Cells and Organs of the Immune System

Jeffrey K. Actor, Ph.D.
Pathology and Laboratory Medicine
The University of Texas-Houston Medical School
Lecture Objectives:

• Identify cell types involved in the innate and adaptive immune response.

• Understand structure and function of primary and secondary lymphoid organs.
• Immune System cells are derived from pluripotent hematopoietic stem cells in the bone marrow.
Maturation of Granular Leukocytes

- Eosinophils
- Neutrophils
- Basophils

Histology Lab Part 11: Slide 12

- Myeloblast
- Promyelocyte
- Myelocyte
- Metamyelocyte
- Stab Cell
Nomenclature of Immune Cells

Location, Location, Location

Leukocytes

- Granulocytes
  - "Polymorphs"
    - Neutrophil
    - Eosinophil
    - Basophil

Mononuclear Cells

- Lymphocytes
  - Phagocyte

- Monocyte

Tissue

- Tissue eosinophil
- Mast cell
- Macrophage (histiocyte)
- T Lymphocyte
- Plasma cell
- Natural killer cell
- Dendritic cell
Leukocytes

White blood cells that provide either innate or specific adaptive immunity.

**Myeloid Cells:** First line of defense, non-specific *innate* immunity
- Neutrophils
- Eosinophils
- Basophils/Mast cells
- Monocytes/Macrophages/Dendritic Cells

**Lymphoid Cells:** *non-specific* immunity
- Natural Killer Cells

**Lymphoid Cells:** Humoral and Cell Mediated *specific* immunity
- B Lymphocytes
- T Lymphocytes (Helper and Cytolytic)
# Leukocytes: Myeloid

| Myeloid Leukocytes and Their Properties |  |
|----------------------------------------|--|---|
| **Phenotype** | **Morphology** | **Circulating Differential Count** | **Effector Function** |
| Neutrophil | PMN granulocyte PMN | 2-7.5x10⁹/L | Phagocytosis and digestion of microbes |
| Eosinophil | PMN granulocyte PMN | 0.04-0.44x10⁹/L | Immediate hypersensitivity (allergic) reactions; defense against helminths |
| Basophil | PMN granulocyte PMN | 0-0.1x10⁹/L | Immediate hypersensitivity (allergic) reactions |
| Mast Cell Monocytes | granulocyte monocytic | Tissue Specific | Circulating macrophage precursor |
| Macrophage Dendritic Cell | monocytic | Tissue Specific | Phagocytosis and digestion of microbes; antigen presentation to T cells |

* Normal range for 95% of population, +/- 2 standard deviations
Neutrophils

- Neutrophils are produced in the bone marrow from myeloblast-type stem cells
  - often called polymorphonuclear cells (PMN's).

- **The neutrophil's main role is in inflammation.**
  - First to arrive at inflammation site
  - Leave blood/endothelium into tissue (extravasation).

- Neutrophils are attracted into the tissue by chemotactic factors stimulated by tissue damage
  - complement proteins, clotting proteins and T cell derived cytokines.
Neutrophils

• In the tissues, **neutrophils are active phagocytes**.
  – They destroy ingested microorganisms via oxygen dependent or independent pathways.

• Produce **myeloperoxidases** to assist oxidated antimicrobial effects.

• Produce **lactoferrin and lysozyme** as direct antimicrobial agents.

• Produce **leukotrienes and prostaglandins**, products of the lipoxygenase and cyclo-oxygenase pathways, to mediate vascular functions.

Deficiencies in pathways increase susceptibility to infections
Eosinophil

- Granulocytes stain intensely with 'eosin’; bilobed nucleus.
- Contain basic crystal granules in cytoplasm to mediate toxic reactions to large parasites.
- Involved in asthma.
- Eosinophils are motile, sometimes phagocytic, and are particularly active in parasitic infection.
Basophil

- Found in low numbers in the **blood**. Act like mast cells.
- Involved in Type I hypersensitivity responses.
  - Have high affinity Fc receptors for IgE on their surface.
    Cross-linking of the IgE causes the basophils to release **pharmacologically active mediators** (histamine, prostaglandins, leukotrienes).
Mast Cells

- Formed in tissue from undifferentiated bone marrow precursors.
- Similar **importance in allergic reactions** as basophils, but only found in tissues.
- Contain granules with preformed mediators to be released after stimulation
  - histamine, prostaglandins
  - leukotrienes
- Stimulation of mast cells occurs by the **anaphylatoxins** (complement proteins C3a and C5a) or by **cross-linking of surface immunoglobulin (IgE)**.
Cells of the Reticuloendothelial System

The “phagocytic system” of the body, including fixed macrophages of tissues. ...rather old fashioned term...

Cells of the RES provide natural immunity against microorganisms.

- Phagocytosis and intracellular killing
- Cell Recruitment via molecular mediators
- Presentation of peptide antigens to lymphocytes

Cells of the RES include:

- circulating monocytes
- resident macrophages in the liver, spleen, lymph nodes, thymus, submucosal tissues of the respiratory and alimentary tracts, bone marrow, and connective tissues
- macrophage-like cells including dendritic cells in lymph nodes, Langerhans cells in skin, and glial cells in the central nervous system.
Monocytes/Macrophages

- Circulate in the blood after leaving the bone marrow.
- Survive only a day or so before they enter the tissue to mature into macrophages.
- Involved in **phagocytosis** and **intracellular killing of microorganisms**.
  - Generation of toxic metabolites through **respiratory burst**.
  - Production of **nitric oxide, hydrogen peroxide, superoxide anion**.

- Monocytes/Macrophages are **antigen processing and presenting cells**.
  - Degrative enzymes in lysosomal granules.
  - Chew ingested proteins.
  - Present to adaptive cells.
Macrophages

• When monocytes enter the tissues and become macrophages:
  – Enlarge and increase production of intracellular lysozymes
  – Greater phagocytosis.
  – Can live for years in tissue; highly motile.

• Activation of these cells occurs by phagocytosis of antigens, or in response to T cell derived cytokines.

• Activated macrophages recognize and remove unwanted particulate matter including products of inflammation and invading organisms, antigens and toxins.
Macrophages

- After activation, these cells secrete cytokines, chemokines, lysosomes and other factors to upregulate immune response. In chronic inflammation, macrophage scavengers can become “giant cells” or “foamy macrophages”.
Dendritic Cells

- Specialized phagocytic cells.
- Found in most tissues.
- Abundant at interfaces between the external and internal environments (skin, lining of the gastrointestinal tract), where they encounter invading pathogens.
- Actively motile; continuously sample surroundings by endocytic processes.

- Dendritic cells are very efficient at activation of T cells.
- Can dictate T cell development to control responses to antigens.
# Lymphoid Leukocytes

## Lymphoid Leukocytes and Their Properties

<table>
<thead>
<tr>
<th>Total Lymphocytes</th>
<th>1.3-3.5x10⁹/L</th>
<th>Effector Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>B Cell</td>
<td>monocytic</td>
<td>Adaptive</td>
</tr>
<tr>
<td>Plasma Cell</td>
<td>monocytic</td>
<td>Adaptive</td>
</tr>
<tr>
<td>T Cell</td>
<td>monocytic</td>
<td>Adaptive</td>
</tr>
<tr>
<td>Natural Killer Cell</td>
<td>monocytic</td>
<td>Innate</td>
</tr>
</tbody>
</table>

- **B Cell**: Adaptive immunity, plasma cell, monocytic, terminally differentiated, antibody secreting B cell
- **Plasma Cell**: Adaptive immunity, monocytic
- **T Cell**: Adaptive immunity, monocytic
- **Natural Killer Cell**: Innate immunity, monocytic

**“Odd man out”**
Natural Killer Cells

- Functionally **cytotoxic** representing an innate population that kill viral infected or tumor target cells.

- Killing is **nonspecific** - they do not need to recognize foreign antigens presented on the target cell.
  - NK cells do not have a specific cell receptor. Target recognition occurs by a Killer Inhibitory Receptor, KIR, which is lacking on infected and tumor targets.

- Kill targets by releasing **perforin** which damages target cell membranes. Can also **induce apoptosis** in the target.

- Do not confuse NK cells with NK T cells.
Specificity and Antigenic Recognition

- B and T cells.

- Splenic Germinal center indicating active B-lymphocytes.
- Helper T-cells mingle with plasma cells at rim of the nodule.
- Note periarterial sheath surrounding central arteriole.
B Lymphocytes

- Develop from stem cells in the bone marrow.
- **Produce antibodies** with specificity for antigens.
- **Plasma cells** = Activated B cells.

- Upon activation, a B cell can switch to produce a different class of antibody, with the same antigen specificity.
Activation of B Lymphocytes

- Activation into antibody secreting cells is antigen-dependent.
- Antigen binding to surface Ig molecules triggers differentiation into plasma cells.
- B cells are the most efficient presenting cell in the body.
- Interaction with T cell secreted factors triggers isotype (class) switching.
Terminology: Cluster Of Differentiation (CD)

- Unique cell surface molecules.
- Molecules given number designations.
- The acronym CD describes the cluster of unique determinant; the number describes the order in which it was discovered.
- As of March, 2010, the list of determinants was to CD350, with another 13 listed as “provisional”.
  - [http://hcdm.org/MoleculeInformation/tabid/54/Default.aspx](http://hcdm.org/MoleculeInformation/tabid/54/Default.aspx)

CD-specific markers (antibodies) have been useful for:
- Determining the functions of CD proteins.
- Identifying the distribution of CD proteins in different cell populations in normal individuals.
Surface Molecules of B Lymphocytes

- Ig H+L, B cell receptor for antigen.
- Ig α/β, signal transduction molecules.
- HLA-D, class II restricted major histocompatibility marker.
- CR21 and CD35, complement receptors.
- CD19, B-cell co-receptor subunit.
- CD20, CD5, signal transduction molecules.
- CD40, co-stimulatory.
- CD5, co-stimulator-activator.
- CD32, FcγRII.
- CD45, leukocyte common antigen.

Receptors (specificity)
Signal Transducers
Co-stimulators/Activators
T Lymphocytes

- T lymphocytes regulate immune responses.
- Integral in cell mediated immunity.
- Critical in B cell-antibody production.
- Mature T cells display either **CD4** or **CD8**.
More on T Lymphocytes

- Develop in the thymus.
- Cells with a CD4 marker are called **helper T cells** (Th cells).
- CD8 marker positive cells are **cytotoxic T cells** (Tc cells).
- Each T cell has a TCR to recognize antigen:
  - a transmembrane heterodimer composed of two polypeptide chains.
Surface Molecules of T Lymphocytes

- **TCR**, T cell receptor.
- **CD3**, TCR signaling complex.
- **Thy-1**, mouse T cell marker.
- **CD45RO**, Leukocyte common antigen for memory T cells.
- **CD45RA**, Leukocyte common antigen for naive T cells.
- **CD2**, LFA-3 adhesion molecule. CD28, co-stimulatory molecule that binds B7.
- **CD5**, co-stimulatory molecule.
- **CD7**, signal transduction.

**Receptors (specificity)**

**Adhesion**

**Signal Transducers**

**Co-stimulators/Activators**
T Helper Cells

- Different phenotypic populations exist.  
  - $T_{H1}$, $T_{H2}$, $T_{H3}$, $T_{H17}$, $T_{FH}$, Treg,.....
- All express the CD4 molecule.
- Aid effector T lymphocytes in cell-mediated immunity.
- Aid antigen-stimulated subsets of B cells to proliferate and differentiate toward antibody-producing cells.
- Regulatory role.
T Helper Cells: Functional Subclasses

**Cell-Mediated Immunity**
- **Th1**
  - IFNγ
  - LT
  - T-bet
  - IL-4
  - IL-12
  - GATA-3
  - Th2
  - IL-4
  - IL-5
  - IL-13
  - IL-25/IL-17E
  - Humoral Immunity

**Inflammation & Autoimmunity**
- **Th17**
  - IL-17A
  - IL-17F
  - IL-6
  - TNFα
  - IL-22
  - RORγt

**Thp**
- IL-4
- IL-12
- TGFβ
- IL-6
- IFNγ
- Foxp3
- Suppression
- TGFβ

**IL-10**
T Cytotoxic Cells

- T cytotoxic cells (CTLs) are cytotoxic against tumor cells and host cells infected with intracellular pathogens.
- These cells express CD8.
T Suppressor/Regulatory Cells

• Suppress T and B cell responses.
• Misconception: Commonly thought these cells were a subpopulation of CD8+ cytotoxic cells.

• Treg:
  – Sub-population of T Helper cells
    • (CD4+CD25++; Foxp3+)
  – Serve as regulators of T cell responses.
Natural Killer T Cells

- Heterogeneous group of T cells
- Share properties of both T cells and natural killer (NK) cells.
- Recognizes self- and foreign lipids and glycolipids.
- Constitute only 0.2% of peripheral blood T cells
- Have a heavy bias in T cell receptor usage.
- Natural killer T (NKT) cells should not be confused with natural killer (NK) cells.
Antigen Presenting Cells

• APCs are found primarily in the skin, lymph nodes, spleen and thymus.

• Main role is present antigens to antigen sensitive lymphocytes.

• APCs are classified according to their ability to phagocytose antigens, location in the body, and expression of MHC related molecules.
### Antigen Presenting Cells

<table>
<thead>
<tr>
<th>Phagocytosis Type</th>
<th>Location</th>
<th>Class II Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phagocytes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(monocyte/macrophage)</td>
<td>monocytes/macrophages/marginal zone/macrophages/Kupffer cells/microglia</td>
<td>blood/tissue/Spleen/lymph node/liver/brain</td>
</tr>
<tr>
<td>non-phagocytic constitutive antigen-presenting cells</td>
<td>Langerhans' cells/Interdigitating dendritic cells/Follicular dendritic cells</td>
<td>skin/lymphoid tissue/lymphoid tissue</td>
</tr>
<tr>
<td><strong>Lymphocytes</strong></td>
<td>B cells and T cells</td>
<td>Lymphoid tissue, site of immune reaction</td>
</tr>
<tr>
<td><strong>Facultative antigen-presenting cells</strong></td>
<td>astrocytes</td>
<td>brain</td>
</tr>
<tr>
<td></td>
<td>follicular cells</td>
<td>thyroid</td>
</tr>
<tr>
<td></td>
<td>endothelium</td>
<td>vascular and lymphoid tissue</td>
</tr>
<tr>
<td></td>
<td>fibroblasts</td>
<td>connective tissue</td>
</tr>
</tbody>
</table>
Critical Molecules in Antigen Presentation

- **LFA-3/LFA-1**, adhesion molecules.
- **CD28**, co-stimulatory molecule that bind B7-1 or B7-2.
- **ICAM**, intracellular adhesion molecule 1 (needed for migration).
- **MHC**, Major Histocompatibility Complex

**Receptors** (specificity)

**Adhesion**

**Signal Transducers**

**Co-stimulators/Activators**
Primary/Secondary Lymphoid Tissues

- The immune system involves multiple organs, tissues, cell types, and proteins.

- Primary and Secondary Lymphoid Tissues.
Lymphoid Tissue:

• Specialized connective tissue and organs where lymphocytes form the major cellular component.

• Physical location for interaction between leukocytes
  – Myeloid (innate)
  – Lymphoid (specific)

• Contains high numbers of lymphocytes that mediate responses.
  – Cellular immunity (pathogen protection)
  – Humoral immunity (immunoglobulin production)
Primary/Secondary Lymphoid Tissues

Primary:
- Foetal Liver
- Adult Bone Marrow
- Thymus Gland

Secondary:
- Spleen
- Lymph Nodes
- Tonsils
- Appendix
- Peyer’s patches
- Aggregates of cells in lamina propria (GALT, BALT, MALT)
- Bone Marrow

- Bursa of Fabricius (near cloaca)
Primary: Thymus
Primary: Thymus

- Thymocytes are educated to become T lymphocytes.
- Expression of specific receptors.
- T cells learn to recognize self as self.
Cortex – dark
Medula - light

Macrophages

Hassal’s Corpuscles
Secondary: The Spleen

- The spleen is a filter for blood.
- White pulp = lymphoid tissue.
- Red pulp = splenic cord and sinuses (RBCs).
Spleen

- Defense against microorganisms.
- Site of removal of aged or abnormal RBCs/platelets
- Capsule with trabeculae
- Comprised of splenic pulp
  - Red
  - White
- Supported by network of reticular fibers
- Largest lymphoid organ
• The white pulp contains the lymphoid tissue, arranged around a central arteriole as a periarteriolar lymphoid sheath (PALS).
• PALS composed of a Germinal Center surrounded by a Mantle and Marginal Zones.

• Central Artery
• Periarterial Lymphatic Sheath
• Follicle/Germinal Center
• Mantle Zone (B cells)
• Marginal Zone (B and T cells)
- Follicle/Germinal Center
- Periarterial Lymphatic Sheath
- Central Artery
- Mantle Zone (B cells)
- Marginal Zone (B and T cells)
Major Organs of the Immune System (Spleen)

- Marginal zone
- Marginal sinus
- Germinal center
- Periarteriolar lymphoid sheath
- Central arteriole
Secondary: The Lymph Node

- Lymphoid secondary (mostly B cells) follicle
- Trabecula
- Antigen presenting cells
- Afferent lymphatic vessel (arrow indicates flow of lymph and lymphocytes)
- Germinal Center
- Mantle zone
- Medulla
- Paracortex (mostly T cells)
- Primary lymphoid follicle
- Subcapsular sinus
- Medullary sinus
- Efferent lymphatic vessel (arrow indicates flow of lymphocytes)
- Capsule
- Cortex
- Post-capillary venule (arrow indicates flow of lymphocytes)
High Endothelial Venule
Role of Lymphatics

- Terminal Lymphatics are blind-ended, endothelium-lined tubes present in most tissues in similar numbers to capillaries. Lymphatics drain into collecting Lymph Nodes.
- In acute inflammation, the lymphatic channels become dilated and drain away fluid (inflammatory exudate); this limits the extent of tissue edema.
- Antigens are carried to the regional lymph nodes for processing by APCs and further recognition by lymphocytes.
Secondary Lymphoid Tissue

Remember: MALT, GALT, BALT (aggregates of cells in the lamina propria of mucosa-, gut- bronchus).
“Mr. Osborne, may I be excused? My brain is full.”
We’re almost finished.....
Clinical Vignette: Congenital Asplenia

Q: How does the lack of spleen effect B cell function, and what are the implications towards immune responses to infective agents?
That's All Folks!
Which cell type is not an antigen presenting cell?

A. Astrocytes  
B. Dendritic cells  
C. Langerhans cells  
D. T lymphocytes  
E. B lymphocytes

Option D (T lymphocytes) is correct. Antigen Presenting Cells (APCs) are found primarily in the skin, lymph nodes, spleen and thymus. They may also be present throughout the diffuse lymphoid system. Their main role is to present antigens to antigen-sensitive lymphoid cells. Facultative antigen presenting cells are those that may be induced to present antigens, and include multiple cell types such as astrocytes in the brain, follicular cells of thyroid and fibroblasts in connective tissue. B lymphocytes are extremely good at presenting antigen, especially after recognition by its specific surface expressed immunoglobulin.
A 7-year old child involved in a car accident developed complications leading to removal of her spleen. Which statement accurately describes the physical characteristics of the spleen?

A. The spleen is a filter for lymph
B. The red pulp contains the lymphoid tissue, arranged around a central arteriole as a periarteriolar lymphoid sheath.
C. Eosinophils cells are found in marginal centers where they present antigen to lymphocytes
D. The periarteriolar lymphoid sheath is composed of a germinal center surrounded by a mantle and marginal zones
E. Hassels corpuscles are located in the medulla

Option D (The periarteriolar lymphoid sheath is composed of a germinal center surrounded by a mantle and marginal zones) is correct. The spleen is a filter for blood that is histologically comprised of red and white pulp. The red pulp is composed of vascular sinusoids containing large numbers of macrophages, and is actively involved in the removal of dying and dead erythrocytes, as well as in the removal of infectious agents. The white pulp contains the lymphoid tissue, arranged around a central arteriole as a periarteriolar lymphoid sheath (PALS). The PALS is composed of T and B cell areas, and follicles containing germinal centers. The germinal centers are where B cells are stimulated to become plasma cells which produce and secrete antibodies.
The appropriate medical care and clinical course of action associated with loss of the spleen in this child includes all except which?

A. Updating immunizations
B. Aggressive antibiotic therapy
C. Vigilant monitoring for bacterial agents
D. Parental education

All answers are correct. Loss of a spleen would be more detrimental to a child than an adult, primarily due to a pre-established immune response (B cells and their ability to produce specific antibodies) to bacterial antigens in the adult. In the adult, pre-existing memory B cells surviving in other tissues (e.g. lymph nodes, GALT, MALT, BALT) may be activated, although the overall response in these adults is typically diminished. In the child, there is less likely to be a preexisting memory population. The lack of splenic lymphoid tissue to process antigen greatly decreases the opportunity for B cell activation and further production of plasma cells and memory B cells. Appropriate medical care involves antibiotic prophylaxis and updating immunizations. Antibiotic prophylaxis is initiated immediately upon the diagnosis because patients are considered immuno-compromised. Patients should receive standard immunizations, with emphasis given to receive conjugated \textit{H. influenzae} type b and pneumococcal vaccines. Asplenic patients are at an increased risk of sepsis, especially from gram-positive organisms.
T Helper Cells
Functional Subclasses

• **T helper 1 (Th1):**
  - Aid in cellular immunity.
  - Characterized by secretion of IL-2 and IFN-γ.

• **T helper 2 (Th2):**
  - Aid B cells to produce certain classes of antibody.
  - Characterized by secretion of IL-4, IL-6, and IL-10.
T Helper Cells
Other T Functional Subclasses

• T helper3 (Th3):
  – Involved in oral tolerance.
  – Provide help for IgA production.
  – Suppressive/regulatory properties for Th1 and Th2
  – Characterized by secretion of IL-4 and TGF-β.

• T helper17 (Th17):
  – Newly identified population.
  – Effector cells for autoimmune disease progression.
  – Characterized by secretion of IL-17.
Cytotoxic T Lymphocytes

CTLs are able to kill target cells directly by inducing apoptosis.

- Preformed perforins are released at the target cell surface which generate transmembrane pores in the target cell, through which granzymes gain entry to the cytosol and induce the apoptotic series of events.

- Apoptotic signaling via membrane-bound molecules can occur via Fas on the target cell surface and Fas ligand on the CTL surface.