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The Role of Erythroferrone Hormone as Erythroid Regulator of Hepcidin and Iron Metabolism during Thalassemia and in Iron Deficiency Anemia- A Short Review

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Authors' contributions

All authors equally contributed for preparing this review article. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Erythroferrone (ERFE) is a hormone produced by erythroblasts in the bone marrow in response to erythropoietin controlling iron storage release through its actions on hepcidin, which acts on hepatocytes to suppress expression of the hormone hepcidin. Erythroferrone now considered is one of potential clinical biomarkers for assessing erythropoiesis activity in patients with blood disorders regarding to iron imbalance. Since discovery of in 2014 by Dr. Leon Kautz and colleagues and till now no more enough studies in Erythroferrone among human, most studies are conducted in animals. In this review we briefly address the Role of Erythroferrone hormone as erythroid regulator of hepcidin and iron metabolism during thalassemia and in iron deficiency anemia. Studies in this review were identified through a search using the following electronic databases: PubMed, Academia, Scopus, Google Scholar, and another open database source. **Conclusion:** 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

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and iron metabolism during thalassemia and in iron deficiency anemia important in the diagnosis and treatment for both conditions. The erythroferrone hormone may act as potential factor in physiological hepcidin suppressor in cases with iron deficiency anemia and thalassemia disease and play a key role in treatment process among those patients in status of iron deficiency or iron overload. 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.

Keywords: Erythroferrone; ERFE; hepcidin; thalassemia; iron deficiency anemia.

1. INTRODUCTION

Erythroferrone (ERFE) is a glycoprotein hormone was identified in 2014 in mice where the transcript was found in bone marrow. Erythroferrone is produced by erythroblasts in response to erythropoietic activity by stimulation of erythropoietin that acts directly on the liver to inhibit production of hepcidin, lead to increases iron delivery for intensified activity of erythropoiesis [1]. 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, ferroportin .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 [2]. 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 [3]. 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 [4]. 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 [5]. 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.

2. 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 [6].

3. ERYTHROFERRONE HORMONE IN IRON DEFICIENCY ANEMIA (IDA)

Iron deficiency anemia (IDA) is one of the most common types of nutritional anemia and considered a major public health problem in developing countries [8]. 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 [9]. Iron homeostasis is essential for maintaining the function of many tissues, particularly the liver, which serves as the major organ for iron metabolism [10]. The main role of Erythroferrone in iron hemostasis inhibit the expression of the liver hormone, hepcidin. This process also can control by the renal hormone, erythropoietin. By lowering hepcidin, Erythroferrone increases the function of the cellular iron export channel, ferroportin. This then

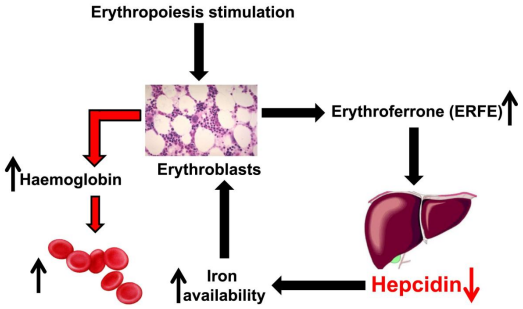

Fig. 1. Function of erythroferrone [7]

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 [6,11]. Till now there are no more studies conducted in human regarding the role of erythroferrone and most studies are conducted in animals. Based on a study conducted by Fady M. et al. Investigate the link between serum erythroferrone levels and iron status parameters in pediatric patients with iron deficiency anemia, serum erythroferrone showed significantly elevated levels among 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 Total iron binding capacity were positively correlated [12].

4. ERYTHROFERRONE HORMONE IN THALASSEMIA

Thalassemia is a genetic blood disorder in which the body cannot produce normal hemoglobin or decreased hemoglobin production. Alpha-thalassemia and beta-thalassemia are the two types of thalassemia, are classified according to the affected part of hemoglobin and it can be classified to the severity of the thalassemia as a trait, carrier, intermedia, or major. Thalssemia manifest inappropriately low hepcidin production and consequent excessive absorption of dietary iron, leading to iron overload. Erythroferrone (ERFE) is an erythroid regulator of hepcidin synthesis and iron homeostasis [10]. In a study conducted at thalassemia center in ALzahra`a hospital/Iraq, included Seventy patients aged about (11-28 year) and 20 subjects healthy as control group, showed significantly elevated Serum ERFE levels in Beta thalassemia and concluded high level of ERFE as new biomarker in patients with major and intermedia beta thalassemia is associated with mild or severe anemia and iron overload especially in patients with splenectomy [1]. A cross-sectional study included seventy beta-thalassemia patients was done at the pediatric thalassemia clinic of Ain Shams University Pediatric Hospital, Egypt to investigate ERFE levels in Egyptian β-Thalassemia major patients seeking to understand its role in the prediction of iron overload states. Patients were divided into two groups based on the degree of iron overload, ERFE gene expression, and serum hepcidin analyzed. The results showed that Both ERFE gene expression levels and transferrin saturation (TS%) values were able to differentiate between cases with different degrees of iron overload, as opposed to hepcidin. Compared with serum hepcidin and ERFE gene levels (AUC 0.807 and 0.677) transferrin saturation was recognized as the best predictor of iron overload (AUC 0.893), and ERFE gene expression was an independent predictor for the estimated TS%. This study proposes that the use of the combination of the ERFE gene expression and serum hepcidin estimation to prove the role of estimated TS% as a successful approach in screening for iron overload in β-TM patients [13]. In mouse models of beta-thalassemia, a small rise in hepcidin resulted in the reduction of iron overloads as well as improvement in anemia, which was seen as induced by either transgenic hepcidin overexpression, knockdown of the negative hepcidin regulator matriptase, or hepcidin agonists administration. This effect induces a lower reactive oxygen species (ROS) apoptosis, and Growth differentiation factor 11(GDF11) in erythroid precursors, and decreased a-globin precipitation, while iron overload is improved by ERFE deficiency in b-thalassemia mice, anemia is not improved, implying that hepcidin can play additional roles locally in the bone marrow or

ERFE may have an auto paracrine function in preventing erythroid maturation [14]. In most studies Erythroferrone levels in blood have been shown by immunoassay to be higher after blood loss or erythropoietin administration. Patients with thalassemia have very high levels, and these decrease after blood transfusion [15]. In the current study, we discovered disordered maternal iron homeostasis in women who had spontaneous abortions during early pregnancy, as characterized by increased serum iron and hepcidin levels, and conversely, reduced serum ERFE levels, compared to healthy control individuals and women with normal pregnancy 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. Few studies conducted in disorders other than Thalssemia. In some study conducted by Shuting Wei et al. they discovered disordered maternal iron homeostasis in women who had spontaneous abortions during early pregnancy, as characterized by increased serum iron and hepcidin levels, and conversely, reduced serum ERFE levels, compared to healthy control individuals and women with normal pregnancy [16].

5. CONCLUSION

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. The erythroferrone hormone may act as potential factor in physiological hepcidin suppressor in cases with iron deficiency anemia and thalassemia disease and play a key role in treatment process among those patients in status of iron deficiency or iron overload. 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.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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