Int. J. Curr. Res. Med. Sci. (2018). 4(10): 42-48

International Journal of Current Research in Medical Sciences

ISSN: 2454-5716

P-ISJN: A4372-3064, E -ISJN: A4372-3061

www.ijcrims.com

Review Article

Volume 4, Issue 10 -2018

DOI: http://dx.doi.org/10.22192/ijcrms.2018.04.10.007

An update on hypoxic regulation of iron homeostasis and bone marrow environment

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Abstract

Iron is very important in the body especially for effective erythropoiesis and should be maintained at a normal level. Some disease conditions may precipitate increased or decreased levels of iron. The body has some iron regulatory proteins which ensure stability in the balance between storage iron and circulatory iron. The availability of sufficient amounts of iron is critically important for normal and stress-induced erythropoiesis. Serum iron levels depend on intestinal absorption from the diet, transport capacity in the blood, recycling of iron released from phagocytosed erythrocytes, and the release of iron from other tissue stores, such as the liver. This paper is written to review the regulation of iron in bone marrow environment.

Keywords: Iron, erythropoiesis, bone marrow environment.

Iron

The availability of sufficient amounts of iron is critically important for normal and stress-induced erythropoiesis. Serum iron levels depend on intestinal absorption from the diet, transport capacity in the blood, recycling of iron released from phagocytosed erythrocytes, and the release of iron from other tissue stores, such as the liver. Most of the iron used for normal erythropoiesis is recycled from phagocytosed erythrocytes (~20 mg /day). When erythropoiesis is stimulated by hypoxia, iron demand in the bone marrow increases. This necessitates increased intestinal iron uptake, an augmentation of serum iron binding capacity and enhanced mobilization of iron from internal stores. Therefore, it is not surprising that some key proteins involved in iron metabolism are oxygen regulated. Bona fide HIF targets involved in maintaining iron homeostasis include transferrin, which transports serum iron in its ferric form (Fe^{3+}) to target organs; its high-affinity receptor transferrin receptor-1 (TfR1); ceruloplasmin, which oxidizes Fe^{2+} to Fe^{3+} and is also important for iron transport; the divalent metal transporter-1 (DMT1), which transports iron into the cytoplasm of cells; duodenal cytochrome *b* (DcytB), which reduces ferric iron to its ferrous form (Fe^{2+}); and heme-oxygenase-1, which is important for the recycling of iron from phagocytosed erythrocytes (Obeagu *et al.*, 2016).

The intestinal uptake of dietary iron is oxygen sensitive and is mediated by DMT1, which moves iron across the cell membrane in its ferrous form. Before this can occur it is necessary to reduce dietary iron from its ferric form to Fe^{2+}, which is accomplished by DcytB. HIF-2 has been shown to increase cellular expression of DMT1 and DcytB and to enhance intestinal iron uptake. Following uptake by enterocytes, iron is then released into the circulation via ferroportin. Ferroportin is the only known membrane-bound iron transporter that exports iron out of cells. It is also expressed in hepatocytes and macrophages. The number of ferroportin molecules on the cell surface determines how much iron is exported, that is, how much iron is either taken up from diet, or released from hepatic or reticuloendothelial iron stores. Ferroportin surface expression is negatively regulated by hepcidin, a small polypeptide produced in the liver, which in the active form of 25 amino acids promotes its internalization and degradation. In physiological settings, hepcidin production is suppressed in low-iron states and under conditions of increased erythropoietic activity. Its synthesis is increased in inflammatory states (interleukin-6 induces *hepcidin* transcription through JAK/STAT), lending support to the notion that hepcidin has a key role in the pathogenesis of the anemia of chronic disease. Chronically elevated serum hepcidin levels result in decreased release of iron from enterocytes, hepatocytes, or macrophages, leading to hypoferremia. Conversely, constitutively low expression of hepcidin is associated with the development of hemochromatosis (Obeagu *et al.*, 2016).

In vitro and in vivo studies have demonstrated that hepcidin synthesis is hypoxia regulated.

Several mechanistic explanations for the hypoxic suppression of hepcidin have been proposed, the simplest model being that HIF-2 increases renal EPO production and “erythropoietic drive,” thereby indirectly suppressing hepcidin. It has been postulated that enhanced erythropoiesis produces a bone marrow-derived systemic signal that leads to hepcidin suppression in the liver, thus permitting increased ferroportin surface expression, which in turn increases iron availability for erythropoiesis. A candidate factor for such signal is growth and differentiation factor 15 (GDF15), an iron- and oxygen-regulated (HIF-independent) member of the TGF-β superfamily. Studies with liver-specific knockout mice have also suggested that hepatic HIF-1 suppresses *hepcidin* directly through HRE-dependent mechanisms. However, this is debatable and experimental evidence exists that contradicts these findings. Another model is based on the effects of hypoxia on iron-dependent regulatory pathways that control *hepcidin* transcription. Regulation of hepcidin expression in the liver involves HFE, a protein, which is mutated in patients with hereditary hemochromatosis, TfR1, and TfR2, and hemojuvelin (HJV), which acts as a coreceptor for bone morphogenetic protein-6 (BMP6) and induces *hepcidin* transcription in a SMAD-dependent fashion. HIF-1 regulates furin, a proprotein convertase that cleaves HJV, generating soluble HJV (sHJV). sHJV reduces hepcidin synthesis by competing for BMP6 binding, thereby antagonizing signaling through membrane-bound HJV.

To add more complexity to the cross talk between iron metabolism and HIF signaling, iron is necessary for HIF prolyl-4-hydroxylation, and its oxidation state and abundance affect the activity of PHDs and the efficiency by which normoxic HIF degradation occurs. An additional feedback loop has been proposed that links intracellular iron levels to HIF-2α translation and would limit HIF-2-induced EPO synthesis when intracellular iron levels are low. The 5′-untranslated region of *HIF-2α* mRNA contains an iron-regulatory element (IRE), which is a stem-loop structure that binds iron-regulatory protein (IRP) in the presence of reduced intracellular iron levels. IRPs (IRP1 and IRP2) function as intracellular iron sensors that control the expression of classic iron-sensitive genes, such as TfR1, ferritin, and DMT1. With regard to IRP1 regulation, iron is incorporated into an iron-sulfur cluster at the center of the protein and converts IRP1 to an enzyme with aconitase activity. In its aconitase form, IRP1 does not bind to the IRE. In contrast, IRP2 does not convert to an aconitase and is regulated via iron-dependent proteasomal degradation. Depending on the location of the

IRE stem loop, the IRP/IRE complex either inhibits translation (5′-IRE), for example in the case of *ferritin*, or it stabilizes mRNAs, which is the case for *TfR1* where the IRE is located in the 3′-end (*TfR1* mRNA levels increase when intracellular iron is low). The IRE in *HIF-2α* is located in its 5′-untranslated region. When intracellular iron levels are low, the IRP/IRE complex inhibits translation of HIF-2α. This in turn limits EPO synthesis, adjusting the hypoxic inducibility of erythropoiesis to iron availability.

In addition to increasing iron availability, hypoxia promotes erythropoiesis through modulation of erythroid progenitor maturation and proliferation, and through its direct effects on the bone marrow microenvironment. Hypoxia stimulates EPO receptor expression and regulates components of the hemoglobin synthesis pathway. It modulates the interaction of erythroid progenitors with other cell types, thereby affecting stem cell maintenance, lineage differentiation, and maturation. Recent studies have highlighted a role for endothelial HIF-2 in facilitating hypoxia-stimulated erythropoiesis. Mice with globally reduced HIF-2α expression developed a defect in erythroid maturation (mutant mice had increased numbers of immature erythroblasts), which appeared to depend on HIF-2-mediated expression of vascular cell adhesion molecule (VCAM)-1, an integrin receptor that binds very late antigen-4 (VLA4) on erythroblasts supporting erythroid maturation. This finding together with its emerging role in the regulation of iron metabolism underscore the notion that HIF-2 has a central function in oxygen-regulated erythropoiesis, which extends beyond the induction of EPO synthesis.

Hypoxia and hematopoiesis

Haematopoiesis is the process by which pluripotent stem cells differentiate into mature erythroid (red blood cells), myeloid (neutrophils, eosinophils, basophils, and monocytes), megakaryocytic (platelets), mast, and lymphoid (B, T, and NK cells) cell types. This results in the steady level of circulating blood cells with each cell type possessing unique function and distinct life spans. Each year, an average adult produces ~200–300 kg of blood cells equivalent to three to four times a person's body weight. The large production numbers and fast turnover of blood cells indicate that hematopoietic cell proliferation and differentiation must be tightly controlled; even a small negative or positive imbalance in their production or life spans would cause anemia and other cytopenias or hyperviscosity due to erythrocytosis/polycythemia and specific complications from various types of leukocytosis and thrombocytosis. Hematopoiesis first appears in the yolk sac and then in the aorta-gonad-mesonephros region of the embryo, subsequently in the fetal liver and, finally, in the bone marrow of an adult. To support this process, stem cells and their progenies must be maintained in close contact with stromal cells, which are nonhematopoietic mesenchymal cells. Hematopoietic growth factors control the development of many blood cell types by sustaining cell viability, proliferation, or differentiation. To support these functions, hematopoietic growth factors must regulate hematopoietic stem cells and their differentiating progenies. These modifications include altering gene expression and interaction of transcription factors and/or signaling to regulate differentiation and proliferation.

The body adapts to hypoxia by numerous mechanisms. One of these adaptive responses is to enhance erythropoiesis and, consequently, increase circulating red blood cells to deliver more oxygen to tissues. The key regulators of the hypoxic response pathway are hypoxia inducible factors (HIFs). HIFs are transcription factors composed of a hypoxia inducible α subunit and a constitutively expressed β subunit. The α subunits consist of three different isoforms: HIF-1α, HIF-2α, and HIF-3α. HIF-1α and HIF-2α share significant sequence identity and regulation. The HIF-1α subunit is ubiquitously expressed, whereas HIF-2α and HIF-3α subunits have tissue-specific expression. In the presence of oxygen, HIF-1α and HIF-2α are prolyl hydroxylated by iron requiring prolyl hydroxylase domain (PHD2) enzymes, and their hydroxylated products interact with von Hippel Lindau (VHL) protein, which leads to ubiquitinization and rapid destruction in proteasomes. In hypoxia, HIF-1 and HIF-2 α subunits escape ubiquitination-dependent

proteasomal protein degradation that takes place in normoxia. The accumulated HIF-1 and HIF-2 α subunits are rapidly translocated into the nucleus and form heterodimers with the β subunit. Thus resultant hypoxia-induced stabilization of HIF α subunits permits the formation of the active HIF heterodimers that bind to the promoter or enhancer region of their target genes and modulate their transcription. However, since HIF-3α has no nuclear localizing sequence or coactivator binding domain, it may have no transcriptional activity. Historically, HIF-1 was identified as a main regulator for erythropoietin (EPO) gene. Subsequently, numerous targets of HIFs have been identified, including vascular endothelial growth factor (VEGF), transferrin (TF), and transferrin receptor (TFR) and an array of other genes. It is estimated that in endothelial cells as many as 3% of genes are hypoxia regulated.

Role of erythropoietin in erythropoiesis

EPO plays a central role in the regulation of erythropoiesis by blocking apoptosis in the late erythroid progenitors (colony forming units-erythroid, CFU-Es) and enhancing proliferation and terminal differentiation of their progenies. It has also been reported that EPO contributes to the expansion of multipotent hematopoietic progenitors. Excessive EPO levels lead to an accumulation of red blood cells, i.e., polycythemia. During fetal development EPO is mainly produced in the liver; its primary site of production then changes to the kidney during late gestation but continues to a lesser extent in the liver. Renal EPO is produced by peritubular fibroblast-like type-1 interstitial cells located in the renal cortex and outer medulla. Hepatic EPO is produced by hepatocytes (Obara et al., 2008) and contributes about 10% of the plasma EPO. However, the central nervous system also expresses EPO and its receptor (EPOR) wherein neurons and astrocytes in the cortex and the hippocampus of murine and human brains are the sources of cerebral EPO. Cerebral EPO may not contribute to the circulating levels of EPO due to the blood-brain barrier, thus the role of cerebral EPO does not directly modulate erythropoiesis; however, EPO likely plays a protective role against hypoxia and ischemia. It has been shown that the astrocyte-specific deletions of Hif-1α and Hif-2α in mouse do not cause anemia but reduce the acute erythropoietic response to hypoxia by ~50%. Besides the kidney, liver, and brain, hypoxia induced EPO transcripts were also found in several other tissues; i.e., spleen, lung, testis, and erythroid progenitors.

Tissue-specific regulatory elements of the erythropoietin gene

Hypoxia is the main regulator of EPO levels. Acute exposure of mammals, including humans, to hypoxia at high altitude enhances plasma EPO more than 10-fold (Abbrecht and Littel,1972). This hypoxia-associated elevation of EPO levels is primarily caused by increased EPO expression in the kidney and the liver and is regulated by HIF-1 and HIF-2-mediated transcription of the EPO gene. Several laboratories identified nucleotide sequences (named hypoxia responsive element; HRE) responsible for hypoxia-inducible EPO gene transcription located immediately after the polyadenylation site of the human and mouse EPO gene. Additional HREs were identified 5′- and 3′-flanking regions of the EPO gene, and the tissue-specific EPO regulation was demonstrated to be mediated by these tissue-specific genomic regions. Transgenic mouse experiments using various deletions of 5′- and 3′-flanking regions of the human EPO gene identified the location of different tissue-specific EPO gene hypoxia regulatory elements; i.e., kidney inducible element (KIE) located between −14 kb and −6 kb of 5′ flanking region of the human EPO gene and the negative regulatory element (NRE) located within −6 kb to 5′ of the human EPO gene. However, these reported elements were composed of too large DNA segments (>4 kb) and need to be delineated to smaller specific nucleotide sequences to properly identify interactive transcription factors and further define their functional relevance and tissue specificity.

More recently, GATA binding motifs were identified in the proximal region (also called the core promoter region) of the mouse EPO gene, where GATA-2 and GATA-3 bind. This GATA binding element serves as a negative regulatory

element and it is reported to have an important role in tissue-specific EPO production (Obara et al., 2008).

Tissue-specific HIF-1 and HIF-2 regulation of erythropoietin

As discussed above, hypoxia increases HIFs by stabilizing HIF-α subunits. Hif-1α−/− deficient mouse embryos are viable only up to day 11.5 and at embryonic stage 9–10 days have low levels of the EPO transcript, even though HIF-2α transcript levels are comparable to wild-type littermates. This demonstrates that HIF-1 plays the central role in EPO production during early mouse embryogenesis and that HIF-2 cannot compensate for the HIF-1 role during this developmental stage.

Differential Effect of HIF-1 and HIF-2 on Renal and Hepatic EPO Production

HIF-1 was first identified by studies of the regulation of EPO production in a hepatic cancer cell line. Yet kidney is the major site of EPO production, as witnessed by the fact that nonrenal EPO does not compensate for the loss of renal EPO production in patients with chronic kidney disease. The following evidence for the relative roles of HIF-1 and HIF-2 regulation of EPO transcription in the kidney and liver is available. In the adult stage, HIF-2 plays a key role in hepatic EPO production: 1) A mouse with inactivated Vhl (a negative regulator of HIF-1α and HIF-2α) and Hif-1α genes in hepatocytes had increased hepatic Epo production and polycythemia Conditional inactivation of Hif-2α in a pVhl-deficient mouse suppressed hepatic EPO transcripts and corrected polycythemia. Work from the same group examined the role of HIF-2α in renal Epo production using kidney cell-specific deletion of Hif-2α . Hif-2α-deficient mice had significantly decreased red blood cell counts and hematocrit levels. In these mice, plasma Epo protein levels were lower (116 ± 12 pg/ml in kidney-specific Hif-2α-deficient mouse vs. 166 ± 9 pg/ml in control) and EPO mRNA levels were ∼12-fold less than control. There was increased HIF-1α protein and HIF-1 target gene transcripts in the kidney, but this could not correct for the Hif-2 deficiency-induced anemia. Furthermore, upon hypoxic exposure, the renal Epo transcript in Hif-2α-deficient mice was not induced in contrast to wild-type littermate control. In addition, these investigators also generated a kidney- and liver-specific Hif-2α-deficient mouse and showed that in hypoxia the kidney- and liver-specific Hif-2α-deficient mouse had ∼70% lower plasma Epo levels compared with only the kidney-specific Hif-2α-deficient mouse. These combined results demonstrate that in adult mice renal EPO production is regulated mainly by Hif-2 and in hypoxia, hepatic EPO contributes to EPO level more than renal EPO.

Erythropoiesis and iron metabolism

Red blood cells, which contain ∼80% of organismal iron, have a particularly intimate relationship with this metal and its ligand oxygen. Since the ferrous iron of each heme group can bind a single oxygen molecule, the hemoglobin tetramer can reversibly bind and transport four molecules of oxygen. Heme iron is central for delivery of oxygen from erythrocytes to tissue. Additionally, the optimal delivery of iron is essential for heme and hemoglobin synthesis. Iron deficiency leads to impaired erythropoiesis resulting in hypochromic anemia, a testimony to the close link of iron metabolism and erythropoiesis and the optimal function of hemoglobin. HIFs play a central role in control of both iron metabolism and erythropoiesis. In turn, iron availability is essential for the activity of the negative regulators of α subunits levels of HIFs; i.e., PHD enzymes (Peyssounaux *et al.*, 2008).

Hif-1α−/− Embryos

Important lessons were learned from Hif-1α−/− embryos. Hif-1α-deficient embryos are embryonic lethal by day 10.5 and have poor vascularization of the yolk sac. At embryonic day 9.5 these Hif-1α−/− embryos have decreased myeloid multilineage and committed erythroid progenitors, as well as decreased hemoglobin content in erythroid colonies from Hif-1α-deficient yolk sac progenitors. These Hif1-α−/− embryos had a significant decrease in EpoR mRNA levels in yolk sac, as well as Epo and EpoR mRNA in the

embryo and a profound defect in iron homeostasis, as demonstrated by aberrant expression of hepcidin, Fpn1, Irp1, and Frascati. The erythropoietic defects in Hif-1α-deficient erythroid colonies could not be corrected by cytokines, including supraphysiological concentrations of EPO and VEGF; the defects were ameliorated but not fully corrected by ferric salicylaldehyde isonicotinoyl hydrazone (Fe-SIH), a compound delivering iron into cells independently of iron transport proteins. These results demonstrated that HIF-1α is not essential for the formation of multipotential hematopoietic progenitors, but that HIF-1 is required for optimal erythropoiesis. These results suggest that HIF-regulated factor(s) besides EPO play an important role in HIF-1-dependent erythropoiesis.

Developing red blood cells are the most avid consumers of iron in the organism. Immature erythroid cells can obtain iron only from plasma TF following its binding to the membrane TFR and internalization of TF-TFR complexes. If hypoxia is unable to augment iron supply to erythroid progenitors, the iron availability could become a limiting factor for hypoxia-stimulated erythropoiesis. Hypoxia increases TF levels and HIF-1 enhances the expression of TF. The TFR promoter region contains a functional HRE, which mediates transcriptional activation of TFR in response to hypoxia. Moreover, a putative HRE has been identified in the promoter region of DMT1 (divalent metal transporter 1) that exports TF-borne ferrous iron from endosomes and transports Fe2+ into duodenal enterocytes. Recent studies demonstrated that although HIF-1α is not necessary for iron absorption, HIF-2α plays an important role in regulating the transcription of DMT1. Taken together, these reports support a model that hypoxia may augment the overall iron transport machinery, resulting in increasing iron uptake into the cells. The rescue of the erythroid differentiation defect in Hif-1α−/− yolk sacs by supplementation with Fe-SIH indicates that defects in iron metabolism significantly contribute to the phenotype seen in these animals.

HIFS and non-erythoid hematopoiesis

HIFs in the early hematopoietic progenitors and microenvironment

During mammalian embryogenesis, oxygen concentrations in the embryo are at hypoxic levels. Vascular endothelial cells and hematopoietic stem cells originate from a common ancestor, i.e., the hemangioblast, and demonstrate hypoxia-induced cell proliferation (Philips *et al.*, 1995).

HIFS and lymphopoiesis

Lymphocyte proliferation depends on glycolysis-derived ATP and HIF-1 regulates essential glycolysis genes including glucose transporter 1 and glycolytic enzymes (Ratcliffe *et al.*, 1998). To test a role of HIF in lymphopoiesis, Kojima et al. (34a) bypassed the embryonic lethality of HIF-1α deficiency by using the recombination activating gene-2 (RAG-2)-deficient blastocyst complementation system. The chimeric mouse Hif1α−/−→Rag2+/+ had reduced B cell progenitors (46% vs. 8%). These results indicate that HIF-1α deficiency impairs the proliferation of immature B cells and modulates the rate of B cell expansion. Whereas these mice had no changes in T cells, HIF-1 induces Foxp3, a member of the forkhead/winged-helix family of transcriptional regulators, in Jurkat T cells and mononuclear cells. Foxp3 mutation in the scurfy mouse resulted in a fatal lymphoproliferative disorder including regulatory T cell deficiency. Foxp3 is highly expressed by regulatory T cells and is associated with regulatory T cell activity and phenotype. Overexpression of Hif-1α increases Foxp3 mRNA and the proportion of regulatory T cells in mouse splenocytes (*Ben-Shoshan et al.*, 2008).

HIFS and macrophages

HIF-1α and VEGF are also expressed in activated macrophages. Although there is no significant defect on myelopoiesis, the macrophage function in inflammation was impaired by the absence of HIF-1 (Cramer *et al.*, 2003).

Conclusion

Iron is very important in the body especially for effective erythropoiesis and should be mainatianed at a normal level. Some disease conditions may precipitate increased or decreased levels of iron. The body has some iron regulatory proteins which ensure stability in the balance between storage iron and circulatory iron. Therefore, it is not surprising that some key proteins involved in iron metabolism are oxygen regulated. Bona fide HIF targets involved in maintaining iron homeostasis include transferring, ceruloplasmin, the divalent metal transporter-1 (DMT1), duodenal cytochrome *b* (DcytB) and heme-oxygenase-1.

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How to cite this article:
Obeagu E. I. Okoroiwu I.L. and Azuonwu O.. (2018). An update on hypoxic regulation of iron homeostasis and bone marrow environment. Int. J. Curr. Res. Med. Sci. 4(10): 42-48.
DOI: http://dx.doi.org/10.22192/ijcrms.2018.04.10.007