Chapter 2. Cells and Organs of the Immune System

Hematopoiesis

- Hematopoiesis - formation and development of WBC and RBC → bone marrow.
- Hematopoietic stem cell - give rise to any blood cells (constant number, self renewing)
  - Yolk sac (2 months) → liver & spleen (3-7 months) → Bone marrow (birth)

Hematopoiesis

- Progenitor commitment depends on the influence of growth factors and cytokines
- In bone marrow stromal cells support the growth and differentiation of hematopoietic cells → direct contact or growth factors.
- Stromal cells – meshwork of fat cells, endothelial cells, fibroblasts & MΦs.
- Hematopoiesis – regulated at the genetic level through several transcription factors (GATA-2, Ikaros, BM11, etc)

Hematopoiesis

- Hematopoiesis maintains steady levels of blood cells
- Regulation:
  - Cytokines produced be bone marrow stromal cells
  - Cytokines produced by non-hematopoietic cells (T cells, MΦs)
  - Regulation of receptors for hematopoietically active cytokines
  - Removal of cells by programmed cell death
Apoptosis

- Programmed cell death
- Changes: shrinking, rearrangement of cytoskeleton, alteration of cell membrane permeability, chromatin condensation, cytoplasm fragmentation

- Difference between apoptosis and necrosis?

### TABLE 2-2 Genes that regulate apoptosis

<table>
<thead>
<tr>
<th>Gene</th>
<th>Function</th>
<th>Role in apoptosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>bcl-2</td>
<td>Prevents apoptosis</td>
<td>Inhibits</td>
</tr>
<tr>
<td>bax</td>
<td>Opposes bcl-2</td>
<td>Promotes</td>
</tr>
<tr>
<td>bcl-X1 (bcl-Long)</td>
<td>Prevents apoptosis</td>
<td>Inhibits</td>
</tr>
<tr>
<td>bcl-X2 (bcl-Short)</td>
<td>Opposes bcl-X1</td>
<td>Promotes</td>
</tr>
<tr>
<td>caspase (several different ones)</td>
<td>Protease</td>
<td>Promotes</td>
</tr>
<tr>
<td>fas</td>
<td>Induces apoptosis</td>
<td>Initiates</td>
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</tbody>
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bcl - B cell lymphoma

Cells of the Immune System

- If heparinized blood is centrifuged, three layers are obtained:
  - Top layer - yellow liquid - plasma
  - Middle layer - white cells (leukocytes)
  - Lowest layer - red cells (erythrocytes)

Separation of blood constituents

If the blood is allowed to clot first, the yellow supernatant is depleted of clotting factors and is referred to as serum.
**Lymphocytes**

- **Three populations:**
  - B cells
  - T cells
  - NK cells
- Naïve lymphocyte $\rightarrow$ Ag exposure $\rightarrow$
  Lymphoblast $\rightarrow$ Effector cells & Memory cells
  - **Effector cells:** Plasma cells, T helper (Th) or T cytotoxic (Tc)

**B Lymphocytes**

- **CD** - cluster of differentiation (unique lymphocyte surface molecules)
- **Surface markers:**
  - Surface Ig (free Ag)
  - MHC-II molecules
  - CD35 (CR1) and CD21 (CR2)
  - CD32 (FcγRII), CD40
  - CD80 (B7-1) and CD86 (B7-2)

**T lymphocytes**

- **T cell receptor (TCR)** – recognizes Ag after processing and presented by major histocompatibility complex (MHC) molecules
- **Surface markers:**
  - TCR (processed Ag + MHC)
  - CD3
  - CD4 or CD8
  - CD28 (interacts with B7 molecules)
T cells

- There are two types of MHC molecule - class I MHC and class II MHC.
- There are two types of T cells: Helper (CD4+) T cells and Cytotoxic (CD8+) T cells.
- CD4+ (Helper) T cells recognize antigen presented on class II MHC. **Role:** Cytokine secretion
- CD8+ (Cytotoxic) T cells recognize antigen presented on class I MHC. **Role:** Cell killing
- Normal ratio: 2:1 (CD4 to CD8)

T cells

- CD4+ (Helper) T cells: Two types based on cytokine production
  - **Th1:** cytokines that support inflammation and activation of T cells and MΦs.
  - **Th2:** cytokines that activate B cells and Ab production.
- CD8+ (Cytotoxic) after activation → Cytotoxic T lymphocyte (CTL).

NK cells

- Lack TCR of T cells or sIg of B cells
- Unique surface markers: CD16 (FcγRIII) and CD56
- Action similar to Tc (CD8+) cells
- **Role:** destroys tumor cells and virus-infected cells
- Recognition due to altered expression of MHC-I and ADCC (Ab-dependent cell cytotoxicity)
- **NK1-T cell:** T cell and NK cell. Expresses TCR, TCR interacts with CD1 (similar to MHC), express CD16, and cell killing.

Leukocytes

(white blood cells)

a) Polymorphonuclear leukocytes
(Polymorphs; Polys; Granulocytes)

b) Mononuclear leukocytes

Granulocytes

Granulocytes consist of:
- **Basophils:** stained by basic dyes
- **Eosinophils:** stained by acidic dyes
- **Neutrophils:** stained by both

The ability to bind basic vs. acidic dyes reflects the charge of the cell, which reflects the molecules present in the cell, which determines the function of the cell. In addition to binding different dyes, these three cell types are functionally different.
The mononuclear leukocytes consist of:

- Macrophage

- Two main functions

<table>
<thead>
<tr>
<th>Cell</th>
<th>Activated function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrophage</td>
<td>Phagocytosis and activation of bactericidal mechanisms</td>
</tr>
<tr>
<td>Macrophage</td>
<td>Antigen presentation</td>
</tr>
</tbody>
</table>

Macrophage (MΦ)
- Monocytes develop in the bone marrow and circulate in blood, becoming macrophages upon entering the tissues – forming the mononuclear phagocyte system.
- Macrophages are long-lived cells.
- Free vs Fixed macrophages

The mononuclear phagocyte system

- Chemotaxis
- Opsonization?
The Respiratory Burst (Oxidative Burst)

- Occurs in activated Macrophages
- Phagocytosis also activates an NADPH oxidase enzyme (cytochrome b558).
- This enzyme is found on the plasma membrane as well as on the membrane of the phagolysosome.
- The NADPH oxidase mediates the following chemical reaction:

$$\text{NADPH} + 2\text{O}_2 \rightarrow 2\text{O}_2^- + \text{NADP}^+ + \text{H}^+$$

The enzyme superoxide dismutase then catalyzes the formation of hydrogen peroxide from the superoxide:

$$2\text{O}_2^- + \text{H}^+ \rightarrow 2\text{H}_2\text{O}_2$$

Macrophages and neutrophils also produce nitrogen compounds that can kill microorganisms. The enzyme iNOS (inducible nitric oxide synthase) generates nitric oxide (NO) which can subsequently be converted into peroxynitrite (ONOO).
Polymorphonuclear leukocytes are also called Granulocytes

They are characterized by having a multilobed nucleus and numerous cytoplasmic granules.

**Granulocytes consist of:**
- Basophils - stained by basic dyes
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The ability to bind basic vs. acidic dyes reflects the charge of the cell, which reflects the molecules present in the cell, which determines the function of the cell. In addition to binding different dyes, these three cell types are functionally different.
**Eosinophils:**
- Somewhat phagocytic; Comprise 1 - 3% of leukocytes
- Thought to be important in defense against invading parasites and worms (helminths)
- Worm infections are often accompanied by eosinophilia.
- Release eosinophilic granules that damage parasites

**Basophils:**
- Comprise <1% of leukocytes
- Non-phagocytic
- Release of pharmacologically active chemicals from granules → allergic reactions

**MAST CELLS:**
- Present mostly in tissues

**Dendritic Cells**
- 4 Types
- Major role: Ag uptake in peripheral sites, and presentation to Th cells in lymph nodes
- Best APC
- Constitutive expression of MHC-II and B7
- Follicular dendritic cells: Unique type of cells, lacks MHC-II but interact with B cells (Ag-Ab complexes)

**Organs of the Immune System**
- **Primary Lymphoid Organs**
  - Bone marrow and Thymus
  - Origen and maturation of lymphocytes
- **Secondary Lymphoid Organs**
  - Lymph nodes, Spleen, Mucosal-associated lymphopid tissues (MALT)
  - Trap antigen for interaction with antigen
Lymphatic System – vessels that collect fluid that escapes the blood and brings it back to the blood

THYMUS
- Site of T cell development and maturation
- Two compartments: CORTEX and MEDULLA
  – CORTEX: Packed with immature T cells (Thymocytes)
  – MEDULLA: Sparsely populated with mature T cells
- Function: Generate populations of T cells with “correct” TCRs
- Only 5% of incoming thymocytes exit the thymus
- DiGeorge’s syndrome (H) and nude mice

LYMPH NODES
- Site for immune responses for antigens in lymph
- Perfect design to encounter antigens
- Three regions: CORTEX, PARACORTEX and MEDULLA
  - CORTEX – Primary follicles containing B cells, MΦ and DC
  - PARACORTEX - T cell area
  - MEDULLA - MΦ and Plasma cells

SPLEEN
- Encounters antigens in blood through the splenic artery. Removes old RBCs
- Two regions: RED and WHITE PULP
  - RED PULP: MΦ and RBC
  - WHITE PULP: surrounds the splenic artery to form the peritrairfoliar lymphoid sheath (PALS). Populated by T cells and DC
  - MARGINAL ZONE: MΦ