Chapter 19

Structure and Function of the Nine Formed Elements
The Nine Formed Elements

Key:
- Progenitor cells
- Precursor cells or "blasts"
- Formed elements of circulating blood
- Tissue cells

PLURIPOTENT STEM CELL

MYELOID STEM CELL
- CFU-E
- CFU-Meg
- CFU-GM

LYMPHOID STEM CELL

Colony-forming unit—erythrocyte
Colony-forming unit—megakaryocyte
Colony-forming unit—granulocyte macrophage

Proerythroblast
Megalocyte
Eosinophilic myeloblast
Basophilic myeloblast
Myeloblast
Monoblast
T lymphoblast
B lymphoblast
NK lymphoblast

Nucleus ejected
Reticulocyte
Megakaryocyte

Red blood cell (erythrocyte)
Platelets

Granular leukocytes
Mast cell

Agranular leukocytes
Macrophage
Plasma cell
Erythrocytes or RBC

- disc-shaped cell with thick rim
  - 7.5 μM diameter and 2.0 μm thick at rim
  - lose nearly all organelles during development

- lack mitochondria // must use anaerobic fermentation to produce ATP

- lack of nucleus and DNA // no protein synthesis or mitosis
7.5 μm

(a) RBC shape

Surface view

Sectioned view
Erythrocytes or RBC

- blood type determined by surface glycoprotein and glycolipids on surface of plasma membrane

- cytoskeletal proteins = spectrin and actin

  • give RBC membrane durability and resilience

  • provide stretch and bend as squeeze through small capillaries

  • Can not be replaced because RBC lack organelles of protein synthesis
Erythrocytes or RBC

- 2.5 million RBCs are produced per second
- average lifespan of about 120 days
- development takes 3-5 days /// reduction in cell size, increase in cell number, synthesis of hemoglobin and loss of nucleus
- first committed cell - erythrocyte colony forming unit /// has receptors for erythropoietin (EPO) from kidneys
- erythroblasts (normoblast) multiply and synthesize hemoglobin
- As erythroblast mature they discard their nucleus and become a reticulocyte
  - named for fine network of endoplasmic reticulum still in cytoplasm /// 0.5 to 1.5% of circulating RBCs are reticulocytes
Erythrocytes

- **principal function**: carry oxygen from lungs to cellular tissues of body
  - Note most of the carbon dioxide transported as bicarbonate in plasma from tissue to lungs
- insufficient RBC function may result in necrosis within 4 – 5 minutes due to lack of oxygen and too much CO2
Hemoglobin (Hb) Structure

- each Hb molecule consists of:
  - globular proteins // four chains per hemoglobin molecule
  - heme groups

- about the heme groups
  - The heme is a nitrogen ring structure which holds an iron atom
  - Iron atom binds $O_2$ // the ferrous ion ($Fe^{2+}$) at its center
Hemoglobin (Hb) Structure

• About the globin molecules
  – two alpha and two beta chains
  – 5% CO₂ in blood is bound to globin moiety

• adult vs. fetal have different type of hemoglobin
  – Which form has the greatest affinity for oxygen?
  – Why?
Globins (beta polypeptide chains)

Heme

Iron (Fe^{2+})

Globins (alpha polypeptide chains)

(b) Hemoglobin molecule
(c) Iron-containing heme
Factors That Influence O2 Transport

- **hematocrit** (packed cell volume) // men 42-52% cells; women 37-48% cells

- **RBC count** // men 4.6-6.2 million/µL; women 4-2-5.4 million/µL

- **hemoglobin concentration** of whole blood // men 13-18g/dL; women 12-16g/dL

- Note: values are lower in women
  
  - androgens stimulate RBC production
  - women have periodic menstrual losses
  - hematocrit is inversely proportional to percentage of body fat
Nutritional Needs for Erythropoiesis

• **Iron** - key nutritional requirement

  – lost daily through urine, feces, and bleeding // men 0.9 mg/day and women 1.7 mg/day

  – low absorption rate of iron requires consumption of 5-20 mg/day

• dietary iron: can be either ferric (Fe$^{3+}$) and ferrous (Fe$^{2+}$) / ferric can not be absorbed

• stomach acid converts Fe$^{3+}$ to absorbable Fe$^{2+}$
Nutritional Needs for Erythropoiesis

• Vitamin $B_{12}$ and folic acid
  – These essential nutrients are required for rapid cell division and DNA synthesis
  – Necessary to produce formed elements // promote extreme mitosis
  – Parietal cells of intestinal crypts must produce intrinsic factor in order to absorb Vit B12 (no B12 - pernicious anemia may occur)

• Vitamin C

• Copper // cofactors for enzymes synthesizing hemoglobin // copper is transported in the blood by an alpha globulin called ceruloplasmin
Regulating Erythrocyte Homeostasis

- **negative feedback regulation**
  - drop in RBC count causes **hypoxemia** // stimulus for kidneys
  - kidney produces **erythropoietin** // hormone // stimulates bone marrow
  - RBC count increases in 3 - 4 days

- **stimulus to increase erythropoiesis**
  - low levels $O_2$ (hypoxemia)
  - high altitude
  - increase in exercise
  - loss of lung tissue as in emphysema
Disrupts homeostasis by decreasing

CONTROLLED CONDITION
Oxygen delivery to kidneys (and other tissues)

RECEPTORS
Kidney cells

Detect low oxygen levels, increasing erythropoietin secretion into blood

CONTROL CENTER
Proerythroblasts in red bone marrow mature more quickly into reticulocytes

More reticulocytes enter circulating blood

EFFECTORS
Larger number of red blood cells in circulation

RESPONSE
Increased oxygen delivery to tissues

Return to homeostasis when oxygen delivery to kidneys increases to normal
Erythrocytes Death and Disposal

• RBCs lyse in the narrow (2 micrometer) capillaries found in the spleen = graveyard for old RBC

• High concentration of macrophages in spleen // resident phagocytes

  – digest and recycle membranes

  – separate heme from globin

  • globins hydrolyzed into amino acids

  • iron removed from heme
Erythrocytes Death and Disposal

• Need to eliminate nitrogen from the heme molecule
  – heme pigment converted to biliverdin (green)
  – biliverdin converted to bilirubin (yellow)
  – released into blood plasma (kidneys excrete - yellow urine)
  – liver removes bilirubin and secretes into bile ///
    concentrated in gall bladder: released into small intestine; bacteria create urobilinogen (brown feces)
Erythrocytes Recycle/Disposal

- Erythropoiesis in red bone marrow
- Erythrocytes circulate for 120 days
- Expired erythrocytes break up in liver and spleen
- Cell fragments phagocytized
- Hemoglobin degraded
- Heme
  - Biliverdin
  - Bilirubin
  - Bile
  - Feces
- Globin
  - Iron
  - Stored
  - Reused
  - Lost by menstruation, injury, etc.
- Amino acids
- Iron
- Folic acid
- Vitamin B₁₂
- Nutrient absorption
- Storage
- Reuse
- Loss by menstruation, injury, etc.
Erythrocyte Disorder

- Polycytemia = an excess of RBCs
  - **primary polycytemia** (polycythemia vera) // cancer of erythropoietic cell line in red bone marrow // RBC count as high as 11 million/μL; hematocrit 80% // note – erythropoietin low concentration in blood
  
  - **secondary polycytemia** // from dehydration, emphysema, high altitude, or physical conditioning // RBC count up to 8 million/μL // note – erythropoietin high concentration in blood
Dangers Associated with Polycythemia

– increased blood volume
– pressure, viscosity
– can lead to embolism
– stroke
– increase in blood viscosity
– heart failure
Anemia

- Not able to supply oxygen to tissue

- Three main categories

  - Inadequate erythropoiesis (or failure to produce functional hemoglobin – e.g. sickle cell anemia)

  - Hemorrhagic anemia

  - Hemolytic anemia
Anemia Types

- Iron-deficiency anemia
- Pernicious anemia
  - Problem often lack of intrinsic factor // required to carry B12 across mucosa / stomach glands fail to produce intrinsic factor
  - Vitamin B12 deficiency (vitamin usually present in diet / meat)
- Sickle cell anemia
- Hypoplastic anemia
- Aplastic anemia
Anemia

• Three potential consequences:
  – Hypoxia // oxygen deprivation / low energy / if severe result in necrosis
  – Reduced blood osmolarity // causes edema
  – Reduced blood viscosity
    • little blood resistance
    • heart beats faster
    • may lead to low blood volume and viscosity to lead to low blood pressure
    • leads to cardiac failure
Leukocytes (WBC)
Leukocytes (WBCs)

- least abundant of all the formed elements // 5,000 to 10,000 WBCs/μL

- Primary function = protect against infectious microorganisms and other pathogens

- WBCs have conspicuous nucleus

- spend only a few hours in the blood stream before migrating out of blood and into connective tissue (i.e. reticuloendothelial system)

- retain their organelles for protein synthesis

- All WBC have granules but some cells don’t stain!
Leukocytes (WBCs)

- All WBC have granules in their cytoplasm but some cell’s granules don’t stain!
  - all WBCs have **lysosomes** called nonspecific (azurophilic) granules /// these don’t stain so called inconspicuous (cytoplasm looks clear) known as the agranulocytes
  - the granulocytes have **specific granules** that stain /// contain enzymes and other chemicals employed in defense against pathogens
Types of Leukocytes

• Granulocytes // these cells stain // known as the “NEBs”
  – neutrophils (60-70)
  – eosinophils (2-4%)
  – basophils (<1%)

• Agranulocytes // these don’t stain
  – lymphocytes (25-33%)
  – monocytes (3-8%)

• How to remember WBC ranking = Never let monkeys eat bananas
Granulocytes

- Neutrophils
- Eosinophil
- Basophil

Scale: 10 µm
Agranulocytes

Lymphocyte

Monocyte

Copyright © The McGraw-Hill Companies, Inc. Permission required for reproduction or display.
Granulocyte Functions

- **Neutrophils**

  - 60-70% of WBC
  - Also known as polymorphonuclear leukocytes
  - Barely visible granules in cytoplasm // 3 to 5 lobed nucleus
  - First WBC to arrive during inflammation
  - Increased numbers in **bacterial infections** / neutrophilia – increase 5x
  - Phagocytosis of bacteria / phagosomes kill bacteria
  - Release antimicrobial chemicals // called the “**respiratory burst**” – like a nuclear bomb! // hypochlorite – hydrogen peroxide – free radicals
Oxidative Burst (The Respiratory)

1. Bacterium adheres to membrane of neutrophil

2. NADPH is produced

3. NADPH oxidase uses electron from NADPH to produce superoxide ($O_2^{-}\cdot$)

4. Superoxide dismutase converts superoxide to hydrogen peroxide ($H_2O_2$)

5. $H_2O_2$ burst kills bacterium

Plasma membrane

Neutrophil

Pentose phosphate pathway

NADPH oxidase

NADPH

NADP+$^+$
Eosinophils

- found especially in the mucous membranes
- 2-4% // large rosy-orange granules, bi-lobe nucleus
- stand guard against parasites, allergens (allergy causing agents), and other pathogens
- kill tapeworms and roundworms by producing superoxide, hydrogen peroxide, and toxic proteins
- promote action of basophils and mast cells
- phagocytize antigen-antibody complexes
- limit action of histamine and other inflammatory chemicals
- Increase numbers in collagen diseases, allergies, diseases of spleen and CNS
Antibody-dependent cell-mediated cytotoxicity (ADCC).

Organisms, such as many parasites, that are too large for ingestion by phagocytic cells must be attacked externally.
Antibody-dependent cell-mediated cytotoxicity (ADCC).

(b) Eosinophils adhering to the larval stage of a parasitic fluke.
Granulocyte // Basophils

- <1% // large, abundant, violet granules (obscure a large S-shaped nucleus)

- Basophils in blood // called mast cells in tissue

- Emigrate from blood to tissue // Change into a mast cells

- acquire surface receptors = E class antibodies

- IgE produced by plasma cells upon “first exposure” // then attached to basophils as surface receptor
Granulocyte // Basophils to Mast Cells

- Upon second exposure foreign antigen cause mast cells to release histamine and heparin

- increased numbers in chicken pox, sinusitis, diabetes

- **histamine** (vasodilator) // speeds flow of blood to an injured area

- secrete **heparin** (anticoagulant) // promotes the mobility of other WBCs in the area
The mechanism of anaphylaxis mediated by mast cell.

IgE antibodies, produced in response to an antigen, coat mast cells and basophils. When an antigen bridges the gap between two adjacent antibody molecules of the same specificity, the cell undergoes degranulation and releases histamine and other mediators.
Agranulocyte Function

Lymphocytes (T cells / B cells / NK cells)

- 25-33% // variable amounts of bluish cytoplasm (scanty to abundant); ovoid/round, uniform dark violet nucleus

- increased numbers in diverse infections and immune responses

- **T lymphocytes** able to destroy cells (cancer, foreign, and virally infected cells) // cellular immunity

- “present” antigens to activate other immune cells

- coordinate actions of other immune cells // cytokines = messenger molecules

- **B lymphocytes** secrete antibodies and provide immune memory // humeral immunity
Agranulocyte Function

Monocytes

- 3-8% // largest WBC; ovoid, kidney or horseshoe shaped nucleus

- increased numbers in **viral infections and inflammation**

- produce and secrete **cytokines** = group of molecules which regulate immune response

- leave bloodstream and transform into **macrophages** (i.e. big eater)

- phagocytize pathogens and debris // the “garbage collector”

- “present” antigens to activate other immune cells // **antigen presenting cells** (APCs)
The Phases of Phagocytosis.

1. CHEMOTAXIS and ADHERENCE of phagocyte to microbe
2. INGESTION of microbe by phagocyte
3. Formation of phagosome (phagocytic vesicle)
4. Fusion of phagosome with a lysosome to form a phagolysosome
5. DIGESTION of ingested microbes by enzymes in the phagolysosome
6. Formation of the residual body containing indigestible material
7. DISCHARGE of waste materials
Diapedis: How Leukocytes Emigrate into Tissue Spaces

• Circulating WBCs do not stay in bloodstream
  – Area of inflammation causes endothelial cells outer face to become “sticky” – results in margination
  – Granulocytes (NEB) leave in 8 hours and live 5 days longer
  – Monocytes leave in 20 hours, transform into macrophages and live for several years
  – Lymphocytes provide long-term immunity // live for decades // continuously recycled from blood to tissue fluid to lymphatic system and back into the blood
Leukocyte Disorders

• **leukopenia** - low WBC count below 5000/μL
  
  – causes: radiation, poisons, infectious disease

  – effects: elevated risk of infection

• **leukocytosis** - high WBC count above 10,000/μL

  – causes: infection, allergy and disease

  – differential WBC count – identifies what percentage of the total WBC count consist of each type of leukocyte
Leukocyte Disorders

- Leukemia - cancer of hemopoietic tissue that usually produces an extraordinary high number of circulating leukocytes and their precursors
  - myeloid leukemia – uncontrolled granulocyte production
  - lymphoid leukemia - uncontrolled lymphocyte or monocyte production
  - acute leukemia – appears suddenly, progresses rapidly, death within months
  - chronic leukemia – undetected for months, survival time three years
  - effects - normal cell percentages disrupted; impaired clotting; opportunistic infections
Normal and Leukemic Blood

(a) Platelets

Monocyte

Neutrophils

Lymphocyte

Erythrocytes

(b) 75 µm
Complete Blood Count

- Hematocrit
- Hemoglobin concentration
- Total count for RBCs, reticulocytes, WBCs, and platelets
- Differential WBC count
- RBC size and hemoglobin concentration per RBC