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Review Article

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Regulation of Intestinal Iron Absorption: Balancing Supply and Demand

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ABSTRACT

Iron, an essential micronutrient, is involved in several physiological activities, including oxygen transport, cellular respiration, and DNA synthesis. Its homeostasis is strictly controlled to avoid overload and deficiency. Ferrous iron is taken up by intestinal enterocytes through the apical membrane with the help of divalent metal transporter 1 (DMT1). Iron can then be discharged into the bloodstream by ferroportin 1 (FPN1) or stored intracellularly in ferritin. Hepcidin, a hormone produced in the liver, binds to FPN1 and causes its internalization and degradation, a key factor in controlling systemic iron levels. Thus, hepcidin limits the absorption and release of iron by decreasing the iron outflow from enterocytes and macrophages. Iron-responsive element/iron regulatory protein (IRE/IRP) system and hypoxia-inducible factor 2 (HIF-2) are important cellular regulators of iron homeostasis. The IRE/IRP system post-transcriptionally regulates the expression of iron-related proteins in response to iron availability. At the same time, HIF-2 promotes the expression of iron transporters and metabolic enzymes under hypoxic conditions. Iron-related disorders can result from disruptions in these regulatory mechanisms; for instance, mutations in the genes encoding hepcidin, FPN1, or hereditary hemochromatosis protein (HFE) can cause iron overload disorders like hemochromatosis, while iron deficiency anemia is caused by impaired iron absorption due to genetic defects or nutritional deficiencies. A deeper understanding of these intricate mechanisms is crucial for developing effective strategies to prevent and treat iron-related disorders.

INTRODUCTION

Iron is a key nutrient that supports multiple processes in the body, especially the transportation of electrons, synthesis of DNA, and oxygen movement [1]. Cells of small intestine are essential for iron management [2]. Since excessive levels of iron and inadequate supply are responsible for several types of diseases, retaining iron homeostasis is important [3]. In the small intestine, the absorption of iron is a carefully monitored process that involves many different proteins and processes [4]. The function of the divalent metal transporter 1 (DMT1) is to transport iron across the apical membrane of enterocytes [5]. Iron may be transported over the basolateral membrane by ferroportin as well as deposited into ferritin once it enters the enterocyte [6, 7]. Iron absorption needs to be appropriately controlled to preserve iron homeostasis. The liver's metabolic hormone hepcidin is crucial for preserving iron absorption because it binds to ferroportin and inhibits iron export [8]. Since iron is an essential ingredient, excessive intake of it will be harmful. Several systems of regulation were established to keep stability in an atmosphere full of iron. The tissue requirements for iron can be fulfilled and not increased

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because of homeostatic processes. Iron deficiency may impact how efficiently various tissue iron-dependent enzymes function. Essentially, for the severe concentration of iron necessary for the synthesis of hemoglobin in developing erythroid cells, anemia is the least known indicator of iron insufficient supply. Mainly through bleeding as well as sloughing of skin and also mucosal cells, iron may escape the body; neither the liver nor the kidneys are capable of controlling the release of iron [9, 10]. Usually, hepatocytes and macrophages preserve excessive amounts of iron. Unsequestered iron produces toxic oxygenated radicals to accumulate as tissue storing capacity reaches its limit, which causes tissue fibrosis and the medical symptoms of endocrinopathies, liver failure, and cardiomyopathy to occur. Initially, iron stores are created through the process of iron transfer from the mother to the developing fetus. After birth, the duodenum's epithelial cells, or enterocytes, consume iron from the meal. It flows throughout the circulatory system linked to transferrin and gets transported to usage and preservation sites. The fundamental consumers, erythroid precursors, are entirely reliant on the receptor-mediated transferrin endocytosis by means of the transferrin cycle [11]. A few years later tissue macrophages consume red blood cells and break down hemoglobin to allow the metal again into the circulatory system to extract iron from aged and damaged erythrocytes [12]. Approximately 5% of the Earth's crust is made up of iron, making it the 2nd most abundant metal on Earth [13]. Being an essential vitamin for the survival of humanity, its significance to humankind becomes critical. It is a d-block transition metal that fluctuates between several oxidation states; it can take part in electron migration and bind to a variety of naturally occurring molecules. Trivalent ferric (Fe^{3+}) and divalent ferrous (Fe^{2+}) are the two most commonly seen iron states. Many hemoproteins and non-hemoproteins that contain iron in the human body depend on iron as a cofactor. Hemoproteins are necessary for many biological functions, such as oxygen metabolism (catalase and peroxidase), electron transport and mitochondrial respiration (cytochromes), and oxygen binding and transport (myoglobin and hemoglobin). Non-haem iron-containing proteins are also vital because they participate in the synthesis of DNA, cell division and proliferation, steroid synthesis, drug metabolism, and gene regulation. A healthy person weighing 70 kg has approximately 3500–4000 mg of iron overall, which corresponds to an average amount of 50–60 mg per kilogram of body weight. A substantial portion of the body's iron (2300 mg, or 65%) is found in the hemoglobin of erythrocytes. About 350 mg, or about a 10th of the total iron, is found in the cytochromes and enzymes of other tissues, such as muscle myoglobin [14]. Reticuloendothelial system (RES) macrophages contain roughly 500 mg of the residual iron, hepatocytes store 200–1000 mg in the same way as ferritin, and bone marrow has 150 mg. About 15–20 mg of iron is consumed daily on average in the Western world, with 10% of this amount occurring in the haem form and the remaining 10% in the non-haem/ionic form. Only around 10% of the iron that is consumed is utilized, mainly through the duodenum as well as partially in the jejunum [15]. Because the duodenum and proximal jejunum have a significantly more acidic environment than more distal gut segments, iron absorption in the gastrointestinal tract occurs proximally. Enterocytes, or polarized intestinal epithelial cells, found in the duodenum and proximal jejunum, the upper part of the intestine, are responsible for considerable iron absorption [16]. Figure 1 illustrates the regulation of iron by enterocytes. These cells can be identified by others by having a basolateral side, which gets into touch with the blood, and an apical side, which gets into touch with the gut lumen and foodstuff. When enterocytes from developing stem cells go towards the villus every three to four days, the intestinal epithelium is completely renewed. Iron absorption may also be significantly affected by physical characteristics of the gastrointestinal system, such as the stomach's pH (low pH increases iron solubility) and the intestine's surface area, which increases under iron-deficient situations. Numerous proteins produced by differentiated duodenal enterocytes aid in iron absorption from food. The main importer of iron on the apical membrane of these cells is divalent metal transporter 1 (DMT-1) [17]. The ferrous form of dietary ferric iron, which serves as DMT-1's substrate, can be produced via ferric reductase activity on the brush boundary. While some of this reductase activity can be supplied by duodenal cytochrome B (DcytB), alternative reductases, like Steap2, might be involved [18]. It is not clear how heme and ferritin iron are absorbed. While receptor-mediated endocytosis has been shown to pick up heme, enterocytes do not yet have a verified high-affinity heme receptor. Heme carrier protein-1/proton-coupled folate transporter (HCP1/PCFT) is now known to essentially act as a folate transporter with a substantially reduced affinity for heme, despite having been discovered as an apical heme transporter [19]. Endocytosis may also be used to transfer dietary ferritin into enterocytes [20]. Iron may be deposited in endogenous ferritin or released into the bloodstream to be transferred to various bodily tissues once enterocytes have consumed it. In addition to ingested ferritin iron released from ferritin, heme oxygenase in enterocytes breaks down ingested heme iron to produce free ferric iron [16]. The makeup of this pool and the intracellular iron trafficking

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pathways are poorly understood, even though dietary iron eventually enters the bloodstream linked to transferrin and seems to converge into a common cellular iron pool within enterocytes. The only known mammalian iron exporter protein, ferroportin 1 (FPN1), helps release iron from enterocytes into the blood. When FPN1 is deleted from intestinal cells, intestinal iron absorption is almost completely blocked, and iron builds up in intestinal enterocytes as a result. Since plasma transferrin (Tf) only binds to ferric iron, ferroxidases are necessary for oxidizing ferrous iron carried by FPN1. FPN1 is internalized and broken down when ferroxidase activity is absent [21, 22]. Although ceruloplasmin (CP) functions as a ferroxidase for FPN1 in various cell types, its function in intestinal iron absorption seems less important, particularly when iron needs are normal. Alternatively, intestinal cells employ hephaestin (HP), a bound by the membrane paralog of CP. Several researches have shown that there may be an interaction between HP and FPN1 [22]. The anemia-associated HP mutation results in systemic anemia and iron accumulation in intestinal enterocyte [23]. Ferroxidase, also known as amyloid precursor protein (APP), is present in intestinal enterocytes and may contribute to intestinal iron absorption [22].

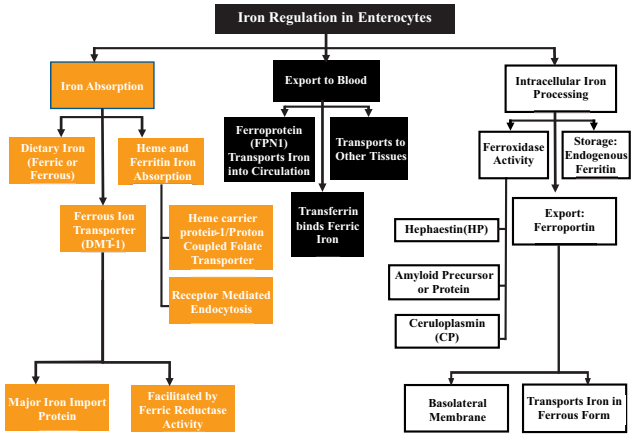

Figure 1: A Visual Representation of Enterocyte Iron Regulation

Meat proteins hemoglobin and myoglobin contain most of the ingested heme iron. These proteins are released from meat at low pH in the stomach, and free hemoglobin is then released by the stomach's and the intestines' subsequent protease activity.Hemoglobin absorption has been attributed to the Haem Carrier Protein 1 transporter (HCP1), which is present on the brush-border membrane of enterocytes. This protein was later identified as a proton-coupled folate transporter (PCFT), which is why the transporter is also referred to as PCFT/HCP1.After haem comes into the enterocyte, it can be broken down by haemoxygenase (HO-1), as shown in Figure 2 and 3, producing free iron that goes into the intracellular labile iron pool (LIP). Moreover, undamaged hemoglobin may also be able to enter the bloodstream through two exporter proteins: the feline leukemia virus subtype C (FLVCR) and breast cancer-resistant protein (BCRP).

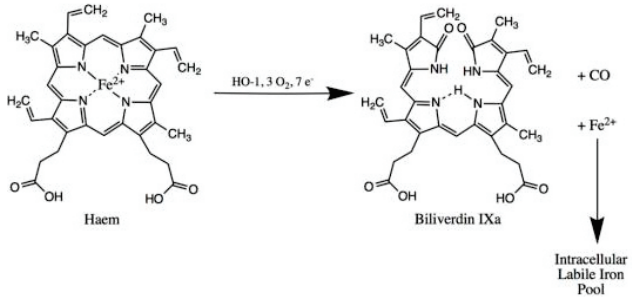

Figure 2: Haem Can Be Broken Down in Enterocytes To Release Free Iron, Which Then Joins The Intracellular Labile Iron Pool.

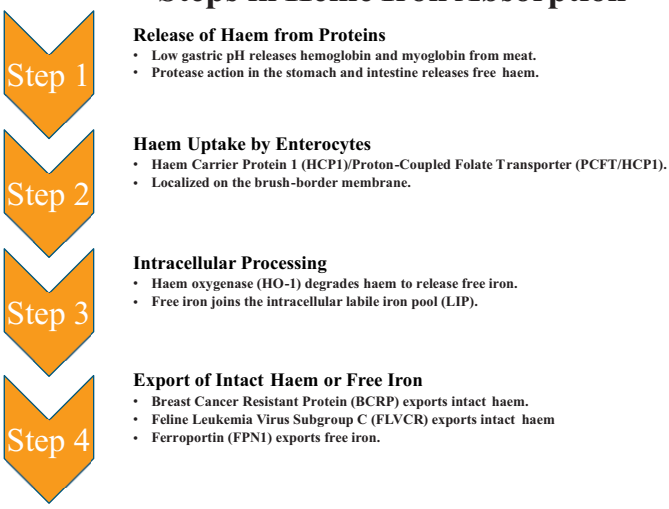

Figure 3: Steps in Heme Iron Absorption

Non-haem iron, primarily found in the ferric (Fe3+) form, is found in meat and plant diets. Ferric iron, unlike ferrous (Fe^{2+}) iron, is very insoluble and challenging to absorb. The steps illustrating the regulation of non-heme iron are represented in Figure 4. Since ferrous iron is the preferred type for absorption, its reduction is crucial; it is done at low pH. Enterocytes can break down hemoglobin to liberate free iron, which moves to the intracellular labile iron pool. The stomach's low pH, and dietary ascorbic acid (vitamin C) cause Fe^{3+} ions to be converted to Fe^{2+} ions, increasing their absorption and solubility.Iron absorption in the gastrointestinal tract occurs proximally because the duodenum and proximal jejunum have a relatively more acidic environment than distal gut segments. Ferrireductase, the duodenal cytochrome b (Dcytb) protein, is found on the brush-border membrane of the enterocyte. It uses electrons from the oxidation of ascorbic acid to dehydroascorbic acid to convert ferric (Fe^{3+}) ions to ferrous (Fe^{2+}) ions as depicted in Figure 5.This process demonstrates how ascorbic acid improves iron absorption. After this reduction process, the divalent metal

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transporter 1 (DMT1) then transports the divalent Fe^{2+} ions into the duodenum enterocytes. Ferrous iron, zinc (II), and copper (II) are among the divalent metal ions that are transported across the membrane by DMT1, another protein that is part of the duodenal brush-border membrane . The presence of luminal H+ ions is necessary for this proton (H+)-coupled transport to occur. Proton recycling across the duodenal luminal membrane is facilitated by the Sodium/Hydrogen Exchanger (NHE), another brush-border membrane transporter.

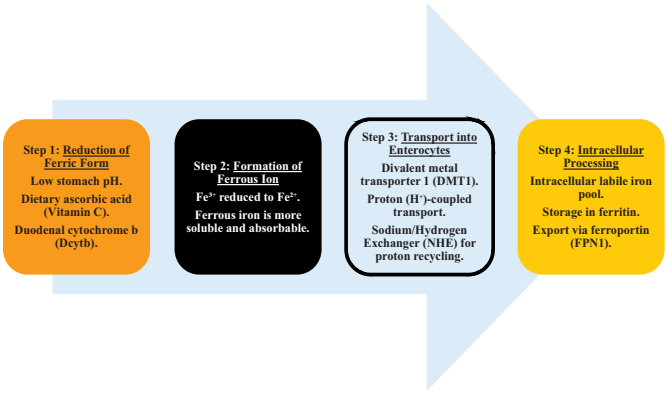

Figure 4: Steps of Non-Heme Iron Absorption

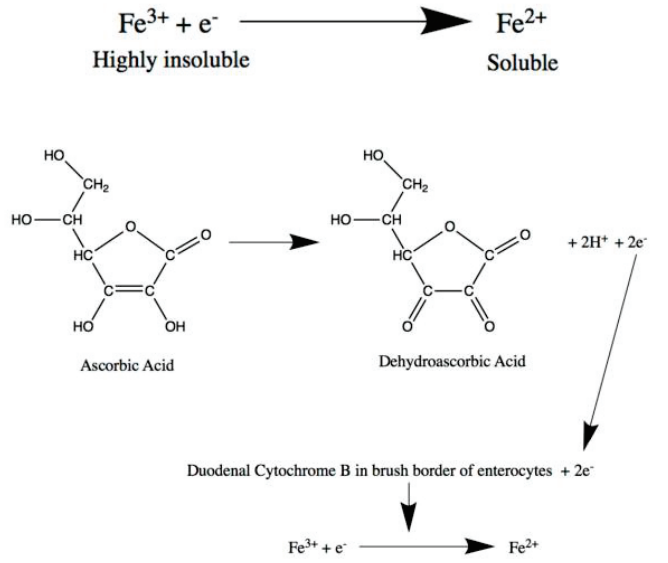

Figure 5: Dietary Ascorbic Acid and Low Stomach Ph Convert Non-Haem Iron from The Very Insoluble Fe^{3+} Form to The More Absorbable Fe^{2+}. Duodenal Cytochrome B Catalyzes the Reduction of Fe^{3+}To Fe^{2+}By Intracellularly Accepting Electrons from The Oxidation of Ascorbic Acid into Dehydroascorbic Acid.

Hepcidin, a 25-amino acid peptide hormone, regulates iron homeostasis by influencing intestinal absorption and macrophage iron release. It is one of the main indicators of anemia.Hepatocytes primarily produce hepcidin and enter the bloodstream, binding to ferroportin 1 (FPN1), an iron exporter found on the basolateral membranes of macrophages and enterocytes. Because of this binding, FPN1 is internalized and degraded, which lowers iron efflux into the bloodstream. Human iron overload illness type IV hemochromatosis is caused by mutations in FPN1 that interfere with hepcidin binding. There are indications that hepcidin may directly affect DMT1 in enterocytes, albeit this has not been proved. Hepcidin is known to rise in reaction to infection, inflammation, and iron overload while falling in response to hypoxia, iron shortage, and elevated erythropoietic demand despite its complicated regulation. Although these processes remain unclear, hepcidin regulation has been clarified by studying animal models and human disorders involving iron imbalance. The BMP6/SMAD pathway seems essential for controlling the hepcidin response to variations in iron status. Although other members of the BMP family, such as BMP2, 6, and 9, can also affect hepcidin expression, BMP6 is significant among the BMP family because in mice, its deletion results in decreased hepcidin expression and systemic iron overload.The systemic regulation of iron is illustrated in Figure 6.

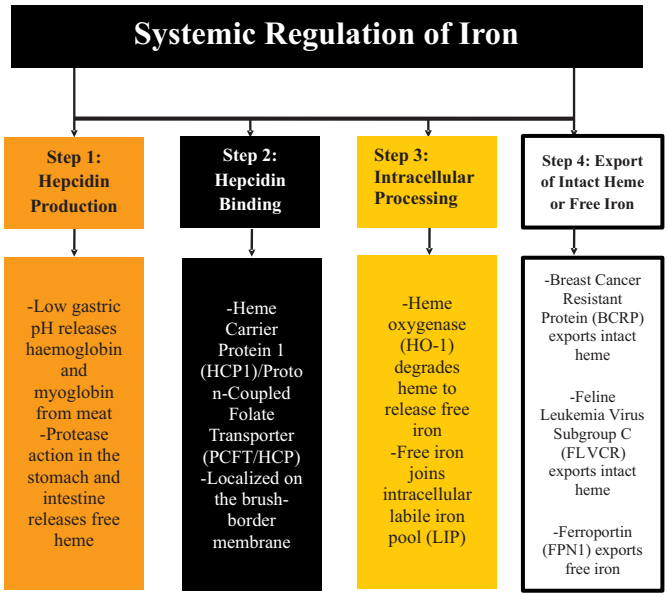

Figure 6: An Outline of The Major Processes and Elements Involved in Iron Intake, Release, And Recycling That Are Part of The Systemic Regulation of Iron.

BMP6 is produced and released by hepatocytes in response to iron load. When receptor-regulated SMADs 1, 5, and 8 bind to the BMP receptor I/II complex in hepatocytes, they become phosphorylated. By interacting with SMAD 4, these phosphorylated proteins create heteromeric complexes that go into the nucleus and trigger the transcription of the HAMP gene, which codes for hepcidin. The activity of this pathway depends on hemojuvelin (HJV), a co-receptor for the BMP6 receptor complex. Hepcidin levels are extremely low in people with a congenital abnormality that prevents HJV production, and they develop juvenile

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hemochromatosis, a severe iron-loading illness. Although HJV is often found attached to cell plasma membranes, the protease furin can create a soluble form of the virus. Because soluble HJV competes with membrane-bound HJV for BMP binding, it can enhance BMP/SMAD signaling. In addition to degrading HJV, the cell surface serine protease TMPRSS6 can also prevent BMP signaling. Furthermore, infection and inflammation can increase hepcidin expression by triggering inflammatory cytokines like JAK-STAT and the interleukin-6 signaling pathway . The degree of iron saturation of TF and the iron-dependent control of BMP6 are the two main pathways most likely to be engaged in transferring body iron levels to hepcidin. At the same time, the precise process is unknown. Both the membrane proteins hemochromatosis protein (HFE) and transferrin receptor 2 (TFR2) might be engaged in detecting the saturation of TF. Mutations in either protein lead to decreased production of hepcidin, increased absorption of iron, and disease due to iron overload. TFR2, an analog of TFR1, is mainly expressed in the liver and is activated by high levels of differentiating TF. Unlike TFR1, HFE can bind to TFR2, increase TFR2 stability, and attach to TFR1 in the same area as distinguishing TF. According to one theory, high levels of differentiating TF may inhibit HFE's ability to attach to TFR1, increasing HFE's binding to TFR2 and setting off a signaling cascade that would activate hepcidin. This would allow HFE and TFR2 to detect the quantity of iron in the blood [34]. Although this hasn't been proven yet, mice without both proteins show a more severe phenotype than mice with just one gene deleted, signifying that both proteins possibly will have different functions [35]. Hypoxia and cellular iron levels in intestinal enterocytes also regulate local iron absorption as explained in Figure 7. A critical regulator of this process that affects the post-transcriptional regulation of proteins engaged in iron metabolism is the iron-responsive element (IRE)/iron regulatory protein (IRP) system. In iron-deficient settings, an IRP (IRP1 or IRP2) stabilizes when it attaches to the IREs in the three UTRs of the mRNAs that produce TFR1 and two isoforms of DMT1. This stabilization lengthens the mRNA's half-life, raising the translated protein quantity IRP1 reversibly binds iron and transitions into its RNA binding state when cellular iron levels drop. IRP2 degrades when low iron levels are low, even though it does not bind iron. APP, one isoform of FPN1, and the five UTR of ferritin all include IREs. The translation is blocked when IRP binding stabilizes the stem loop in low iron circumstances. However, the 5 IRE is absent from the predominant splice version of FPN1 seen in intestinal cells, meaning that FPN1 protein levels may be upheld even in the presence of low iron levels in the cell .

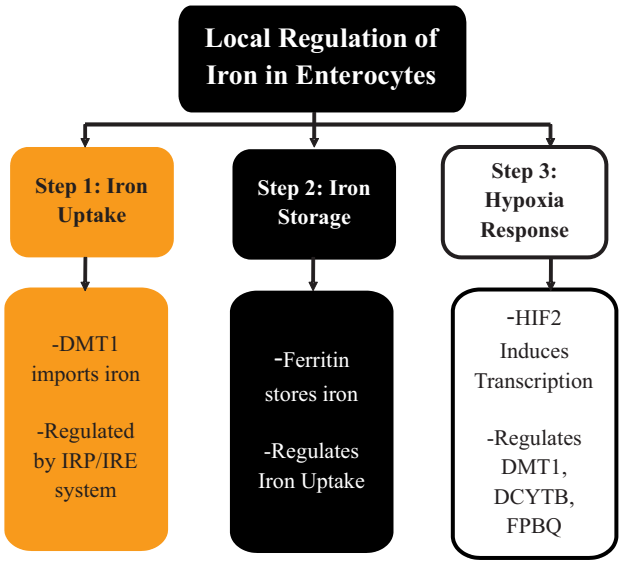

Figure 7: Illustration of the Three Main Processes Involved in Local Iron Regulation.

The body can engross iron with a low dietary iron level or systemic iron deficiency. Enterocyte ferritin, which stocks most of the iron in the enterocytes that are not present in the labile iron pool, may be essential for handling iron uptake because intestinal-specific ferritin H protein deletion causes improved iron absorption [37]. It is unknown if ferritin regulates enterocyte iron flow under typical physiological circumstances. Hypoxia-inducible factor 2 (HIF2) regulates the transcriptional levels of proteins involved in iron and oxygen status absorption because hypoxia is a potent inducer of iron absorption. A transcription factor complex comprising HIF2 attaches itself to promoters with HIF-responsive elements (HREs) to initiate transcription [38]. HREs are found in iron metabolism genes such as FPN1, DMT1, and DCYTB. HIF2 is constitutively produced by cells but is hydroxylated by iron- and oxygen-dependent prolyl hydroxylase proteins (PHDs), leading to its rapid ubiquitination and degradation in proteasomes. When oxygen and iron levels fall, HIF2 levels rise, increasing target gene transcription and limiting PHD activity. Higher production of Hif2 in the colon of genetically modified mice resulted in increased expression of DCYTB and DMT1 and improved iron absorption; however, intestinal deletion of HIF2 causes low levels of DMT1, Fpn1, and DCYTB as well as systemic iron deficit regardless of low hepcidin levels . These results imply that HIF2 is essential for the local regulation of iron absorption. It is not surprising that certain illnesses of iron homeostasis are brought on by disorders in the process of absorption of iron, which determines the body's iron concentration. Hemochromatosis and primary iron loading disorders are the most well-known; they are described by increased iron absorption even when adequate body iron stores [39, 40].

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Even when the body's iron stores are sufficient or high, primary iron overload illnesses like hemochromatosis are typified by excessive iron absorption. Reduced hepcidin levels and, thus, elevated FPN1 expression on the enterocyte basolateral membrane are the causes of this enhanced absorption. One such condition is ferroportin disease, which is brought on by mutations in FPN1 [30]. FPN1 is unable to react to the body's cues to reduce iron absorption in this scenario because it is no longer sensitive to hepcidin. The high iron load linked to several other clinical disorders, particularly iron-loading anemias like thalassemia and sideroblastic anemia, is also significantly influenced by elevated iron absorption [40]. The body's natural physiological reaction to elevated erythropoiesis linked to severe diseases is to enhance iron intake. While several recognized hereditary iron-loading syndromes exist, iron refractory iron deficiency anemia (IRIDA) is a well-characterized inherited iron deficiency illness [31]. Subjects in this circumstance exhibit severe anemia that makes oral iron treatment ineffective. In most cases, the gene that is changed is hepatocyte plasma membrane protease, transmembrane serine protease 6 (TMPRSS6), which efficiently suppresses the synthesis of hepcidin and breaks down HJV. Hepcidin levels are relatively high, FPN1 expression is reduced, and body iron intake decreases when TMPRSS6 is altered .The absorption of iron in the intestine depends on several factors, some of which have been covered in detail above. The type of iron consumed plays a key role: Iron heme gotten from animal products is better absorbed in the body than non-heme iron gotten from plant products. The other factors are related to diet; vitamin C increases the absorption of non-heme iron by reducing it into a soluble ferrous form; other inhibitors include calcium, phytates (grains and legumes), polyphenols (tea and coffee) and oxalates. The absorption of iron is high in acidic environments such as the stomach hence conditions that reduce the secretion of gastric acid such as achlorhydria or the use of proton pump inhibitors are counterproductive. Again, the iron status of the body affects the extent of absorption, higher with low levels of iron in the body. Other factors include inflammation, infections particularly those affecting hepcidin pathway and hereditary disorders like hemochromatosis diseases [42]. In general, the achievement of iron balance depends on dietary intake, physiological requirement and health state.

CONCLUSIONS

Iron absorption in the intestine is a finely tuned process that ensures the body maintains iron homeostasis. This review article has explored the various proteins, hormones, and signaling pathways that work in concert to regulate iron uptake. We have highlighted the critical roles of DMT1, FPN1, hepcidin, HIF-2, and the IRE/IRP system. Understanding the intricate interplay of these factors is crucial for developing effective strategies to prevent and treat iron overload disorders and iron deficiency anemia. Future research should focus on elucidating the precise mechanisms by which hepcidin interacts with DMT1 and FPN1 and exploring the potential therapeutic targets within the iron regulatory pathways. By continuing to unravel the complexities of intestinal iron absorption, we can strive toward a future where iron-related disorders are a thing of the past.

Authors Contribution

Conceptualization: SY, RHA, KZ, MR, PE, NF, FK
Methodology: SY, BA
Formal analysis: SY, RHA, KZ, MR, PE, NF, FK
Writing, review and editing: SY, RHA, BA, ML

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

All the authors declare no conflict of interest.

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