11.2: Defense Cells in the Blood: The Leukocytes

Skills to Develop

1. State what each of the following determine: CBC and leukocyte differential count.
2. State the significance of the following:
   a. an elevated white blood cell count
   b. a shift to the left (elevated bands)
3. Describe and state the major functions of the following leukocytes:
   a. neutrophils
   b. basophils
   c. eosinophils
   d. monocytes
   e. B-lymphocytes
   f. T4-lymphocytes
   g. T8-lymphocytes
   h. NK cells
4. State what type of cell monocytes differentiate into when they enter tissue.
5. State 2 functions of platelets.

All leukocytes are critical to body defense. There are normally between 5,000-10,000 leukocytes per cubic millimeter (mm$^3$) of blood and these can be divided into five major types: neutrophils, basophils, eosinophils, monocytes, and lymphocytes. The production of colonies of the different types of leukocytes is called leukopoiesis and is induced by various cytokines known as colony stimulating factors or CSFs.
The complete blood count (CBC) is a laboratory test which, among other things, determines the total number of both leukocytes and erythrocytes per ml of blood. In general, an elevated WBC count (leukocytosis) is seen in infection, inflammation, leukemia, and parasitic infestations. A decreased WBC count (leukopenia) is generally seen in bone marrow depression, severe infection, viral infections, autoimmune diseases, malignancies, and malnutrition. For example, infections may increase the total leukocyte count two to three times the normal level by dramatically increasing the number of neutrophils.

The differential white blood cell count (leukocyte differential count) determines the number of each type of leukocyte calculated as a percentage of the total number of leukocytes. This information can be useful diagnostically because different diseases or disorders can cause an increase or a decrease in the various types of WBCs. For example, when doing a differential WBC count, neutrophils are usually divided into segs (a mature neutrophile having a segmented nucleus) and bands (an immature neutrophil with an incompletely segmented or banded nucleus). During an active infection, people are generally producing large numbers of new neutrophils and therefore will have a higher percentage of the immature band forms. (An increase in band forms is sometimes referred to as a "shift to the left" because on laboratory slips used for differential WBC counts, the heading for bands is to the left of the heading for mature neutrophils or segs.)

The five types of leukocytes fall into one of two groups: the polymorphonuclear leukocytes and the mononuclear leukocytes.

**Polymorphonuclear Leukocytes**

Polymorphonuclear leukocytes (granulocytes) have irregular shaped nuclei with several lobes and their cytoplasm is filled with granules containing enzymes and antimicrobial chemicals. They include the following:

**Neutrophils**

Neutrophils are the most abundant of the leukocytes, normally accounting for 54-75% of the WBCs. An adult typically has 3,000-7,500 neutrophils/mm$^3$ of blood but the number may increase two- to three-fold during active infections. They are called neutrophils because their granules stain poorly - they have a neutral color - with the mixture of dyes used in staining leukocytes. The nucleus of a neutrophil has multiple lobes.

Neutrophils are important phagocytes. Their granules contain various agents for killing microbes. Primary azurophil granules contain acid hydrolase, myeloperoxidase, defensins, cathepsin G, cationic proteins, and bactericidal permeability increasing protein (BPI). Secondary specific granules contain such defense chemicals as lysozyme, lactoferrin, collagenase, and elastase. These agents kill microbes intracellularly during phagocytosis but are also often released extracellularly where they kill not only microbes but also surrounding cells and tissue, as will be discussed later under phagocytosis.

They release the enzyme kallikrein that catalyzes the generation of bradykinins. Bradykinins promote inflammation by causing vasodilation, increasing vascular permeability, and increasing mucous production. They are also chemotactic for leukocytes and stimulate pain. They produce enzymes that catalyze the synthesis of prostaglandins from arachidonic acid in cell membranes. Certain prostaglandins promote inflammation by causing vasodilation and increasing capillary
permeability. They also cause constriction of smooth muscles, enhance pain, and induce fever.

They are short-lived, having a life span of a few hours to a few days, and do not multiply. They circulate in the blood for around 6 hours and if they are not recruited, they undergo apoptosis. In tissue, they function for several hours and die. However, the bone marrow makes about 80,000,000 new neutrophils per minute to replace these.

- To view an electron micrograph of a neutrophil, see the Web page for the University of Illinois College of Medicine.
- Scanning electron micrograph of a neutrophil engulfing *Escherichia coli* from sciencephotogallery.com.
- Transmission electron micrograph of a neutrophil engulfing *Neisseria gonorrhoeae* from sciencephotogallery.com.

**Eosinophils**

Eosinophils normally comprise 1-4% of the WBCs (50-400/mm$^3$ of blood). They are called eosinophils because their granules stain red with the acidic dye eosin, one of the mixture of dyes used when staining leukocytes. The nucleus of an eosinophil typically appears lobed.

Their granules contain destructive enzymes for killing infectious organisms. These enzymes include acid phosphatase, peroxidases, major basic protein, RNase, DNases, lipase, and plasminogen. They are capable of phagocytosis but primarily they release their contents into the surrounding environment to kill microbes extracellularly. The substances they release defend primarily against fungi, protozoa, and parasitic worms (helminths), pathogens that are too big to be consumed by phagocytosis. They secrete leukotrienes, prostaglandins, chemicals that promotes inflammation by causing vasodilation and increasing capillary permeability. They also secrete various cytokines such as IL-1, IL-2, IL-4, IL-5, IL-6, IL-8, IL-13, and TNF alpha. Their life span is 8-12 days.

- To view an electron micrograph of an eosinophil, see the Web page for the University of Illinois College of Medicine.
- Transmission electron micrograph of an eosinophil from sciencephotogallery.com.

**Basophils**

Basophils normally make up 0-1% of the WBCs (25-100/mm$^3$ of blood). They are called basophils because their granules stain a dark purplish blue with the basic dye methylene blue, one of the dyes that are used when staining leukocytes. Basophils have a lobed nucleus. Basophils release histamine, leukotrienes, and prostaglandins, chemicals that promotes inflammation by causing vasodilation, increasing capillary permeability, and increasing mucous production. Basophils also produce heparin, platelet-activating factor (PAF) and the cytokine IL-4. Their life span is probably a few hours to a few days.

**Mononuclear Leukocytes**

Mononuclear leukocytes (agranulocytes) have compact nuclei and have no visible cytoplasmic granules. The following are agranulocytes:
**Monocytes**

Monocytes normally make up 2-8% of the WBCs (100-500/mm$^3$ of blood). Monocytes are important phagocytes. Monocytes differentiate into macrophages and dendritic cells when they leave the blood and enter the tissue. Macrophages and dendritic cells are very important in phagocytosis and serve as antigen-presenting cells in the adaptive immune responses (see below). They produce a variety of cytokines that play numerous roles in body defense. They are long-lived (life span of months) and can multiply.

- To view an electron micrograph of a monocyte, see the Web page for the University of Illinois College of Medicine.
- Transmission electron micrograph of a monocyte from sciencephotogallery.com.

**Lymphocytes**

Lymphocytes normally represent 25-40% of the WBCs (1,500-4,500/mm$^3$ of blood). Lymphocytes mediate the adaptive immune responses (Unit 6). Only a small proportion of the body's lymphocytes are found in the blood. The majority are found in lymphoid tissue. In fact the collective mass of all the lymphocytes in the human body is about the same as the mass of the brain! Lymphocytes circulate back and forth between the blood and the lymphoid system of the body. They have a life span of days to years. There are 3 major populations of lymphocytes:

B-lymphocytes (B-cells) mediate humoral immunity, the production of antibody molecules against a specific antigen, and have B-cell receptors (BCR) on their surface for antigen recognition. Generally 10-20% of the lymphocytes are B-lymphocytes. Once activated, most B-lymphocytes differentiate into antibody-secreting plasma cells.

T-lymphocytes (T-cells) are responsible for cell-mediated immunity, the production of cytotoxic T-lymphocytes (CTLs), activated macrophages, activated NK cells, and cytokines against a specific antigen. They also regulate the adaptive immune responses. Generally 60-80% of the lymphocytes are T-lymphocytes. Based on biochemical markers on their surface, there are two major classes of T-lymphocytes:

- T4-lymphocytes (CD4$^+$ T-lymphocytes) have CD4 molecules and T-cell receptors (TCRs) on their surface for protein antigen recognition. They function to regulate the adaptive immune responses through cytokine production. Once activated, they differentiate into effector T4-lymphocytes such as Th1 cells, Th2 cells, and Th17 cells.
- T8-lymphocytes (CD8$^+$ T-lymphocytes) have CD8 molecules and T-cell receptors (TCRs) on their surface for protein antigen recognition. Once activated, they differentiate into cytotoxic T-lymphocytes (CTLs).

Invariant natural killer T (iNKT) cells are a subset of lymphocytes that bridge the gap between innate and adaptive immunity. They have T-cell receptors (TCRs) on their surface for glycolipid antigen recognition. Through the cytokines they produce once activated, iNKT cells are essential in both innate and adaptive immune protection against pathogens and tumors. They also play a regulatory role in the development of autoimmune diseases and transplantation tolerance.

NK cells (natural killer cells) are lymphocytes that lack B-cell receptors and T-cell receptors. They function to kill infected cells and tumor cells. NK cells are able to kill cells to which antibody molecules have attached through a process called antibody-dependent cellular cytotoxicity (ADCC). They also kill human cells lacking MHC-I molecules on their surface. Lymphocytes will be discussed in greater detail in Unit 6.
Although not white blood cells, platelets (thrombocytes) are another formed element in the blood. They promote clotting by sticking together after becoming activated and forming platelet plugs to close up damaged capillaries. They also secrete cytokines and chemokines to promote inflammation.

Exercise: Think-Pair-Share Questions

1. Why are there more neutrophils and, specifically, more band form neutrophils found in the blood during an active infection?
2. Compare and contrast the functions of B-lymphocytes, T4-lymphocytes, and T8-lymphocytes in immune responses.

Summary

1. The complete blood count (CBC) is a laboratory test that, among other things, determines the total number of both leukocytes and erythrocytes per ml of blood.
2. In general, an elevated WBC count (leukocytosis) is seen in infection, inflammation, leukemia, and parasitic infestations.
3. Neutrophils are the most abundant of the leukocytes, normally accounting for 54-75% of the WBCs. Neutrophils are important phagocytes and also promote inflammation.
4. Eosinophils normally comprise 1-4% of the WBCs. They are capable of phagocytosis but primarily they release their contents into the surrounding environment to kill microbes, especially parasitic worms, extracellularly. They also promote inflammation.
5. Basophils normally make up 0-1% of the WBCs and release histamine, leukotrienes, and prostaglandins, chemicals that promotes inflammation.
6. Monocytes normally make up 2-8% of the WBCs and differentiate into macrophages and dendritic cells when they leave the blood and enter the tissue.
7. Lymphocytes normally represent 25-40% of the WBCs and mediate the specific immune responses.
8. B-lymphocytes (B-cells) mediate humoral immunity, the production of antibody molecules against a specific antigen, and have B-cell receptors (BCR) on their surface for antigen recognition. Most B-lymphocytes differentiate into antibody-secreting plasma cells.
9. T-lymphocytes (T-cells) are responsible for cell-mediated immunity, the production of cytotoxic T-lymphocytes (CTLs), activated macrophages, activated NK cells, and cytokines against a specific antigen.
10. T4-lymphocytes have CD4 molecules and T-cell receptors on their surface for antigen recognition. They function to regulate the adaptive immune responses through cytokine production. Once activated, they differentiate into effector T4-lymphocytes.
11. T8-lymphocytes have CD8 molecules and T-cell receptors on their surface for antigen recognition. Once activated, they differentiate into T8-suppressor cells and cytotoxic T-lymphocytes (CTLs).
12. NK cells (natural killer cells) are lymphocytes that lack B-cell receptors and T-cell receptors. They function to kill infected cells and tumor cells.
Contributors

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