Influence Of Oxidative Stress On Erythrocyte’s Formation And Function Resulting In Anemia

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Abstract

Anemia is a condition with a reduced amount of total blood cell (RBC) or blood hemoglobin or reduced blood oxygen-carrying capacity. Blood loss, decreased production of red blood cells and increased breakdown of red blood cells can cause anemia. Trauma and gastrointestinal bleeding are a source of blood loss, but certain factors, including iron deficiency, vitamin B12 deficiency, lower erythropoietin level, slight bone marrow neoplasm thalassemia, genetic disorders such as sickle cell, parasitic infection including malaria and other autoimmune diseases are the causes of lower erythrocytes. Anemia is also associated with oxidative stress owing to two processes. Oxidative stress affects the function of the kidney resulting in lower erythropoietin production, which ultimately affects erythropoiesis and therefore reduces erythrocyte production. In other way, oxidative stress also reduces the amount of erythrocyte by increasing the rate of programmed cell death of erythrocytes (eryptosis) by activating the calcium channels and cell loss of KCl. This review provides insight into the mechanism followed by oxidative stress to reduce the amounts of erythrocytes in the body resulting in the development of anemia.

Keywords: Anemia, Oxidative Stress, Red blood cell, Erythropoiesis, Hemoglobin

I. Introduction

Lee van Hock identified erythrocytes as the most common physiologically active nucleate cells in human blood samples. The estimated blood in healthy women is 14.8 million cells and in males 15.4 million cells per cubic millimeter. Approximately 4200 to 12000 leukocytes are measured with a minimum of 1 μL of human blood containing 150,000–400,000 platelets and 20–30 trillion red cells. People at high altitude have more erythrocytes with reduced oxygen tension (Pierige et al., 2008). Erythrocytes are versatile cells that can be squeezed by narrow capillaries. Red blood cells are 2 μm (6-8 μm in diameter) thick (Goodman et al., 2007). Erythrocyte plasma membrane encloses metalloprotein for transporting O2 to the tissue and CO2 back to the lungs. Hemoglobin contains 4 heme groups in the center of each molecule, and the protein gives red color to erythrocytes. RBCs have about 270 million hemoglobin (Mclaren et al., 1987). Nucleated red blood cells have enough room to transport oxygen. Energy is produced anaerobically due to mitochondrial absence, and oxygen from these cells is not consumed (Tavassoli, 1978). Erythrocytes have a natural lifespan of 120 days following liver and spleen degradation and circulation removals (Wesseling et al. 2016).

Erythropoiesis is a mechanism that generates red blood cells (erythrocytes) from erythropoietic cells to mature red blood cells (Pelley, 2007). It is stimulated by decreased circulation of O2 and is sensed by the kidneys, which then secrete the erythropoietin hormone (Sherwood et al., 2012). The hormone enhances the proliferation and differentiation of red cell precursors, which triggers increased hemopoietic tissue erythropoiesis, which eventually produces red blood cells (erythrocytes) (Sherwood et al., 2012).
The dynamic multiphasic process is the product of human erythropoiesis, varying from multipotent hematopoietic stem cell (HSC) to mature red blood cells (Orkin, 2000). The early phases of erythroid differentiation involve the interaction mechanism through which HSCs differentiate between more committed erythroid progenitors, the specific myeloid progenitor, Megakaryotic erythroid progenitor and the burst-forming erythroid unit (BFU-E). The 1st precursor cells to be assigned to the erythroid line are BFU-Es (Gregory and Eaves 1977). These BFU-Es distinguish between unit-erythroid (CFU-E) and helps to differentiate terminals (Zivot et al., 2018).

The second stage of erythroid growth includes the differentiation of nuclear prerequisites from proerythroblast. This cycle is defined by a slow deposition of hemoglobin, a slow decrease in cell size and an eventually enucleating nuclear condensation (Granick and Levere, 1964).

Reticulocyte maturation into erythrocytes is the last stage. During this process, the erythrocyte is biconcave and circulates through the bloodstream before it is eliminated by macrophages in the reticuloendothelial system (Gifford et al., 2006).

**Erythropoietin**

Erythropoietin (EPO) is a cytosecretory protein that primarily responds to a hypoxia of the cells and causes the formation of RBCs in the bone marrow (Hoseini-Zara, 2012). In order to account for the natural red blood cell turnover, low EPO levels (approximately 10 mU/mL) are continuously isolated. Popular causes of cellular hypoxia leading to increased EPO rates include any type of anemia (Hodges et al., 2007).

Erythropoietin develops by interstitial fibroblast in the kidney. This is also formed in the perisinoidal hepatic cells. Thrombopoietin is its homologous agent (Broxmeyer 2013).

The particular role of the EPO is to control the supply of oxygen to peripheral tissue and to promote the hypoxic induction of the transcription of EPO genes (Zivot et al., 2018). This process includes many transcript factors including the comparatively weak hypoxia inducibility factor and GATA binding protein (Bunn 2013). This process involves many transcript factors. Binding EPO mRNA expression in the area supporting the EPO has been negatively regulated by the GATA (1-3) proteins (Imagawa et al. 1997). The transcription rate ofthis gene is hence controlled by the local oxygen. GATA-1 is essential to maintain and proliferate the hematopoietic stem and progenitor cells for the endurance and terminal differences of the erythroid progenitor. Targeted genes for promoting erythroid maturation and ultimate β-globin expression are a relative proportion of GATA-1 and GATA-2 expression (Mooriguchi and Yamamoto 2014).

This protein binds to the receptor causing homodimerization. This temporarily controlled the regulation of erythropoiesis and human studies have proven its linkage to the receptor from the CFU-E stage to the polychromatophilia process (Wu et al. 1995). JAK2, which ultimately phosphorylates and stimulates STAT5 induction, is one of the major signaling channels via the relationship between erythropoietin and receptor (Witthuhn et al., 1993). The JAK2 and STAT5 pathway has shown that it stimulates the genes required in order to withstand the erythroid progenitor (Grebien et Al., 2008). Furthermore, STAT5 phosphorylation is essential in times of hypoxic stress to accelerate erythropoiesis. Included are MAP-K and PI3-K, other downstream pathways for activation. Similarly, these pathways involve the distribution and development of erythroid progenitors (Zhang et al., 2014).

There is a high-level expression of erythropoietin receptors in erythroid progenitor cells (Elliott et al., 2006). Functional EPO receptors are not detected in these tissues during controlled experiments (Sinclair et al. 2010). Red cells do not express the bloodstream receptor for erythropoietin themselves, so they cannot respond to the EPO. In the blood, however, there has been indirect reliance on plasma erythropoietin, a mechanism called neocytolysis, for the survival of red cells (Risso et al., 2014). There is also clear evidence that the expression of the EPO receptor in brain injury is highly regulated (Ott et al., 2015).
Oxidative stress

The state of imbalances between excessive (free) radicals and the degradation of antioxidant radicals (Locatelli et al. 2003) is characterized as oxidative stress (OS). Multiple antioxidant defense pathways are used to manufacture oxidizing compounds like ROS and RNS under physiological condition (Birben et al. 2012). Reactive species don't destroy cells necessarily. These oxidizing compounds serve as second messengers at mild concentrations and control the intracellular pathways. The development of OS leads to metabolic dysregulation or oxidation at cellular level in the case of imbalances in the prooxidant/antioxidants equilibrium (Daenen et al., 2019). This eventually leads to a number of disorders due to cellular molecular inactivation (Di Meo et al., 2016).

![Diagram of oxidative stress pathways](image)

**Fig. 2:** Inflammation and ROS role in tissue damage

Anemia

Anemia (also called anemia) is a reduction in the total blood cell (RBC) or blood hemoglobin (or reduced blood oxygen-carrying capacity) (Qaseem et al., 2013). When anemia occurs gradually, there are always ambiguous symptoms that can include fatigue, exhaustion, shortness of breath, and low exercise capacity. Anemia can lead to confusion, a feeling of dying, a loss of consciousness, and an increased thirst when anemia occurs quickly (Stein et al., 2016).

Loss of blood, reduced red blood cell production and increased red blood cell breakdown can cause anemia. Trauma and gastrointestinal bleeding are a source of blood loss (Beutler and Waalen 2006). Reduced developmental factors include iron deficiency, vitamin B12 deficiency, lower erythropoietin level, thalassemia, and some neoplasms of the bone marrow. Genetic disorders such as sickle cell anemia, oxidative stress, infection with parasites including malaria, and other autoimmune diseases are the causes of increased erythrocyte breakdown (Patel, 2019). Anemia is often graded by the size and hemoglobin of the red blood cells in each cell. If the cells are small, they are considered to be microcytic anemia; when larger, macrocytic anemia; and if average in size, normocytic anemia are considered (Aapro and Linkb, 2008). Males have a diagnosis of hemoglobin of less than 130 g/L (13-14 g/dL) and females have a diagnosis of hemoglobin of less than 120 g/L-130 g/L (12-13 g/dL) (Beutler and Waalen, 2006).

Oxidative stress and anemia

Anemia is one of the big issues of health. Around 30 percent of the world’s population is suffering anemia according to WHO. The most severe factor of anemia is iron deficiency; however, recent research has shown that erythrocyte ROS (reactive oxygen species) is the leading cause of anemia (Iuchi, 2012). ROS in erythrocytes may be increased either by activating the ROS generation or by suppressing the antioxidant/redox mechanism. Oxidative stress occurs when erythrocytes undergo increased levels of free radicals (Amer et al. 2008).

Oxidative status leads to and modulates various biological cell functions (Fibach & Rachmilewitz, 2008). Oxidative stress, however, is cytotoxic and oxidizes proteins, lipids and DNA that lead to organ and cell injury. Apoptosis and neuronal ageing, and various diseases such as obesity, atherosclerosis, diabetes, coronary, thromboembolic and neurodegenerative disorders are all known to be linked with oxidative stress. Hemolytic anemia is also considered to be related (Chan et al., 2001). While the primary etiology of these different anemias does not include oxidative stress, they mediate several conditions, such as hemolysis (Fibach and Rachmilewitz, 2008).
Oxidative stress may contribute to the development of anemia in two ways. One is by affecting the function of the kidney, thus reducing the production of erythropoietin that ultimately affects erythropoiesis (Căpuşă and Mircescu, 2010). Increased cell death of erythrocytes is another form of OS in the development of anemia.

**Oxidative stress influence on RBCs formation**

A large-scale analysis of the involvement of OS to the development of renal disorder and subsequent kidney failure was conducted (Modaresi et al., 2015). ROS are involved in regulating the physiology of the kidney system, making the kidney particularly compromising to redox imbalances and OS (Daenen et al. 2018). ROS formation or ROS developmental changes may take place both in renal cortex and in medulla, with various repercussions of sodium/fluid retention alterations, fibrotic alterations and producing proteinuria (Nistala et al., 2008). Anemia is also associated with mild to severe chronic kidney disease (CKD). Understanding the pathogenesis of renal anemia is the basis for an effective treatment strategy. Renal anemia is well known to have multifactorial pathogenesis (Căpuşă and Mircescu, 2010). Although erythropoietin deficiency is the key cause of erythropoietin impairment, several other causes play a significant role. In addition, OS may also lead to a reduction in RBCs life and a deterioration in erythropoietin activity to hypo proliferative normochromic normocytic renal anemia (Usberti et al. 2002).

**Increased cell death of RBCs (Eryptosis)**

Iron deficiency (ID) is the most common type of anemia affecting between 500 and 600 million people worldwide (Pretorius et al., 2016) Impairing iron absorption, loss of iron, or chronic bleeding that leads to insufficient erythrocyte production can be the root causes of iron insufficiency. Anemia, however, is not only the product of compromised erythropoiesis, but also may be the result of eryptosis when iron-deficient erythrocytes have shortened their lives (Bissinger et al., 2019). Research by Kempe and others indicated that PS exposure at membrane in mice under iron-deficient diets increased from 2.4% to 3.7% compared to control dietary mice models. In addition, other experiments show an increase in cation channel activity and cytosolic calcium\([Ca^{2+}]_i\) in these cells (Kempe et al., 2006). Because cation canals in erythrocytes are stimulated by oxidative stress, improved clearance such cells and therefore ID anemia is likely to result (Bissinger et al., 2019).

Oxidative stress is partially effective when Ca2 + channels are activated with Ca2 + input and increased cytosolic concentration of Ca2 + ([Ca2+]i) (Duranton et al. 2002). In erythrocytes without TRPC6 channels, [Ca2+]i levels are significantly reduced (Foller et al., 2008). In addition to the increase of [Ca2+]i, Ca2 + -sensitive K+ canals with subsequent hyperpolarization of the cell membrane, the output of Cl- and cell shrinkage is activated by cellular loss of KCl with the water being osmotically driven. Increased cytosolic calcium level is also followed by stimulation of cell membrane scrambling with phosphatidylserine translocation from the inner membrane leaflet to the surface of the erythrocyte (Lang and Lang, 2015). Ceramide generated by sphingomyelinase increases the calcium sensitivity of the cell membrane scrambling. Platelet Activating Factor (PAF) activates the enzyme generated by A2 phospholipase (Mandal et al., 2003).

In addition, caspase stimulation is partially effective for oxidative stress, leukotrienes and lipoic acid. Anion exchanger AE1 is cleared from oxidative stress triggered by caspases and allows phosphatidylserine to be detected on the outer surface of the inner leaflet (Mandal et al. 2002). However, Ca2 + and Ca2 + dependent phosphatidylserine exposure is not required for activation of Caspases. In addition, Cl-channels in erythrocytes required for cell shrinkage, a typical feature of eryptosis, are stimulated by oxidative stress (Lange et al., 2004). In addition, heterotrimeric G-protein subunit Gut2 is used to signal regulatory eryptosis. Several kinases have been shown to be involved in the regulation of eryptosis (Lang et al., 2015).
**II. Conclusion**

Erythrocytes are the most common nucleated cells that are physiologically active. Erythrocytes are versatile cells that can be compressed by narrow capillaries with a thickness of 2 μm (6-8 μm in diameter). Erythrocyte plasma membrane encloses metalloprotein for transporting O2 to the tissue and CO2 back to the lungs. Hemoglobin contains 4 heme groups in the center of each molecule, and the protein gives red color to erythrocyte. Erythropoiesis is a mechanism that generates red blood cells (erythrocytes) from erythropoietic cells to mature red blood cells, stimulated by a kidney producing hormone erythropoietin that is involved in the production of red blood cells in the bone marrow. ROS are continuously generated in the body during cell metabolism and removed by the body's defense system. But if ROS is not properly removed or produced in an increased amount, oxidative stress is produced in the body. Oxidative stress (OS) is the cause of many diseases, including cardiovascular disorders, impaired kidney function, diabetes, cancer, etc. OS is also involved in the development of anemia. Anemia is a condition with lower RBCs level or hemoglobin content in the body. Oxidative stress causes anemia in two ways. In one way, as oxidative stress causes damage at the organ level, it influences the proper functioning of the kidneys, as a result of which the kidney does not produce enough erythropoietin hormone to influence the production of red blood cells. In other way, oxidative stress reduces the level of RBCs in the body by increasing the rate of their programmed cell death (eryptosis). As erythrocytes are in direct contact with oxygen, they are more likely to be attacked by ROS/OS. Oxidative stress increases the calcium intake of the cell by activating K-sensitive Ca-channels. This results in cellular loss of KCl and water, resulting in cell shrinkage, which is a hallmark of eryptosis. Oxidative stress also stimulates the translocation of phosphatidylserine and the symmetry of the cell membrane. Lower erythrocyte production and increased cell death are two possible mechanisms for the development of anemia by OS.

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