Red Blood Cells: Life Cycle, Structure, and Function

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Course Objectives

After completing this course, the student is expected to:

1. Identify the components of blood

2. Know the role of erythropoiesis in RBC production

3. Describe the basic structures of the RBC, the cell membrane, and hemoglobin

5. Understand the role of the Na^{+}- K^{+} pump in maintaining cell integrity

6. Know the role of hemoglobin give examples of hemoglobin abnormalities

7. Explain the process of gas exchange between blood and the cells

9. Understand the role and effects of hemolysis

The Evolution of Hematology

Since ancient times, blood has been regarded as integral to life and health and has been the subject of much research and experimentation. Thus hematology, the study of blood, has long been a part of our efforts to understand the workings of the human body.

With the development of the microscope in the 1600s, researchers could view objects and processes previously invisible to the naked eye. In 1674, Antonie van Leeuwenhoek was able to observe the presence of blood cells under the microscope. This discovery proved that blood is not simply a dark-red liquid flowing within our veins; it actually contains microscopic components with unique characteristics.

A further understanding of the structure and functions of blood cells would gradually emerge within the field of hematology. In 1840 Hünefeld described the presence of hemoglobin, and subsequent research determined its role in oxygenation. Technological advancements would eventually make it possible to study the blood cells at the molecular level, allowing researchers to study them in greater detail.

Today, the knowledge gained about blood and its components has proven to be an invaluable tool for healthcare. The medical industry' deeper understanding of blood's physical, chemical, and physiologic properties has significantly contributed to advancements in the prevention and treatment of disease, diagnostic testing, and therapeutic procedures. Yet, many questions still remain, necessitating continued study.

Components of Blood

Blood has two components: plasma and the formed elements.

Plasma is the liquid which makes up the majority (55%) of blood and is referred to as the *fluid portion* of the blood. Plasma itself consists of approximately 90% water. The remaining 10% are substances dissolved in the plasma (such as gases, nutrients, minerals, and hormones) which are transported by the bloodstream. When isolated from whole blood, plasma normally has a pale-yellow color.

The *formed (cellular) elements* are the different cell types (red blood cells, white blood cells and platelets) which float within the plasma and make up 45% of the blood. Unlike plasma, which is a liquid, the cells are solid elements of the blood. The majority of the formed elements are the red blood cells (also called RBCs or erythrocytes). Their primary function is to carry oxygen within the bloodstream. Oxygenated (oxygen-rich) blood is essential for the nourishment of cells within the various body organ systems and for the body's overall health.

Within the bloodstream, plasma and the cells remain mixed. Although plasma by itself has a pale-yellow color, blood as a whole appears dark-red due to all the red blood cells flowing within the plasma. The fact that blood has two portions becomes evident when blood is collected into a tube, after which plasma can be separated from the cells via centrifugation. (Insert picture of separated plasma and cells in collection tube)

Red Blood Cell Formation and Development

The process of creating new blood cells is known as *hematopoiesis* or *hemopoiesis*. Constant blood cell formation is necessary for replacing older and damaged cells, as well as replacing cells that are lost due to bleeding. Hematopoiesis is part of a cycle which maintains the normal population of cells circulating in the bloodstream.

Erythropoiesis refers specifically to the formation of red blood cells. It begins early during the embryonic stage of development, within a primitive structure called the yolk sac. It continues through the fetal stage where the liver, spleen and bone marrow become involved in RBC production.

In adults, all RBCs are formed in the bone marrow. Within this tissue are *hemopoietic stem cells* from which all mature blood cells originate. Stem cells, which are present since embryonic development, have the ability to differentiate to other cell types. They give rise to the *progenitor* cells (cells of different lineages) which in turn will produce the three blood cell groups. Each line of cells undergoes several stages of development until eventually mature cells emerge and are released into the bloodstream.

To produce RBCs, stem cells in the marrow differentiate into *proerythroblasts*, the progenitor cells which undergo further stages of maturation. Part of this process involves each cell losing its nucleus and organelles (cellular organs) as it matures. Towards the end of cell development, *reticulocytes* are immature RBCs which still have remnants of their nucleus present. Upon entering the bloodstream, they completely lose all their nuclear material and organelles, becoming mature erythrocytes within 1 to 2 days. Once fully formed, RBCs live in the circulation for an average of 120 days. (Insert diagram of erythropoiesis in bone marrow)

RBC production is stimulated by *erythropoietin* (EPO), a hormone secreted from the kidneys. In situations where oxygen demand of the body is increased or when RBC numbers fall below normal levels, EPO causes the bone marrow to produce greater numbers of red blood cells.

RBC Structure

RBCs have a diameter of about 6-8 µm, with a thickness of about 2.5 µm*. They have a *biconcave* shape, meaning the cell has the form of a flattened disc with an indentation on both sides at the center. Unlike most other cells, mature RBCs contain no nucleus or organelles; instead, they only contain the protein *hemoglobin*. Both the characteristic shape of the cell and the presence of hemoglobin contribute to the RBC's properties and function. (Insert picture of RBC structure)

In adults the normal number of RBCs in the bloodstream is between 4.5 to 5 million erythrocytes per cubic millimeter**. Constant production of new cells is necessary for maintaining the population of circulating RBCs as old or damaged cells are lost. The rate of erythropoiesis can restore almost one percent of the body's RBCs daily. (Britannica)

*A micrometer or micron (µm) is a unit of length equivalent to 0.001 mm, or about 0.00004 inch

**The unit of measurement for cell counts is the *number of cells per cubic millimeter*. As a measure of volume, a cubic millimeter (mm^3) or *microliter*, describes a cube whose sides are each 1mm long. A simplified description of this measurement would be the number of cells in a blood drop roughly the size of a pin head. Cell counts are routinely included in blood testing.

The RBC Membrane

The cell membrane is the outer covering of the RBC. It maintains cellular integrity and mediates interactions between the extracellular (outside the cell) environment and the cell's interior. The membrane is composed of a double layer of lipid (fat) molecules, within which specialized protein molecules are interspersed. These proteins perform different functions, including preservation of membrane stability and pliability, transportation of substances across the membrane, and providing a negative surface charge which keeps RBCs from sticking to each other or to the blood vessel wall. (ScienceDirect) (Insert diagram of RBC membrane)

One of the cell membrane proteins is an enzyme called the *Na^+- K^+ pump*. The pump actively transports ions (charged particles) through the membrane, facilitating their entry or exit from the cell. The ions involved are Sodium (Na^+) and Potassium (K^+), both of which have a *positive* charge. To transport these ions, the pump utilizes ATP (adenosine triphosphate, an energy-providing compound for cells) as an energy source. For each unit of ATP spent, 3 Na^+ ions are pumped *out* of the cell, while 2 K^+ ions are pumped *in*. (NIH)

The pump needs to constantly perform this function to assure that there are always higher concentrations of Na^+ *outside* the cell, higher concentrations of K^+ *inside* the cell, and as a result, a net *negative* charge within the cell itself (in part because there are more positive ions being pumped out than are pumped in). These conditions make it ideal for important cellular physiological functions to take place, promoting the overall health of the cell.

Maintaining stable ion concentrations is also crucial to keeping the cell intact. Without the action of the Na^+- K^+ pump, Sodium and other ions would build up inside the cell. These ions attract water, which would then enter the cell causing increased intracellular volume. If too much fluid were to enter the RBC it would result in the cell swelling and eventually rupturing, effectively destroying the cell. By preserving the right levels of ions within the cell, the pump also regulates the cell's fluid volume, thus maintaining cellular integrity.

Hemoglobin and Gas Exchange

Within the cytoplasm of RBCs is an iron-based protein called *hemoglobin*, which as a pigment is responsible for giving these cells (and blood as a whole) their typical red color. More importantly, hemoglobin is crucial to the processes of blood oxygenation and cellular respiration.

The typical hemoglobin molecule in adults has a *quaternary* configuration, being comprised of 4 protein subunits called *globins*. Adult hemoglobin has 2 alpha-globins and 2 beta-globins (also called alpha chains and beta chains); the 2 globin types are coded by different genes and have unique amino acid structures. (Insert diagram of hemoglobin structure)

Each globin subunit is bound to a *heme* group, which is a molecule containing an iron atom. As the bloodstream passes through the lungs, the iron atoms in the 4 heme groups each attract and bind to oxygen. Thus, when oxygenated each RBC transports 4 oxygen molecules. The biconcave shape of the cell provides optimum surface area for transporting gases. (Front Physiol) (Insert pictures of hemoglobin molecule and RBC transporting Oxygen)

Once bound to oxygen, hemoglobin is called *oxyhemoglobin* and has a bright red appearance, while in the deoxygenated state it appears purplish blue. This is reflected in the appearance of (oxygenated) arterial blood versus (deoxygenated) venous blood. (Insert picture of arterial and venous blood)

The presence of hemoglobin allows red blood cells to bind oxygen, take it out of the lungs, and carry it throughout the body via the bloodstream. As blood enters organ tissues, hemoglobin then *releases* the oxygen, which is utilized by cells for metabolic processes. This capability of hemoglobin to reversibly bind oxygen is what allows RBCs to transport oxygen throughout the body and deliver it to the cells.

Upon obtaining oxygen from the blood, the body's cells in turn release carbon dioxide to the blood in a process called *gas exchange*. CO_2 is a waste product of cell metabolism; its build-up is detrimental to cell health, so it needs to be cleared from the tissues. RBCs are able to participate in gas exchange since hemoglobin *can also bind carbon dioxide* to some extent. Furthermore, the constant flow of

blood ensures that cells receive both a steady supply of oxygen and removal of carbon dioxide. (Insert diagram of gas exchange)

Hemoglobin Abnormalities

Iron deficiency is a common cause of anemia, where lack of iron prevents the body from adequately producing hemoglobin. Possible causes include dietary insufficiency, blood loss, intestinal conditions, and pregnancy. As a result of scant hemoglobin, RBCs are smaller and pale in appearance, and have reduced capability for oxygenation. Those affected have symptoms including weakness, fatigue, pallor, cold extremities, and difficulty breathing. Severe forms of iron deficiency can lead to delayed growth and heart failure.

Genetic mutations can cause either decreased production of normal hemoglobin, or the production of abnormal hemoglobin variants with altered protein structure. Thalassemia and Sickle Cell disease are examples.

Thalassemia involves various gene mutations which lead to reduced production of either the alpha or beta subunit. Depending on the type and severity of the mutation, affected individuals' symptoms may range from being asymptomatic carriers of the disease to severe anemia, delayed development, infections, and systemic complications.

Sickle cell disease is another genetic condition. Affected individuals may either be asymptomatic carriers of the disease or experience symptoms of varying severity. When the mutation is expressed, abnormal hemoglobin is formed which causes RBCs to have a sickle or crescent shape. Sickle cells lose their pliability and become stuck to each other, interfering in normal blood flow. They also have a shorter lifespan of 10 to 20 days. As the abnormal cells are removed from the circulation, the RBC population is depleted leading to symptoms of anemia. Blockage of blood flow results in mild to severe bouts of pain as well as swelling of the extremities. (Insert picture of sickle cells)

RBCs in the Circulation

Each RBC completes one round trip of the entire circulatory system approximately 1400 times a day, (UBristol) and by the end of its lifespan it will have traveled a distance of roughly 310 miles. (NIH2) As they are carried within the bloodstream, RBCs must navigate blood vessels of varying sizes and withstand different pressure levels. Particularly when passing through tiny capillaries, RBCs exhibit the ability to deform (temporarily change their shape then regain their original biconcave configuration), allowing them to squeeze through passageways less than half their size (UBristol), which is attributed to the RBC's biconcave shape, its intracellular contents, (Front Physiol) and the flexibility of the cell membrane. (Biophys J) (NIH2) However, as RBCs age, they are exposed to repeated wear and tear from passing through the microcirculation, resulting in decreased RBC deformability over time. (Front Physiol) (Insert picture of RBCs passing through a capillary)

RBC Destruction

Having been subjected to repeated wear and tear over time, older RBCs become less effective in navigating the microcirculation. Cells may also become damaged by various injuries, toxins or infections, and certain genetic disorders lead to the production of abnormal cells. *Hemolysis*, the destruction of RBCs, is the body's way of removing old, damaged, and abnormal cells from the circulation. This process is normally carried out by the spleen and liver, where components of lysed (destroyed) cells are processed and recycled.

Within the spleen, RBCs must pass through narrow channels that act as a filter, trapping abnormal cells while allowing healthy RBCs (those with the capacity to deform) to pass through. Older, damaged, and abnormal cells are therefore prevented from returning to the circulation. A study published by Massachusetts General Hospital showed that the liver is the primary site for destruction of RBCs and recycling of their contents. (Science Daily) In both spleen and liver, specialized white blood cells called *macrophages* target unwanted cells for *phagocytosis* (wherein a macrophage engulfs and digests the RBC), thereby destroying them. Since this process takes place within the liver and spleen (and not in the bloodstream), it is referred to as *extravascular* hemolysis (hemolysis occurring *outside the blood vessels*). Macrophages within these organs efficiently

hemolyze roughly 5 million RBCs every second. (Front Physiol) (Insert picture of macrophage destroying an RBC)

The mechanism by which old or damaged RBCs are identified is not yet fully understood. Prevailing hypotheses describe physicochemical changes which take place in aging cells (such as decreased deformability and altered cell membrane proteins) that serve as catalysts for their destruction. The RBC function itself seems to play a role in these changes. When RBCs release oxygen during gas exchange, small amounts of oxidizing byproducts are generated which can damage the cell membrane and hemoglobin. Studies have shown that aging RBCs lose the enzymes which protect against such damage. (Front Physiol)

The liver and spleen break down and recycle the hemoglobin released from destroyed RBCs. The efficiency of extravascular hemolysis prevents most of the hemoglobin from destroyed cells from being released to the plasma. (Front Physiol) Iron from the heme groups is sent to the bone marrow, where hemoglobin is reconstituted within newly formed RBCs. Hemoglobin is also repurposed by the liver to make *bilirubin*, a chemical with a yellow-brown color. Bilirubin from the liver is mainly used and eliminated by the digestive system; a small portion is excreted by the kidneys and gives urine its yellow color. Other proteins from RBC breakdown are also recycled or eliminated.

In situations where there is an *excess* of oxygen in the tissues, the need for oxygenation (and therefore RBCs) in the bloodstream is decreased. The liver and spleen can rapidly reduce the number of circulating RBCs by selectively removing erythrocytes which are 10 or 11 days old. This process is called *neocytolysis*. (Royal Society) This phenomenon demonstrates that the RBC life cycle is not always fixed but can be altered in response to physiologic processes.

Abnormal Forms of Hemolysis

When extravascular hemolysis is carried out normally, the circulating RBC population is maintained, and products of lysed cells are properly reused or disposed of. However, hemolysis can become abnormal due to various stressors and diseases, including splenic disorders, genetic defects, and immune hyperactivity. When hemolysis is excessive, it causes more RBCs to be destroyed

than are being produced, leading to anemia. With significant numbers of RBCs lost, blood oxygenation and gas exchange in the tissues become compromised. Thus, anemic patients can exhibit symptoms of pallor, weakness, fatigue, and shortness of breath. As the bone marrow increases erythropoiesis in an effort to repopulate RBCs, immature reticulocytes are seen in the circulation. Bilirubin levels in the blood may also increase as more hemoglobin is released from lysed cells.

In contrast to extravascular hemolysis taking place in the liver and spleen, *intravascular* hemolysis is the abnormal destruction of RBCs *within the blood vessels*. Healthy RBCs in the arteries, veins, and capillaries can be destroyed prematurely if they are exposed to forces which exceed cell membrane tolerance, or if disease processes cause the cell membrane to stop functioning properly. As a result, the membrane loses its integrity and hemolysis occurs.

Intravascular hemolysis can be due to a variety of factors, including injury, infection, genetic defects, immune hyperactivity, drugs, toxins, or foreign objects in the circulation. As the RBCs hemolyze within the blood vessels, hemoglobin spills into the plasma instead of being processed and recycled by the liver. Hemoglobin released directly into the bloodstream in high amounts is associated with kidney damage. (Advances in Clinical Chemistry) Other intracellular contents are also released to the bloodstream. Increased levels of Potassium (the ion found in higher concentrations within RBCs) and LDH (Lactate Dehydrogenase, an enzyme used in cell metabolism) are seen in the blood as a consequence of hemolysis.

Conclusion

Red blood cells were first observed under the microscope many centuries ago. Since then, much has been learned regarding the complexity of their formation and development, the molecular structure which optimizes their oxygen-binding capacity, the mechanisms by which they maintain their integrity within the circulation, and the means by which they are cleared from the circulation. Studying these intricate processes and the abnormal conditions related to them has made it possible for various diseases to be detected, diagnosed, and better

treated. As we obtain greater insight into blood's complexities, we generate more questions. Much has yet to be understood, leaving room for further discoveries.

Quiz

1. How many heme groups does hemoglobin contain?

    a. 1

    b. 2

    c. 3

    d. 4

2. Erythropoiesis is the process of

    a. red blood cell production

    b. hemoglobin recycling

    c. red blood cell destruction

    d. oxygen and carbon dioxide exchange

3. Which of the following is true regarding the effects of the Na^+-K^+ pump?

    a. there are higher concentrations of Na^+ inside the cell

    b. there are higher concentrations of K^+ inside the cell

    c. both A and B

    d. none of the above

4. Intravascular hemolysis is the destruction of RBCs

a. within the bone marrow

b. within the blood vessels

c. within the spleen

d. none of the above

5. RBCs have a lifespan of approximately

a. 60 days

b. 90 days

c. 120 days

d. 180 days

6. In order to pass through tiny capillaries, the RBC membrane uses the property of

a. hemolysis

b. gas exchange

c. oxygenation

d. deformability

7. Which of the following statements is false?

a. hemoglobin allows blood to transport oxygen from the lungs to the tissues

b. hemoglobin is a sodium-based molecule within the RBC

c. oxygen-bound hemoglobin and has a bright red appearance

d. hemoglobin is important in facilitating gas exchange

8. Which of the following is a genetic disorder involving the production of abnormal hemoglobin?

a. Iron deficiency anemia

b. Sickle cell disease

c. Neocytolysis

d. none of the above

9. As a result of abnormal hemolysis, which substance is released directly into the bloodstream?

a. Hemoglobin

b. Potassium

c. LDH

d. all of the above

10. Hemoglobin structure consists of

a. 4 heme groups which contain iron

b. 2 alpha-globins and 2 beta-globins

c. a quaternary configuration

d. all of the above