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Review of Physiological Aspects of Erythropoiesis: A Narrative Literature Review

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A B S T R A C T

Erythropoiesis is the development of red blood cells. Within the confines of the bone marrow, erythroid progenitor cells proliferate and differentiate into large nucleated proerythroblasts, which are committed to producing cells of the erythroid series. This literature review aimed to describe the physiology of erythropoiesis and its application in medical science. All stages of erythroid development are referred to as the erythron. Proerythroblasts, which possess ribosomes and can produce proteins, differentiate through several forms between erythroblasts while synthesizing hemoglobin and progressively removing most of the intracellular structures, including the nucleus. Thus the mature erythroblast becomes more compact and progressively takes on the shape and characteristics of the erythrocyte. Hemoglobin is easily seen, and its amount increases as the size of the nucleus decreases during the basophilic and polychromatophilic stages. The orthochromatic erythroblast (normoblast) is the smallest of the nucleated erythrocyte precursors.

1. Introduction

Erythropoiesis is the process of forming red blood cells or erythrocytes in the human body. Erythrocytes are blood cells whose function is to transport oxygen from the lungs to all parts of the body and bring back carbon dioxide from all over the body to the lungs for disposal.[1-3] The erythropoiesis process starts from pluripotent or hematopoietic stem cells present in the bone marrow and then progresses through several stages of red blood cell formation. These stages include the formation of precursor cells called erythroblasts, the formation of immature erythrocytes, and finally, the formation of mature erythrocytes that are ready to be released into the blood circulation. Process erythropoiesis is controlled by the hormone erythropoietin, which is produced by the kidneys and live, and is influenced by many factors such as iron deficiency, deficiency of vitamin B12 and folic acid, and certain medical conditions such as anemia. This literature review aimed to describe the physiology of erythropoiesis and its application in medical science.

The process of erythropoiesis

Within the confines of the bone marrow, erythroid progenitor cells proliferate and differentiate into large nucleated proerythroblasts, which are committed to producing cells of the erythroid series. All stages of erythroid development are referred to as erythron. Proerythroblasts, which possess ribosomes and can produce proteins, differentiate through several forms between erythroblasts while synthesizing hemoglobin and progressively removing most of the intracellular structures, including the nucleus. Thus the mature erythroblast becomes more compact and progressively takes on the shape and characteristics of the erythrocyte. Hemoglobin is easily seen, and its amount increases as the size of the nucleus decreases during

the basophilic and polychromatophilic stages. The orthochromatic erythroblast (normoblast) is the smallest of the nucleated erythrocyte precursors.[1-3]

The final immature form of the erythroblast is the reticulocyte, which is nucleated and contains a network (reticular) such as the ribonucleic acid ribosome (rRNA) network that is visible microscopically after being stained with certain dyes. The reticulocyte contains polyribosomes (for globin synthesis) and mitochondria (for oxidative metabolism and heme synthesis). Reticulocytes mature into erythrocytes within 24 to 48 hours. During this period, mitochondria and ribosomes disappeared, and cells became smaller and more disc-like. With these final changes, the erythrocyte loses its capacity for hemoglobin synthesis and oxidative metabolism. Reticulocytes remain in the marrow for about 1 day and are released into the venous sinuses. They continue to mature in the bloodstream and may travel to the spleen for several days for additional maturation. The normal reticulocyte count is 1% of the total red blood cell count. Approximately 1% of the body's normally circulating erythrocyte mass is produced every 24 hours. The reticulocyte count is, therefore, a useful clinical index of erythropoietic activity and indicates whether new red blood cells are being produced.[4-7]

Regulation of erythropoiesis

In healthy individuals, the total volume of circulating erythrocytes remains surprisingly constant. Increased circulating erythropoietin levels lead to a compensatory increase in proerythroblast proliferation and differentiation in the bone marrow. Cellular erythropoietin receptor density decreases progressively during erythroid maturation to levels that are barely detectable in reticulocytes. The normal steady-state production rate of about 2.5 million erythrocytes per second can increase to 17 million per second during anemia or under conditions of low oxygen concentration, such as high-altitude environments or lung disease. The body thus responds to reduced blood oxygenation in two ways: (1) stimulation of the chemoreceptors of the carotid bodies and the aortic arch, which signal the brain to increase oxygen intake through increased ventilation; and (2) stimulation of receptors on the peritubular cells of the kidney to increase the synthesis and release of erythropoietin, thereby increasing the oxygen-carrying capacity of the blood.[8,9] Recombinant human erythropoietin (r-HuEPO) is used in individuals with anemia due to decreased erythropoietin production due to chronic renal failure. The direct effect of an increase in endogenous or exogenous erythropoietin is an increase in the number of blood reticulocytes, followed by an increase in the level of erythrocytes. The most significant side effect associated with r-HuEPO is an increase in blood pressure.

Synthesis of hemoglobin

Hemoglobin (Hb), the oxygen-carrying protein of erythrocytes, makes up about 90% of the dry weight of cells. Blood cells packed with hemoglobin pick up oxygen in the lungs and exchange it for carbon dioxide in the tissues. One erythrocyte can contain as many as 300 hemoglobin molecules. Hemoglobin increases the oxygen-carrying capacity of blood by up to 100 times. Each hemoglobin molecule is made up of two pairs of polypeptide chains (globins) and four iridescent complexes of iron plus protoporphyrin (heme), which are responsible for the ruby-red color of blood and the oxygen-carrying capacity.

Hemoglobin is a spherical tetramer weighing about 64,500 daltons. It contains two subunits and an iron-containing heme group for each protein subunit. Each heme group can bind four oxygen molecules (Figure 1). Several hemoglobin variants have differences in primary structure based on the use of different polypeptide chains: alpha, beta, gamma, delta, epsilon, or zeta (α β, γ, δ, ε, or ζ,). Each polypeptide chain contains about 150 amino acids and is arranged in a sausage-linked configuration as shown in Hemoglobin A, the most common type in adults, consisting of two α- and two β-polypeptide chains ($\alpha_2\beta_2$). A normal variant, fetal hemoglobin (hemoglobin F), is a complex of two α- and two γ polypeptide chains ($\alpha_2\gamma_2$) which binds oxygen with much greater affinity than mature hemoglobin.[10,11]

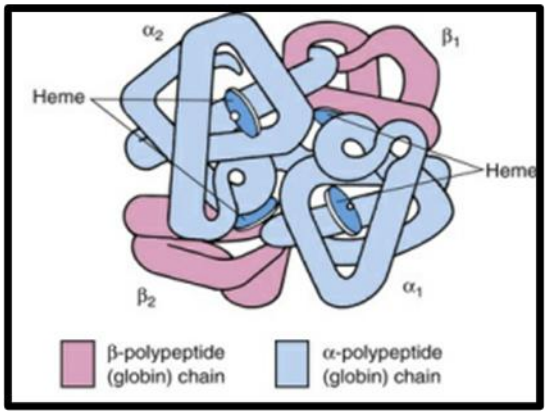

Figure 1. The structure of the hemoglobin molecule.

Table 1. Normal structure of the hemoglobin molecule.

Type of hemoglobin (Hb)	**Polypeptide chain identity**	**Significance**
HbA	a2β2	92% of adults Hb
HbA1c	a2(β-*NH*-glucose)	5% of adult Hb; increased in diabetes
HbA2	α2δ2	2% of adult Hb; increased in β-thalassemia
HbF	a2γ2	Fetal major Hb of the first three months during nine months of pregnancy; promotes oxygen transfer across platelets; increased in β-thalassemia
Hb Gower I	ε4 or ζ2β2	Present in the early embryo; unknown function
Hb Gower II	α2ε2	Present in the early embryo; unknown function
Hb Portland	ζ2γ2	Present in the early embryo; unknown function

Heme is a large, flat disk containing iron-protoporphyrin, which is synthesized in mitochondria and can carry one molecule of oxygen (O_2). So an individual hemoglobin molecule with four heme can carry four oxygen molecules. If all four oxygen binding sites are occupied by oxygen, the molecule is said to be saturated. Through a series of complex biochemical reactions, protoporphyrin, a complex four-ringed molecule, is produced and bound to Fe^{2+}. Reduced Fe (Fe^{2+}) can bind oxygen in the lungs and release it in the tissues, where the oxygen concentration is less, whereas Fe^{3+} Can't. The binding of oxygen to oxyhemoglobin temporarily oxidizes $Fe^{2+}$to be Fe^{3+}, but after the release of oxygen, the body reduces iron to Fe^{2+} (deoxyhemoglobin or reduced hemoglobin) and reactivates the capacity of hemoglobin to bind oxygen. Without reactivation by methemoglobin reductase, Fe^{3+} hemoglobin containing methemoglobin cannot bind oxygen. Iron overload occurs with certain drugs and chemicals, such as nitrates and sulfonamides, and reduces the oxygen-carrying capacity. Hemoglobin also undergoes a conformational change when it binds to oxygen. When one of the iron molecules binds to oxygen, the porphyrin ring changes shape, increasing the exposure of the three remaining iron atoms to oxygen. This greatly increases the affinity for the capacity of hemoglobin to carry oxygen, as occurs in the lungs. When oxygen is derived from hemoglobin, the oxygen-carrying capacity of

hemoglobin is low, facilitating the transport of carbon dioxide back to the lungs.[12,13]

Several other molecules can competitively bind deoxyhemoglobin. Carbon monoxide (CO) directly competes with oxygen for binding to ferrous ions with an affinity about 200 times that of oxygen. So even small amounts of CO can dramatically decrease the ability of hemoglobin to bind and transport oxygen. Hemoglobin also binds carbon dioxide (CO_2) but at a binding site separate from the oxygen binding site. In the lungs, CO_2 released, allowing hemoglobin to bind oxygen.

Erythrocytes may play a role in the maintenance of vascular relaxation. Nitric oxide (NO) produced by blood vessels is the main mediator of relaxation and dilation of blood vessel walls. In the lungs, hemoglobin can simultaneously bind oxygen to iron and NO ions with cysteine residues in globin. As hemoglobin transfers its oxygen to the tissues, it can also release small amounts of nitric oxide, contributing to the dilation of blood vessels and helping oxygen gain access to the tissues.[14,15]

Nutritional requirements for erythropoiesis

Normal development of erythrocytes and synthesis of hemoglobin depends on an optimal biochemical environment and an adequate supply of the necessary building blocks, including proteins, vitamins, and minerals. If this component is deficient for a long time, the production of erythrocytes slows down, and anemia (insufficient number of functional erythrocytes) may occur.

Table 2. Nutritional requirements for erythropoiesis.

Nutrients	Role in erythropoiesis	As a result of nutrient deficiency
Proteins (amino acids)	The structural component of the plasma membrane	Decreased strength, elasticity, and flexibility
	Hemoglobin synthesis	Decreased erythropoiesis and life span of erythrocytes
Cobalamin (vitamin B12)	DNA synthesis, maturation of erythrocytes, facilitator of folate metabolism	Macrocytic (megaloblastic) anemia
Folic (folic acid)	Synthesis of DNA and RNA, maturation of erythrocytes	Macrocytic (megaloblastic) anemia
Vitamin B_6 (pyridoxine)	Heme synthesis	Microcytic-hypochromic anemia
Vitamin B_2 (riboflavin)	Oxidative reactions	Anemia normocytic-normochromic
Vitamin C (ascorbic sour)	Iron metabolism; acts as a reducing agent retaining iron in the ferrous form (Fe++)	Normocytic anemia
Pantothenic acid	Heme synthesis	Not known in humans*
Niacin	None, but necessary for respiration in mature erythrocytes	Not known in humans
Vitamin E	Heme synthesis (?); protection against oxidative damage in mature erythrocytes	Hemolytic anemia with increased fragility of cell membranes; shortened erythrocyte life span in individuals with cystic fibrosis
Iron	Synthetic hemoglobin	Iron deficiency anemia
Copper	Necessary for optimal mobilization of iron from tissues to plasma	Microcytic-hypochromic anemia

*Notes: Although pantothenic acid is essential for the optimal synthesis of heme, a deficiency is experimentally induced fail cause anemia or other hematopoietic disorders

DNA, deoxyribonucleic acid; RNA, ribonucleic acid.

Erythropoiesis cannot proceed in the absence of vitamins, especially B_{12} (cobalamin), folate (folic acid), B_6, riboflavin, pantothenic acid, niacin, ascorbic acid, and vitamin E. Dietary B $vitamins_{12}$ are large molecules that require a protein secreted by the parietal cells into the stomach (intrinsic factor [IF]) for transport across the ileum. Once absorbed, the B $vitamins_{12}$ are stored in the liver and used as needed in erythropoiesis. A defect in production if it causes a

decrease in B_{12} absorption and pernicious anemia (Table 2).

Folate is the second most important vitamin for the production and maturation of red blood cells. Folate is required for DNA synthesis, being a component of three of the four DNA bases (thymine, adenine, and guanine), and for RNA synthesis. Folate absorption occurs primarily in the upper small intestine and is stored in the liver. Folate deficiency is more common than vitamin B_{12} deficiency, and it happens faster. Folic acid reserves can run out in a few months, while vitamin B_{12} thinning can take years. Folate supplements are prescribed for pregnant women because pregnancy increases folate requirements and can cause anemia. Supplements can protect against neural tube defects and can prevent anemia.[16,17]

Normal destruction of senescent erythrocytes

After about 100 to 120 days in circulation, senescent erythrocytes are removed by tissue macrophages, mainly in the spleen. Although mature erythrocytes lack a nucleus, mitochondria, and endoplasmic reticulum, they do possess cytoplasmic enzymes capable of glycolysis (anaerobic glucose metabolism) and production of small amounts of ATP, which provide the energy needed to maintain cell function and membrane flexibility. Metabolic processes decrease as red blood cells age, so less ATP is available to maintain plasma membrane function. Disruption of the binding between the cytoskeleton and the plasma membrane causes red blood cells to become increasingly brittle and lose their reversible deformability, and thus become prone to rupture as they pass through a narrowed microcirculatory area.[18]

In addition, the plasma membrane of old red blood cells undergoes phospholipid rearrangement (movement of phospholipid phosphatidylserine from the cytoplasmic surface of the membrane to the outer surface) which is recognized by phosphatidylserine receptors on macrophages (especially in the spleen) which selectively remove and absorb red cells. If the spleen is not functioning or absent, macrophages in the liver (Kupffer cells) are responsible for this process. Erythrocytes are digested by proteolytic and lipolytic enzymes in the phagolysosomes (digestive vacuoles) of macrophages. The heme and globin of methemoglobin dissociate easily, and the globin is broken down into its component amino acids. The iron in hemoglobin is oxidized, forming Fe^{3+} (methemoglobin), and recycled.[19]

Porphyrins are reduced to bilirubin, which is transported to the liver, conjugated, and finally excreted in the bile as glucuronides. About 6 g of hemoglobin is catabolized daily, producing 200 mg of bilirubin. Bacteria in the intestinal lumen convert conjugated bilirubin into urobilinogen. Although a small part is reabsorbed for further metabolism by the liver or excreted by the kidneys in the urine, most of the urobilinogen is excreted in the feces. Conditions that cause accelerated erythrocyte destruction increase the burden of bilirubin for hepatic clearance, leading to increased serum levels of unconjugated bilirubin and increased urinary excretion of urobilinogen. Gallstones (cholelithiasis) can occur due to chronically increased excretion of bilirubin.

Iron cycle

About 67% of total body iron is bound to heme in erythrocytes (hemoglobin) and muscle cells (myoglobin), and about 30% is stored in mononuclear phagocytes (i.e., macrophages) and liver parenchymal cells as either ferritin or hemosiderin. The remaining 3% (less than 1 mg) is lost daily by excretion of urine, sweat, or bile; exfoliation of epithelial cells from the skin and intestinal mucosa; and minor bleeding. About 25 mg of iron is required daily for erythropoiesis; only 1 to 2 mg of iron is dietary, and the rest is obtained from iron recycling of erythrocytes. Methemoglobin released from the breakdown of old or damaged erythrocytes is dissociated by the enzyme heme oxygenase, and iron is released into the bloodstream, where it is free to rebind with transferrin or be stored in the cytoplasm of macrophages as ferritin or hemosiderin. Small amounts of iron are stored in muscle cells by the heme-containing protein myoglobin. Stored iron that is not available is in cytochromes, catalase, and peroxidase enzymes.

The protein ferritin is the main intracellular iron storage protein. Apoferritin, which is ferritin without attached iron, can store thousands of iron atoms. Several apoferritin complexes combine to form ferritin micelles. Large micelle aggregates (if there is a large amount of iron) produce many ferritin micelles, known

as hemosiderin. Hemosiderin is visible as an iron-based pigment under the light microscope as cell inclusions. Iron in hemosiderin deposits is less available to supply iron when needed. The most common cause of hemosiderin deposition is simple bruising. Small amounts of hemosiderin in iron-rich tissues (i.e., spleen, liver, bone marrow) are considered normal. Large aggregates or their presence in tissues such as the lung or subcutaneous tissue indicate a pathological condition.

Iron is obtained through the utilization of food sources, the release of iron stores, or the catabolism of erythrocytes is transported in the blood bound to apotransferrin so that it becomes transferrin. Under normal conditions, only one-third of the iron-binding site on the transferrin molecule is occupied. Apotransferrin is a glycoprotein synthesized primarily by hepatocytes in the liver but also produced in small quantities by tissue macrophages, submaxillary and mammary glands, and the ovaries or testes. Iron for hemoglobin production is carried by transferrin to the bone marrow, where it binds to transferrin receptors on erythroblasts. Transferrin receptors are present on the plasma membrane of all nucleated cells, although they are present at very high levels in erythroid precursors and rapidly proliferating cells (e.g., lymphocytes) and are considered the sole route of cellular entry for transferrin-bound iron. Transferrin is recycled (transferrin cycle) via intracellular dissociation of iron with the resulting secretion of apotransferrin into the bloodstream.

Iron is transported to the mitochondria of the erythroblasts (where hemoglobin is produced), Where heme synthetase enzymes incorporate iron into protoporphyrin to form heme. Heme then binds to globin to form hemoglobin. The iron that is not used in erythropoiesis is temporarily stored as ferritin or hemosiderin and is then excreted. Spleen red pulp macrophages are specialized for iron recycling by increasing the expression of proteins for hemoglobin uptake, heme breakdown, and iron export. Body iron homeostasis is primarily controlled by the hormone hepcidin. Hepcidin is synthesized in the liver and released as a 25-amino acid peptide, most of which is bound in the plasma with a high affinity for$_2$-macroglobulins and a relatively lower affinity for albumin. Hepcidin production of hepatocellular hepcidin is regulated physiologically by iron absorption by the body, the rate of erythropoiesis, and the level of oxygen saturation. Hepatocytes sense circulating iron levels through receptors for transferrin, the main transporter of iron in plasma. Excess iron is stored in hepatocytes and macrophages. Hepatocytes sense these levels via bone morphogenetic protein (BMP), most likely BMP-6, which is a growth factor produced mostly by bone marrow sinusoid endothelial cells and the mother against the decapentaplegic protein (SMAD) pathway (BMP SMAD). Hepcidin production can also be induced by inflammation via IL-6.

Hepcidin regulates iron levels through its binding capacity with ferroportin, which is a transmembrane iron exporter found in the plasma membrane of cells that transport or store iron, including macrophages, hepatocytes, and enterocytes. Total body iron balance is maintained through controlled absorption rather than excretion. Dietary iron (mainly as Fe^{2+}) is transported directly across the epithelial cell membrane (enterocytes) in the duodenum and proximal jejunum. Hepcidin induces the internalization and degradation of ferroportin, resulting in increased intracellular iron stores, decreased absorption of dietary iron, and decreased circulating iron levels. Decreased hepcidin production leads to the release of stored iron and increased absorption of food. Thus, when body iron stores are low, or the demand for erythropoiesis is increased, dietary iron is transported rapidly through the epithelial cells and into the plasma. If body stores are high and erythropoiesis is not increased, iron transport stops, although iron can cross the plasma membrane of epithelial cells and be stored as ferritin.[20]

2. Conclusion

Erythropoiesis is the development of red blood cells. Erythroid progenitor cells proliferate and differentiate into large nucleated proerythroblasts, which are committed to producing cells of the erythroid series.

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