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The associations between erythroferrone and hepcidin during iron deficiency anemia, iron overload and pregnancy

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***Abstract*---**Erythroferrone (ERFE) is a hormone produced by erythroblasts in the bone marrow in response to erythropoietin. Erythroferrone is a potential clinical biomarker for assessing erythropoiesis in patients with blood disorders and till now no more enough studies in erythroferrone among human, most studies are conducted in animals. Erythroferrone inhibition of hepcidin allows ferroprotein, the sole known iron exporter, to mediate the release of iron stored in gut, spleen and liver in the blood plasma. Erythroferrone functions as erythroid modulator of iron metabolism and hemoglobin synthesis. Erythroferrone is therefore a biomarker for different types of anemia, for cardiological diseases and potentially also for metabolic disease. However, few studies of the function of ERFE in humans because is recently discovered and remains to be investigated. In this review we briefly address the between erythroferrone and hepcidin during iron deficiency anemia, iron overload and pregnancy. Studies in this review were identified through a search using the following electronic databases: PubMed, Academia, Scopus, Google Scholar, and another open database source. The erythroferrone hormone may act as potential factor in physiological hepcidin suppressor in cases with iron deficiency anemia and play a key role in treatment process among those patients in status of iron deficiency or iron overload. We hypothesize that ERFE is a sensitive biomarker of iron deficiency, iron overload and anemia in pregnancy and neonates also research is needed to understand the relationship between maternal ERFE and neonatal.

***Keywords*---**Erythroferrone, Pregnancy, ERFE, Hepcidin, Iron Deficiency Anemia.

Introduction

Erythroferrone (ERFE) is the main erythroid regulator of hepcidin, the homeostatic hormone controlling plasma iron levels and total body iron. When the release of erythropoietin from the kidney stimulates the production of new red blood cells, it also increases the synthesis of ERFE in bone marrow erythroblasts [(1)]. The hormone erythroferrone (ERFE) is produced response to hemorrhage, hypoxia, or other erythropoietic stimuli, and it suppresses the hepatic production of the iron-regulatory hormone hepcidin, thereby mobilizing iron for erythropoiesis. Suppression of hepcidin by ERFE is believed to be mediated by interference with paracrine bone morphogenetic protein (BMP) signaling that regulates hepcidin transcription in hepatocytes. In anemias with ineffective erythropoiesis, ERFE is pathologically overproduced, but its contribution to the clinical manifestations of these anemias is not well understood [(2)]. The coordination between erythropoietic activity and iron homeostasis is provided by hepcidin, which controls body iron balance by negatively regulating the activity of the iron exporter, ferroprotein. Hepcidin expression is inhibited by iron deficiency and high erythropoietic activity, a response that increases iron availability to meet iron needs for hemoglobin (Hb) synthesis [(3)]. Erythroferrone is a mediator of the response to erythropoietic stress, suppressing hepcidin to promote the mobilization of stored iron and the absorption of dietary iron. Erythroferrone inhibits hepcidin synthesis by binding bone morphogenetic proteins and thereby inhibiting the bone morphogenetic protein pathway that controls hepcidin expression [(4)]. Dysregulation of hepcidin production results in a variety of iron disorders. Hepcidin deficiency is the cause of iron overload in hereditary hemochromatosis, iron-loading anemias, and hepatitis C. Hepcidin excess is associated with anemia of inflammation, chronic kidney disease and iron-refractory iron deficiency anemia [(5)]. Also, another dysregulation form is iron deficiency (ID), is one of the world's most common nutritional deficiencies and affects >2 billion people. Many of these individuals are so iron deficient that RBC production is impaired, thus resulting in anemia. Insufficient dietary intake is the major cause of ID and low iron bioavailability in a plant-based diet enhances susceptibility. In rare cases, ID can result from genetic disturbances in iron homeostasis [(6)]. Defining the mechanisms of this dysregulation is important for understanding the pathogenesis of common conditions associated with disordered iron metabolism, increasing, decreasing and erythropoiesis activity. Stress erythropoiesis causes suppression of hepcidin to increase iron availability for hemoglobin synthesis. The erythroid hormone erythroferrone (ERFE) was identified as the mediator of this process.

Structure and Function of Erythroferrone

Erythroferrone in humans is transcribed as a precursor of 354 amino acids, with a signal peptide of 28 amino acids. The function of Erythroferrone is iron-regulatory hormone, that regulates iron metabolism through its actions on hepcidin and this acts as an erythroid regulator after hemorrhage, produced by erythroblasts following blood loss and mediates suppression of hepcidin (HAMP) expression in the liver, thereby promoting increased iron absorption and mobilization from stores [(7)].

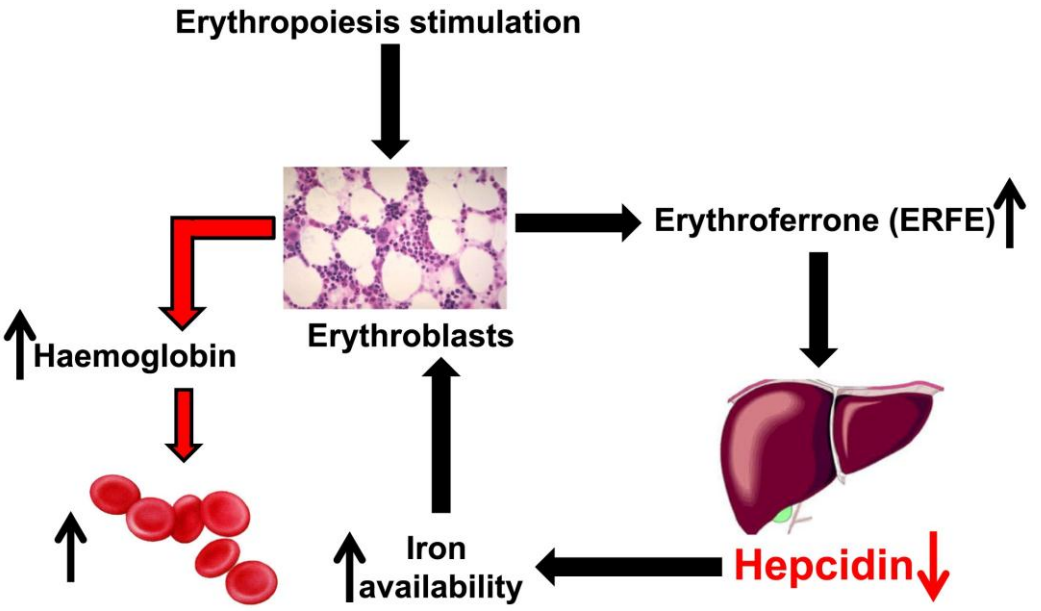

Fig I: (Leuenberger, et al.2017)[8]

Erythroferrone hormone in Iron deficiency anemia (IDA):

The WHO has recognised iron deficiency anaemia (IDA) as the most common nutritional deficiency in the world, with 30% of the population being affected with this condition. Although the most common causes of IDA are gastrointestinal bleeding and menstruation in women, decreased dietary iron and decreased iron absorption are also culpable causes[9]. Iron deficiency anemia occurs when the body doesn't have enough iron to produce hemoglobin. Erythroferrone is a hormone that regulates iron hemostasis and metabolism through its actions on hepcidin [10]. Iron homeostasis is essential for maintaining the function of many tissues, particularly the liver, which serves as the major organ for iron metabolism [11]. The main role of Erythroferrone in iron hemostasis inhibit the expression of the liver hormone, hepcidin. This process also it controlled by the renal hormone, erythropoietin. By lowering hepcidin, Erythroferrone increases the function of the cellular iron export channel, ferroportin. This then results in increased iron absorption from the intestine and mobilization of iron from stores, which can then be used in the synthesis of hemoglobin in new red blood cells [7,12]. In anemias, decreased oxygen tension in the kidney drives increased erythropoietin production, which induces ERFE secretion by erythroblasts and thereby suppresses the hepatic production of hepcidin. In anemias with ineffective erythropoiesis, the erythroblast population is greatly expanded but many erythroblasts undergo apoptosis before completing differentiation, so that relatively few erythrocytes are produced. Because there are many more erythroblasts when erythropoiesis is ineffective, ERFE production is further increased and the suppression of hepcidin is greater than in effective erythropoiesis. Very low hepcidin levels cause hyperabsorption of iron and the release of iron from macrophages. Transferrin saturation rises and the generation of no transferrin-bound iron (NTBI) is increased. NTBI is taken up by the liver and other parenchymal organs, leading to organ damage [13]. However, few studies of

the function of ERFE in humans because is recently discovered and remains to be investigated. Based on a study conducted by Fady M. El Gendy MD, elt. To investigate the link between serum erythroferrone levels and iron status parameters in pediatric patients with iron deficiency anemia, serum erythroferrone showed significantly elevated levels in iron-deficient patient (197.00 ± 85.51 pg/ml) compared to those in the control group (42.22 ± 16.55 pg/ml) ($P < 0.001$). As well as a negative correlation found between serum erythroferrone and hemoglobin concentration, serum iron, transferrin saturation, and serum ferritin. While serum erythroferrone concentrations and TIBC were positively correlated [14]. The discoveries of hepcidin as a central regulator of iron metabolism and erythroid regulation of hepcidin by ERFE have enabled a more comprehensive exploration of aberrant iron metabolism and molecular mechanisms underlying this effect in many clinical scenarios. Specifically, the predictive value of iron stores and erythropoietic iron responsiveness to support the management of anemias has not yet been fully explored [15].

Erythroferrone and Iron Overload

Iron overload can occur in people of any age, any ethnicity, or gender; iron overload is a condition of excess (too much) iron in the body. There are multiple diseases or conditions such as hereditary hemochromatosis, hemophilia, thalassemia, sickle cell disease, aging, and estrogen deficiency that can cause iron overload in the human body [16]. Several studies have confirmed that elevated iron accumulation complicates diseases with βthalassemia as resultant a major constituent of ineffective erythropoiesis, in which erythroblast count are greatly expanded, but the erythroblasts undergo intramedullary apoptosis before completing differentiation [17,18]. Hepcidin is a key regulator of iron homeostasis and a mediator of anemia of inflammation. Its deficiency is the likely cause of most types of hereditary hemochromatosis. The peptide inhibits cellular iron efflux by binding to the iron export channel ferroportin and inducing its internalization and degradation. Either hepcidin deficiency or alterations in its target, ferroportin, would be expected to result in dysregulated iron absorption, tissue maldistribution of iron, and iron overload [19]. In preclinical studies, increasing hepcidin levels prevented iron overload or redistributed iron to sites of safe stor age. Potentially useful in hemochromatosis, whose treatment is still based on phlebotomy [20]. Most of studies concluded that, in people with thalassemia and iron deficiency anemia, erythroferrone levels in the blood are higher than in people without thalassemia and iron deficiency anemia. Knowing the mechanisms of erythroferrone as erythroid regulator of hepcidin and iron metabolism during thalassemia and in iron deficiency anemia important in the diagnosis and treatment for both conditions. However, till now few studies of the function of ERFE in humans because is recently discovered and remains to be investigated and most studies are conducted among animals [21]

Erythroferrone during Pregnancy

Pregnant women are at an increased risk of iron deficiency, and this condition has been associated with adverse maternal and neonatal outcomes [22]. Complications can arise in pregnancies for many reasons. Sometimes a woman's existing health conditions contribute to problems. Other times, new conditions

arise because of hormonal and body changes that occur during pregnancy, sometime inherited and acquired disorders play a major role among these complications leas to pregnancy loss [23,24,25].Maintaining adequate iron status during pregnancy is important for the mother and her developing fetus. Iron homeostasis is influenced by 3 regulatory hormones: erythropoietin (EPO), hepcidin, and erythroferrone (ERFE). To date, normative data on ERFE across pregnancy and its relations to other hormones and iron status indicators are limited [26].During iron replete pregnancy, ERFE plays a minor role in maternal and fetal iron homeostasis and erythropoiesis. However, in response to iron-deficiency anemia during pregnancy, ERFE is important for the redistribution of iron within the embryo to support embryo erythropoiesis [27]. Delaney, Katherine et al. conducted an study aimed to characterize concentrations of ERFE across gestation and evaluate this hormone in relation to other Fe status biomarkers and regulatory hormones in mothers across pregnancy and concluded that the ERFE was significantly higher in anemic women across pregnancy and, as expected, was positively associated with indicators of erythropoietic drive. ERFE however, was not significantly associated with hepcidin, possibly because hepcidin is regulated by multiple competing signals. More research is needed to understand the relationship between maternal ERFE and neonatal Fe status at birth [28]

Conclusion

The erythroferrone hormone may act as potential factor in physiological hepcidin suppressor in cases with iron deficiency anemia and play a key role in treatment process among those patients in status of iron deficiency or iron overload. We hypothesize that ERFE is a sensitive biomarker of iron deficiency, iron overload and anemia in pregnancy and neonates also research is needed to understand the relationship between maternal ERFE and neonatal.

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Conflicts of Interest
The author declares no conflict of interest

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