STRUCTURE AND FUNCTIONS OF LEUKOCYTES

Hematopoietic System and Disorders (MED202)

Assoc. Prof. Güvem GÜMÜŞ AKAY

Ankara University School of Medicine
Department of Physiology

Lecture outline

- General characteristics of leukocytes
- Classification of leukocytes
- Diapedesis, chemotaxis, phagocytosis
- Main structural features and primary functions of different types of leukocytes
  - Neutrophils
  - Eosinophils
  - Basophils
  - Monocytes
  - Lymphocytes

We are constantly exposed to bacteria, viruses, fungi, and parasites and our bodies are always fighting off invasions

- ✓ Many of these infectious agents are capable of causing serious abnormal physiological function or even death if they invade the deeper tissues.
- ✓ We are also exposed intermittently to other highly infectious bacteria and viruses besides those
  that are normally present.

Our bodies have a special system for combating the different infectious and toxic agents.

- ✓ This system is composed of
  - Blood **leukocytes** (**white blood cells** [**WBCs**])
  - Tissue **cells derived from leukocytes**.
- ✓ These cells work together in two ways to prevent disease:
  - by actually destroying invading bacteria or viruses by ***phagocytosis***
  - by forming ***antibodies*** and ***sensitized lymphocytes*** that may destroy or inactivate the invader.

Leukocytes:
White Blood Cells (WBCs)

- ✓ Mobile units of the body's protective system

- ✓ Formed partially
  - in the **bone marrow**: granulocytes, monocytes and a few lymphocytes
  - in the **lymph tissue (lymh glands, spleen, thymus, etc.)**: lymphocytes and plasma cells.

- ✓ After formation, they are transported in the blood to different parts of the body where they are needed.

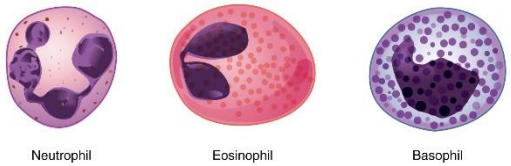
- ✓ Most of them are specifically transported to areas of serious infection and inflammation, thereby providing a rapid and potent defense against infectious agents.

General Characteristics of Leukocytes:
Types of WBCs

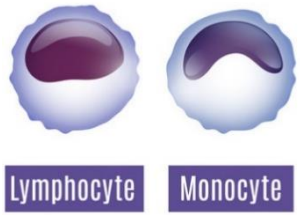
Six types of WBCs are normally present in the blood:

1. **Neutrophils**
2. **Eosinophils**
3. **Basophils**
4. **Monocytes**
5. **Lymphocytes**
6. **Plasma cells**

Polymorphonuclear cells
Granulocytes



Agranulocytes



WBC count

- At birth,in full term infant: 10,000-25,000/µl of blood
- Infants upto 1 yr of age:6000-16,000/µl of blood
- Adults:4000-11,000/µl of blood

General Characteristics of Leukocytes:
Types of WBCs

Six types of WBCs are normally present in the blood:

1. **Neutrophils**
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3. **Basophils**
4. **Monocytes**

protect the body against invading organisms by ingesting them (i.e., by ***phagocytosis***) or by **releasing antimicrobial or inflammatory substances** that have multiple effects that aid in destroying the offending organism

5. **Lymphocytes**
6. **Plasma cells**

function mainly in connection with the immune system

- ✓ The WBCs formed in the bone marrow are stored within the marrow until they are needed in the circulatory system.
- ✓ When the need arises, various factors cause them to be released.
- ✓ Normally, about three times as many WBCs are stored in the marrow as circulate in the entire blood.
- ✓ This quantity represents about a 6-day supply of these cells.
- ✓ The lymphocytes are mostly stored in the various lymphoid tissues, except for a small number that are temporarily being transported in the blood

Life Span of White Blood Cells: **Granulocytes**

After being released from the bone marrow is normally

- ✓ 4 to 8 hrs circulating in the blood
- ✓ 4 to 5 days in tissues where they are needed
- ✓ In serious tissue infection is often shortened to only a few hrs

Life Span of White Blood Cells: **Monocytes**

After being released from the bone marrow is normally

- ✓ 10 to 20 hours in the blood
- ✓ Once in the tissues, they swell to much larger sizes to become *tissue macrophages*
- ✓ in this form, they can live for months unless destroyed while performing phagocytic functions

Life Span of White Blood Cells: **Lymphocytes**

Enter the circulatory system continually, along with drainage of lymph from the lymph nodes and other lymphoid tissue

- ✓ After a few hrs, they pass out of the blood back into the tissues by *diapedesis*
- ✓ They re-enter the lymph and return to the blood again and again
- ✓ Have life spans of weeks or months

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Granulocytes

- ✓ Produced in the red bone marrow and have a short lifespan of hours to days
- ✓ Typically have a lobed nucleus and are classified according to which type of stain best highlights their granules that contain lysosomal enzymes
- ✓ Have 3 subtypes classified using Wright's stain
  - Neutrophils
  - Eosinophils
  - Basophils

Granulocytes: **Neutrophils**

- **50-70%** of all WBCs
- 10–12 μm in diameter, significantly larger than erythrocytes
- Their granules show up most clearly with stains that are chemically neutral
- The nucleus has a distinct lobed appearance and may have two to five lobes, the number increasing with the age of the cell
- Younger and immature neutrophils begin to develop lobes and are known as “bands.”
- Attack and destroy bacteria even in the circulating blood
- **Strong phagocytes,** exhibit chemotaxis

Granulocytes: **Eosinophils**

- **2-4 %** of all WBCs
- 10–12 μm in diameter
- The granules of eosinophils stain best with an acidic stain known as **eosin**
- The nucleus of the eosinophil will typically have two to three lobes
- Often produced in large numbers in people with parasitic infections
- Granules have a distinct red to orange color.
- They migrate into tissues diseased by parasites
- Weak phagocytes

Granulocytes: **Eosinophils**

- Most parasites are too large to be phagocytized by eosinophils or any other phagocytic cells
- Eosinophils attach themselves to the parasites by way of special surface molecules and release substances that kill many of the parasites
- They do so in several ways:
  - by releasing **hydrolytic enzymes** from their granules, which are modifed lysosomes
  - probably by also releasing highly **reactive forms of oxygen** that are especially lethal to parasites
  - by releasing from the granules a highly **larvacidal polypeptide** called ***major basic protein***

Granulocytes: Eosinophils

- Also have a special propensity to collect in tissues in which allergic reactions occur
  - peribronchial tissues of the lungs in people with asthma
  - in the skin after allergic skin reactions

- This action is caused at least partly by the fact that many mast cells and basophils participate in allergic reactions
- The mast cells and basophils release an ***eosinophil chemotactic factor*** that causes eosinophils to migrate toward the inflamed allergic tissue.
- The eosinophils are believed to detoxify some of the inflammation inducing substances released by the mast cells and basophils and probably also phagocytize and destroy allergen-antibody complexes, thus preventing excess spread of the local inflammatory process
- The granules of eosinophils include **antihistamine** molecules

Granulocytes: **Basophils**

- **< 1 %** of all WBCs
- 8-10 μm in diameter
- Granules of basophils stain best with basic (alkaline) stains.
- Contain large granules that pick up a dark blue stain and they may make it difficult to see the two-lobed nucleus.
- Intensify the inflammatory response
- The granules of basophils release **histamines**, **bradykinin**, **serotonin** and **heparin**

Granulocytes: **Basophils**

- The basophils in the circulating blood are similar to the large tissue *mast cells* located immediately outside many of the capillaries in the body.
- The mast cells and basophils play an important role in some types of allergic reactions because the type of antibody that causes allergic reactions, the immunoglobulin E (IgE) type, has a special propensity to become attached to mast cells and basophils

Agranulocytes

- ✓ Contain smaller, less-visible granules in their cytoplasm than do granular leukocytes
- ✓ The nucleus is simple in shape, sometimes with an indentation but without distinct lobes
- ✓ There are two major types of agranulocytes:
  - ✓ Monocytes
  - ✓ Lymphocytes

Agranulocytes: Monocytes/Macrophages

- **2-8 %** of all WBCs
- 12–20 μm
- Indented or horseshoe-shaped nucleus
- The nucleus has a distinct lobed appearance and may have two to five lobes, the number increasing with the age of the cell
- Monocytes, which are immature cells while still in the blood and have little ability to fight infectious agents at that time
- Once they enter the tissues, they begin to swell—sometimes increasing their diameters as much as fivefold—to as great as 60 to 80 micrometers, a size that can barely be seen with the naked eye: ***Macrophages***

Agranulocytes: **Monocytes/Macrophages**

- Macropahges are **strong phagocytes**
  - debris, foreign pathogens, worn-out erythrocytes, and many other dead, worn out, or damaged cells.
- Macrophages also release **antimicrobial defensins** and **chemotactic chemicals** that attract other leukocytes to the site of an infection
- Some macrophages occupy fixed locations, whereas others wander through the tissue fluid.

Monocyte-Macrophage Cell System (Reticuloendothelial System)

The total combination of ***monocytes***, ***mobile macrophages***, ***fixed tissue macrophages***, and a few ***specialized endothelial cells*** in the bone marrow, spleen, and lymph nodes is called the *reticuloendothelial system*

- ✓ Tissue macrophages in the skin and subcutaneous tissues (histiocytes)
- ✓ Macrophages in the lymph nodes
- ✓ Alveolar macrophages in the lungs
- ✓ Macrophages in the liver sinusoids (kupffer cells) .
- ✓ Macrophages of the spleen and bone marrow.
- ✓ Macrohages in the CNS (microglia)

Agranulocytes: Lmphocytes

- **20-30 %** of all WBCs
- The size range of lymphocytes is quite extensive
  - Large cells: 10–14 µm and have a smaller nucleus-to-cytoplasm ratio and more granules.
  - The smaller cells: 6–9 µm with a larger volume of nucleus to cytoplasm
- Although they form initially in the bone marrow, much of their subsequent development and reproduction occurs in the lymphatic tissues
- Responsible for **acquired immunity**

Agranulocytes: Lmphocytes

- ✓ Located most extensively in the lymph nodes, but they are also found in special lymphoid tissues
  - Spleen
  - submucosal areas of the gastrointestinal tract
  - Thymus
  - Bone marrow.

- ✓ Most lymphocytes in normal lymphoid tissue look alike when
  studied under a microscope, these cells are distinctly divided into 3 major populations
  - ✓ **T lymphocytes**
  - ✓ **B lymphocytes**
  - ✓ **Natural killer (NK) cells**

T lymphocytes

- The most common lymphocyte in the circulation: 75 %
- Formed in bone marrow and matured in Thymus gland
- Responsible for forming the activated lymphocytes that provide **“cell- mediated” immunity**

Types of T lymphocytes

- Helper T cells (T_H: CD4+)
- Cytotoxc T cells (T_C: CD8+)
- Suppressive/regulatory T cells
- Memory T cells

Name of T Cell Subset	Functions
Helper T Cell	assist other white blood cells in immunologic processes.
Cytotoxic T Cell	destroy virally infected cells and tumor cells.
Memory T Cell	subset of infection- as well as potentially cancer-fighting T cells.
Regulatory T Cell	Regulatory T cells actively suppress activation of the immune system and prevent pathological self-reactivity.

B lymphocytes

- Formed and matured in bone marrow
- Responsible for forming the plasma cells that provide **“humoral” immunity**

Natural Killer (NK) Cells

- Large granular lymphocytes and play a critical role in the innate immune system
- Often lack antigen-specific cell surface receptors
- In a direct manner or after activation of receptors on the NK cell's surface that bind ligands on the infected / cancer cell's surface.
- Upon this activation, the cytotoxic granules released by the NK cells are vectorially secreted into the intercellular space formed during conjugation of the NK cell and the target cell.
- The granules contain a number of proteins, including perforin, that induce the formation of membrane lesions on the target cell, resulting in NK cell mediated lysis of target cells.

Properties of WBCs

- Diapedesis
- Ameboid movement
- Chemotaxis
- Phagocytosis

WBCs enter the tissue spaces by Diapedesis

- Neutrophils and monocytes can squeeze through the pores of the blood capillaries by ***diapedesis***
- Even though a pore is much smaller than a cell, a small portion of the cell slides through the pore at a time; the portion sliding through is momentarily constricted to the size of the pore
- **Extravasation**

WBCs move through tissue spaces by ameboid motion

- Both neutrophils and macrophages can move through the tissues by ameboid motion
- Some cells move at velocities as great as 40 µm/min, a distance as great as their own length each minute.

WBCs are attracted to inflammed tissue areas by chemotaxis

- ✓ Many different chemical substances in the tissues cause both neutrophils and macrophages to move toward the source of the chemical: ***chemotaxis***
- ✓ Chemotaxis is effective up to 100 micrometers away from an inflamed tissue.
- ✓ When a tissue becomes inflamed at least a dozen different products that can cause chemotaxis toward the inflamed area are formed.
  - Some of the bacterial or viral toxins
  - Degenerative products of the inflamed tissues
  - Several reaction products of the “complement complex”
  - Several reaction products caused by plasma clotting in the inflamed area, as well as other substances.

Neutrophils and Macrophages Can Kill Bacteria.

- In addition to the digestion of ingested bacteria in phagosomes, neutrophils and macrophages contain *bactericidal agents* that kill most bacteria even when the lysosomal enzymes fail to digest them.
- *superoxide* (O2-), *hydrogen peroxide* (H2O2), and *hydroxyl ions* (OH-), which are lethal to most bacteria, even in small quantities
- Lysosomal enzymes, myeloperoxidase, catalyzes the reaction between H_2O_2 and chloride ions to form hypochlorite, which is exceedingly bactericidal.

Phagocytosis

- ✓ The most important function of the neutrophils and macrophages is *phagocytosis*
- ✓ Cellular ingestion of the offending agent
- ✓ Phagocytes must be selective of the material that is phagocytized; otherwise, normal cells and structures of the body might be ingested

Inflammation: Role of neutrophils and macrophages

- When tissue injury occurs, whether caused by bacteria, trauma, chemicals, heat, or any other phenomenon, multiple substances are released by the injured tissues and cause dramatic secondary changes in the surrounding uninjured tissues.
- This entire complex of tissue changes is called *inflammation*

- When activated by the products of infection and inflammation, the first effect is rapid enlargement of tissue macrophages.
- Next, many of the previously sessile macrophages break loose from their attachments and become mobile, forming the **first line of defense** against infection during the first hour or so.
- Within the first hour or so after inflammation begins, large numbers of neutrophils begin to invade the inflamed area from the blood. This invasion is caused by inflammatory cytokines
- Because the blood neutrophils are already mature cells, they are ready to immediately begin their scavenger functions of killing bacteria and removing foreign matter: **Second line of defence**

- Second macrophage invasion into the inflammed tissue is a **Third line of defense**
- Increased production of granulocytes and monocytes by the bone marrow is a **Fourth line of defense**