Physiology of Immune System

Lect 1: Organization of Immune System (Organ, Cell)
Lect 2: Innate Immunity, antigen, antibody
Lect 3: Adaptive Immunity
Lect 4: Inflammation in Organ Systems
Components of Immune System

- Cells: White blood cells, macrophage

- The cells of the immune system originate in the bone marrow (ไขกระดูก), where many of them also mature

- The cells of the immune system then migrate to
  - guard the peripheral tissues
  - circulate in the blood
  - circulate in a specialized system of vessels called the lymphatic system

- Organ: Lymph node, spleen, thymus, lymphatic vessels, mucosal lymphoid tissue
All cellular elements of blood, including RBC, WBC, platelets derive from the same progenitor or precursor cells – the **hematopoietic stem cells** in the bone marrow

These stem cells can give rise to all of the different types of blood cells → pluripotent hematopoietic stem cells

Pluripotent hematopoietic stem cells can give rise to another level of progenitor cells

- 1. RBC progenitor (erythroblast)
- 2. platelet progenitor (megakaryocyte)
- 3. myeloid progenitor
- 4. lymphoid progenitor
Cells from Lymphoid Progenitor

- Lymphoid progenitor cells
  - Differentiate in thymus
  - T lymphocyte, naïve
    - Effector T lymphocytes with variety of functions
      - CD4+ - helper T cells
        » Th1 lymphocyte
        » Th2 lymphocyte
      - CD8+ - cytotoxic T cells

→ = differentiation
Cells from Lymphoid Progenitor

- Lymphoid progenitor cells
  - Differentiate in bone marrow
    - B lymphocyte
      - final differentiation to antibody-secreting plasma cells
  - Differentiate in bone marrow
    - Natural killer lymphocyte or NK cell
      - = differentiation
Lymphocyte Development

- Bone marrow
  - Lymphoid stem cell
  - B cell
  - T cell

Blood, lymph, and lymphoid tissues (lymph nodes, spleen, and others)
Lymphocytes

TEM
Lymphocyte

- Lymphocyte is important to develop a specific immune response against virtually any foreign antigen.
- Each individual lymphocyte matures bearing a unique variant of a prototype antigen receptor.
- The population of T and B lymphocytes collectively bear a huge repertoire of receptors that are highly diverse in their antigen-binding sites.
- The B-cell antigen receptor is a membrane-bound form of the antibody.
- After activation, B cell will secrete antibody (Ab) as known as immunoglobulin (Ig) and differentiate to plasma cells.
- The T-cell antigen receptor can detect antigens derived from foreign proteins or pathogens that have entered into host cells.
Antigen and Antigen Determinants

- Antigen = any foreign molecule that is specifically recognized by lymphocytes and elicit a response from them
- Most antigens are large molecules, either protein or polysaccharides
- A lymphocyte actually recognizes and binds to just a small, accessible portion of an antigen, called an epitope or antigen determinant
- A single antigen usually has several different epitopes
- Antibody, which is secreted by B lymphocytes, likewise binds to specific epitope
Antigen and Antigen Determinants

The diagram represents the interaction between antigens and antibodies. The antigen has multiple binding sites for different antibodies (Antibody A, Antibody B, and Antibody C). The epitopes (antigenic determinants) are indicated on the right side of the diagram.
Antigen Receptors on Lymphocyte

(a) A B cell receptor consists of two identical heavy chains and two identical light chains linked by several disulfide bridges.

(b) A T cell receptor consists of one α chain and one β chain linked by a disulfide bridge.
Antigen Receptors on Lymphocyte

- A single B or T cell bears about 100,000 of these antigen receptors, and all the receptors on a single cell are identical—that is, they all recognize the same epitope.

- Each lymphocyte displays specificity for a particular epitope on an antigen and defends against that antigen or a small set of closely related antigens.

- Secreted antibodies, or immunoglobulins, are structurally similar to B cell receptors, but they lack the transmembrane regions that anchor receptors in the plasma membrane.
Cells from Myeloid Progenitor

- Myeloid progenitor cells
  - granulocytes (granules in their cytoplasm with staining) or polymorphonuclear leukocytes
    - Composed of neutrophil, eosinophil, basophil
  - mast cell
  - dendritic cells (immature → mature)
  - monocyte in circulation → macrophage in tissue
Cells from Myeloid Progenitor

- tissue-resident phagocytic cells
- differentiation from monocyte, once entering tissue
- critical part in innate immunity

- immature cells travel via blood to enter peripheral tissues, where they ingest antigens
- phagocytic and micropinocytic
- then they mature and migrate to lymphoid tissue, where they activate antigen-specific T lymphocytes

- are the most numerous and most important cellular component of the innate immune response
- circulate in the blood and enter the tissues when recruited to sites of inflammation
- important for phagocytosing bacteria
### Cells from Myeloid Progenitor

<table>
<thead>
<tr>
<th>Cell</th>
<th>Activated function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eosinophil</td>
<td>Killing of antibody-coated parasites</td>
</tr>
<tr>
<td>Basophil</td>
<td>Unknown</td>
</tr>
<tr>
<td>Mast cell</td>
<td>Release of granules containing histamine and other active agents</td>
</tr>
</tbody>
</table>

- circulate in the blood and enter the tissues when recruited to sites of allergic inflammation
- important in defending against parasites
- circulate in the blood and enter the tissues when recruited to sites of allergic inflammation
- important in defending against parasites
- arise from precursors but complete their maturation in tissues
- source of histamine
- important in allergic responses
Macrophage in Various Tissues
Mast Cells in Skin
Lymphoid Organs

- Primary (central) lymphoid organs, where lymphocytes are generated and develop
  - Thymus (a large organ in upper chest) for T lymphocyte
  - Bone marrow for B lymphocyte and NK cells

- Secondary (peripheral) lymphoid organs, where adaptive immune responses are initiated and where lymphocytes are maintained
  - Lymph nodes, spleen, mucosal lymphoid tissues
1. Interstitial fluid bathing the tissues, along with the white blood cells in it, continually enters lymphatic capillaries.

2. Fluid inside the lymphatic capillaries, called lymph, flows through lymphatic vessels throughout the body.

3. Within lymph nodes, microbes and foreign particles present in the circulating lymph encounter macrophages, dendritic cells, and lymphocytes, which carry out various defensive actions.

4. Lymphatic vessels return lymph to the blood via two large ducts that drain into veins near the shoulders.
Lymph Nodes

- The lymph nodes are located at the points of convergence of lymphatic vessels.
- *Lymph* is extracellular fluid from the tissues produced continuously by filtration from the blood.
- *Lymph* carries antigen to the lymph nodes and recirculating lymphocytes from the lymph nodes back into the blood.
- Lymphatic vessels collect lymph from the tissues through the lymph nodes and into the thoracic ducts, which empties into the left subclavian vein.
Organization of Lymph Node

- Afferent lymphatic vessels drain fluid from the tissues and carry antigen-bearing cells (*macrophage and dendritic cells*) and antigens from inflamed tissues to the lymph nodes.

- Cortex – outer cortex: lymphoid follicles
  - Deeper cortex: paracortical areas (T cell, dendritic cells)

- In the lymph nodes, B lymphocytes are localized in follicles including germinal centers, where B cells are undergoing intense proliferation after encountering their specific antigen and their cooperating T cells.

- T cells are more diffusely distributed in surrounding paracortical areas, T-cell zones.
Organization of Lymph Node

- Lymph leaves by the efferent lymphatic in the medulla
- The medulla consists of strings of macrophages and antibody-secreting plasma cells known as the medullary cords
- Naïve lymphocytes enter the node from the bloodstream through specialized postcapillary venules or High Endothelial Venules (HEVs) and leave with the lymph through the efferent lymphatic
Antigen and Lymphocytes

- Antigen and lymphocytes eventually encounter each other in the peripheral lymphoid organs.
- Lymphocytes are continually recirculating through these tissues, to which antigen is also carried from sites of inflammation, primarily within macrophages and dendritic cells.
- Within the lymphoid organs, specialized cells such as mature dendritic cells display the antigen to lymphocytes.
Dendritic cell: Professional Antigen Presenting Cells
Tracing Dendritic Cell Migration
Afferent Lymphatic Vessels
Cell Trafficking: Into and Out of Lymph Nodes
Cell Trafficking: Into and Out of Lymph Nodes

- Most lymphocytes migrating to lymph nodes enter from the peripheral blood.
- Only lymphocytes can interact with and extravasate through high endothelial venules (HEVs) to migrate into the lymph node.
- Most dendritic cells (DCs) enter lymph nodes through the afferent lymphatics and accumulate in the vicinity of HEV.
High Endothelial Venules (HEV)

- HEVs are postcapillary venules
- Located mainly in the T-cell zones, paracortical areas of lymph nodes
- Composed of prominent vascular sheath, thick basal lamina, and a layer of tall endothelial cells
**High Endothelial Venules (HEV)**

<table>
<thead>
<tr>
<th></th>
<th>Normal venule</th>
<th>Peripheral lymph-node HEV</th>
<th>Peyer’s-patch HEV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endothelium</strong></td>
<td>Flat</td>
<td>Tall and plump</td>
<td>Tall and plump</td>
</tr>
<tr>
<td><strong>Basal lamina</strong></td>
<td>Thin</td>
<td>Thick</td>
<td>Thick</td>
</tr>
<tr>
<td><strong>Perivascular sheath</strong></td>
<td>Scanty</td>
<td>Prominent</td>
<td>Prominent</td>
</tr>
<tr>
<td><strong>CD31</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>ICAM2</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>ICAM1</strong></td>
<td>−/+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td><strong>VE-cadherin</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Sialomucins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Core protein</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>PNAD epitope</td>
<td>−</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Sulphation</td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>MADCAM1</strong></td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td><strong>Chemokines</strong></td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>(CCL19, CCL21, CXCL12 and CXCL13)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CCL, CC-chemokine ligand; CXCL, CXC-chemokine ligand; VE, vascular endothelial.*
Lymphocytes Circulate between Blood and Lymph
Lymphocytes Circulate between Blood and Lymph

- **Naïve lymphocytes** are lymphocytes which have not yet encountered antigen.
- Naïve lymphocytes circulate continually from the blood into the peripheral lymphoid tissues, which they enter by squeezing between the endothelial cells of postcapillary venule.
- They then return to the blood via the lymphatic vessels.
- In the event of infection, lymphocytes that recognize the antigens stay in the lymphoid tissue, where they proliferate and differentiate into the **effector cells** capable of combating the infection and boosting immune response.
Lymphocytes Circulate between Blood and Lymph

- When an infection occurs or an exposure to antigen occurs in the periphery
  - large amounts of antigen are taken up by dendritic cells in the periphery
  - dendritic cells travel through the afferent lymphatic vessels into the draining lymph nodes
  - in lymph nodes, dendritic cells display the antigen to recirculating T lymphocytes and activate naïve T lymphocytes into effector T lymphocytes
  - B cells are also activated by activated T lymphocytes (some of effector T lymphocytes)
  - Activated antigen-specific lymphocytes have been in a period of proliferation and differentiation
  - Activated antigen-specific lymphocytes leave the lymph nodes through the efferent lymphatic vessels
Lymphocytes Circulate between Blood and Lymph

- These processes are involved in initiating adaptive immune response
- With the proliferation of B cell follicles to form germinal centers, the entire lymph node enlarges, a phenomenon familiarly known as swollen glands
Mucosal-associated Lymphoid Tissues

- Gut-associated lymphoid tissue (GALT): tonsil, adenoid, appendix, Peyer’s patch in small intestine
- In Peyer's patches, the antigen is collected by specialized epithelial cells called multi-fenestrated or M cells
- Bronchial-associated lymphoid tissue (BALT) is composed of diffuse aggregates of lymphocytes beneath the respiratory epithelium
Mucosal Immune System

Inductive sites
- Antigen
- Epithelial cell
- NALT
- M cell
- Peyer's patches
- Conventional lymph nodes
- Mesenteric lymph nodes
- Thoracic duct
- Blood circulation

Effector sites
- Secretory IgA
- Polymorphic Ig receptor
- Dimeric IgA
- Plasma cell
- CD4+ T cell
- IL-6

TOR
- Peptide-MHC
- B cell
- CD4+ T cell

Blood circulation