute follicle

Germinal center
Mantle zone
Marginal zone

Arteriole

Spleen: higher power of follicle

Germinal center
Mantle zone
Marginal zone

Spleen: periarteriolar lymphatic sheath (PALS)

Periarteriolar lymphatic sheath
Arteriole

Red Pulp of the Spleen

Splenic sinuses (sinusoids)
- Leaky vessels lined by specialized endothelial cells ("stave cells") and surrounded by rings of reticular fibers like hoops on a barrel
- Healthy red cells easily squeeze through!
- Old or damaged red cells get stuck

Splenic cords (cords of Billroth)
- Located between sinuses
- Contain red cells, granulocytes, lymphocytes, macrophages, platelets, and plasma cells

Open and closed circulation

Sinusoid
Splenic cord
Open circulation

Closed circulation
Sinusoid
Reticular fibers

Splenic sinusoids, cords and macrophages
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Mucosa-Associated Lymphoid Tissue (MALT)

- Lymphoid tissue in mucosa and submucosa of digestive, respiratory, reproductive and urinary systems.
- Examples: tonsils, Peyer’s patches (ileum), lymphoid tissue in oral mucosa.
• Tonsils are aggregates of lymphoid follicles beneath the epithelium of the posterior oral cavity and nasopharynx.
  • Three tonsils:
    • Pharyngeal
    • Palatine
    • Lingual

Three Types of Tonsils

• Pharyngeal
• Palatine
• Lingual

Three Types of Tonsils

• Pharyngeal
  • One tonsil in midline of nasopharynx
  • Surface epithelium: pseudostratified ciliated columnar (sometimes with areas of stratified squamous)
  • Surface has gentle folds but no crypts
  • Thin partial capsule along deep portion

Three Types of Tonsils

• Pharyngeal
• Palatine
  • Two tonsils in lateral oropharynx
  • Surface epithelium: stratified squamous
  • 10-20 deep invaginations (crypts)
  • Thick partial capsule along deep portion

Palatine tonsil: super low power view
Palatine tonsil: stratified squamous epithelium

Palatine tonsil: lymphoid follicles

Palatine tonsil: crypt

Palatine tonsil: sequestered crypt

Palatine tonsil: lymphocytes traversing epithelium

Three Types of Tonsils

- Pharyngeal
- Palatine
- Lingual
  - Numerous small tonsils at base of tongue
  - Surface epithelium: stratified squamous
  - Each tonsil has one short crypt
  - No capsule
  - Closely associated skeletal muscle and mucous salivary glands
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