

Review Article

Regulation of Iron Homeostasis and Related Diseases

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The liver is the organ for iron storage and regulation; it senses circulating iron concentrations in the body through the BMP-SMAD pathway and regulates the iron intake from food and erythrocyte recovery into the bloodstream by secreting hepcidin. Under iron deficiency, hypoxia, and hemorrhage, the liver reduces the expression of hepcidin to ensure the erythropoiesis but increases the excretion of hepcidin during infection and inflammation to reduce the usage of iron by pathogens. Excessive iron causes system iron overload; it accumulates in never system and damages neurocyte leading to neurodegenerative diseases such as Parkinson's syndrome. When some gene mutations affect the perception of iron and iron regulation ability in the liver, then they decrease the expression of hepcidin, causing hereditary diseases such as hereditary hemochromatosis. This review summarizes the source and utilization of iron in the body, the liver regulates systemic iron homeostasis by sensing the circulating iron concentration, and the expression of hepcidin regulated by various signaling pathways, thereby understanding the pathogenesis of iron-related diseases.

1. Introduction

Iron is the maximum trace element in the body. As a transition metal, iron readily donates and accepts electrons to participate in biologic processes like oxygen transport, mitochondrial respiration, nucleic acid replication, intermediary, xenobiotic metabolism, and cell signaling [1]. Iron is so important is that its deficiency is one of the major risk factors for disability and death worldwide, and it is estimated to affect 2 billion people [2, 3]. On the other hand, excessive iron is harmful; it damages the liver and the brain, causing oxidative stress on the nerve to cause neurodegenerative diseases such as Parkinson's syndrome. Mutations in multiple iron-regulated pathways lead to heredity iron overload diseases like hereditary hemochromatosis (HH) and iron-refractory iron deficiency anemia (IRIDA) [4].

2. Absorption of Iron in the Food and Cellular Iron Acquisition

Dietary iron includes the heme iron and nonheme iron; 90% of them are nonheme iron, mainly present as the form of $\text{Fe}(\text{OH})_3$ complexation. Nonheme dietary iron is absorption at the brush border of duodenal enterocytes and exhibited diurnal rhythms [5]. The cytochrome b (Dcytb) on the duodenal enterocyte membrane reduced Fe^{3+} to Fe^{2+} , then the Fe^{2+} through the divalent metal transporter 1 (DMT1) on the membrane into the cell. The heme iron absorption mainly uptakes by the heme carrier protein 1 (HCP-1) [6, 7]. When the heme gets into the cell, it is degraded into iron, carbon monoxide, and biliverdin by heme oxygenase 1 or 2 (HO-1/2) [8]. Intracellular iron is efflux to the extracellular by the ferroportin1(FPN1), the only iron transmembrane

efflux protein in vertebrate cells [9–11]. Excess cellular iron is stored in ferritin, which has a large cavity to store thousands of iron atoms; it prevents dissociative iron from causing oxidative damage to cells [12]. After the Fe^{2+} efflux into the circulation, it oxidized to Fe^{3+} by the ferroxidases such as hephaestin (HEPH) or its homologue ceruloplasmin (CP) [13, 14] and succeedingly loaded onto the transferrin (Tf) and transported by the bloodstream.

The majority of the blood iron participates in hematopoiesis in the bone marrow, and a minor part transports to the liver. The liver is the essential organ for the body to store the iron, and the iron in hepatocytes is mainly stored in ferritin. For the excess iron, it is engulfed by the Kupffer cells of the reticuloendothelial system and deposited in the system as the form of hemosiderin [15].

Iron in the blood binds to the cell surface transferrin receptor (TfR), Tf-Fe/TfR complex sag, and endocytose into the cell, subsequently the conformational of the complex is changed triggered by the acidified endosomes [16, 17], which releases iron from the Tf [18]. The iron in the endosome is restored to Fe^{2+} by prostate six-transmembrane epithelial antigen of prostate 3 (STEAP3) and transported into the cytolymph by DMT1 [19]. The apo-Tf and TfR complex in the endosome are recycled to the cell surface. The sorting nexin 3 (SNX3) is one of the proteins of the phosphoinositide-binding protein family [20], is required for the recycling of Tf/TfR in endocytosis, and increases iron absorption by Tf recycling and bound ability [21]. We summarized the iron absorption and cellular iron acquisition in Figure 1.

2.1. Iron Cycle Is Associated with the Production and Clearance of Erythrocyte. In humans, 200 billion red blood cells are producing every day, requiring more than 2×10^{15} iron atoms per second to maintain erythropoiesis. The demand for iron is majorly obtained from recycling erythrocytes, so the production and clearance of erythrocytes are critical for iron homeostasis [22].

The erythropoiesis occurs in the erythroblastic island of the late fetal liver and adult bone marrow which surrounds a central macrophage, termed as nurse macrophage. The nurse macrophage promotes erythropoiesis in the erythroblastic island niche [23], phagocytosing the nuclei expelled from erythroid precursor cells in the late stage of erythropoiesis [24]. Other than that, macrophage in the erythroblastic island produces and releases ferritin by exocytosis [25]; then, the ferritin is endocytosed into the erythroblasts [26]. After entering the cell, iron releases from ferritin after acidification and proteolysis, which is used for heme production during the development of erythrocytes [27]. It seems that macrophages provide ferritin to nurture erythroblastic but have others also point out that the transferrin is the sole iron source during erythropoiesis; ferritin endocytosis is just a tiny force for the erythroblastic acquisition iron [28].

While the life of the erythrocyte is about to end or get irreparable damage, the bloodstream takes their last ride to the reticuloendothelial system in the splenic and hepatic. There, it is known that splenic red pulp macrophage cleans up senescent and damaged red blood cells then recycles iron

for erythropoiesis after hemoglobin catabolism [29]. There, firstly, the residential macrophage scrutinizes the passaged erythroid [30], then triggered engulf and digest the erythrocytes when macrophages contact to erythrocyte receptors and detect the specific markers on its surface [31], like phosphatidylserine and band 3 [32, 33]. Whereafter, the red blood cell is phagocytosed by macrophages into macrophage phagolysosome, causing hemoglobin breakdown and the heme release [34]. Subsequently, heme in phagolysosome is exported to the cytosol via the heme transporter (HRG1) and is decomposed into iron by HO-1/HO-2 [35, 36], then the iron is utilized by macrophages or effluxed extracellularly by FPN1. [8]. Macrophages for the iron cycle are shown in Figure 1.

Fe^{3+} in food is reduced to Fe^{2+} by Dcytb on the duodenal epithelium; it absorbs Fe^{2+} from the intestinal cavity through DMT1. HCP1 intakes heme in food, and HO-1 degrades it into Fe^{2+} in the cytoplasm. Excessive iron storage in the ferritin and other export into the blood through by FPN1; after that, Fe^{2+} is oxidized by CP and HEPH at the basolateral side then loads onto Tf.

Macrophage phagocytosed erythrocytes and releases heme in the phagolysosome. HRG1 exports heme from phagolysosome into the cytosol; then, HO-1 degrades heme into Fe^{2+} and efflux into the bloodstream by FPN1.

Tf-Fe combine with TfR on cytomembrane. SNX3 induce Tf-TfR sag and endocytose into the cell. Acidified endosomes release Fe^{3+} and restored to Fe^{2+} by STEAP3 and Fe^{2+} into the cytoplasm through the DMT1. Apo-Tf and TfR complex is recycled to the cell surface, and Tf is released into the blood.

The miR-Let-7d and miR-16 family decreases DMT1 expression. Hepcidin internalizes and degrades FPN1. miR-485-3p and miR-20b regulate the expression of FPN1. miR-200b induces downregulation of ferritin, and miR-320 suppresses the expression of TfR1.

2.2. Hepcidin-FPN1 Axis Sensing and Regulating the Systemic Iron Homeostasis in the Liver. Except for the storage of iron, the liver is the most important organ to regulate the systemic iron homeostasis by secreting the hepcidin. Hepcidin (HAMP) is a polypeptide that synthesizes regulatory hormone; it regulates iron homeostasis by combining FPN1 at extracellular to internalize and degrade FPN1 in the lysosome [37]. Iron in the blood loads on the Tf and transports with the bloodstream after being exported from the FPN1. While the concentration of circulating iron floats, hepatocytes sense and regulate hepcidin expression through the BMP/SMAD pathway to regulate the iron output from FPN1 [38]. This way, hepatocyte controls the amount of iron in circulation within the normal range, and unregulated hepcidin in the liver can cause iron deficiency or iron overload.

In the BMP/SMAD pathway, bone morphogenetic protein (BMP) and its coreceptor hemojuvelin (HJV) are the most critical hepcidin that regulate signaling pathway in quantitation [39]. BMP6 is predominantly secreted from liver endothelial cells [40]; its expression is regulated by iron [41], so it reflects the hepatic iron level [42, 43]. BMP6 and HJV together activate the BMP serine threonine kinase

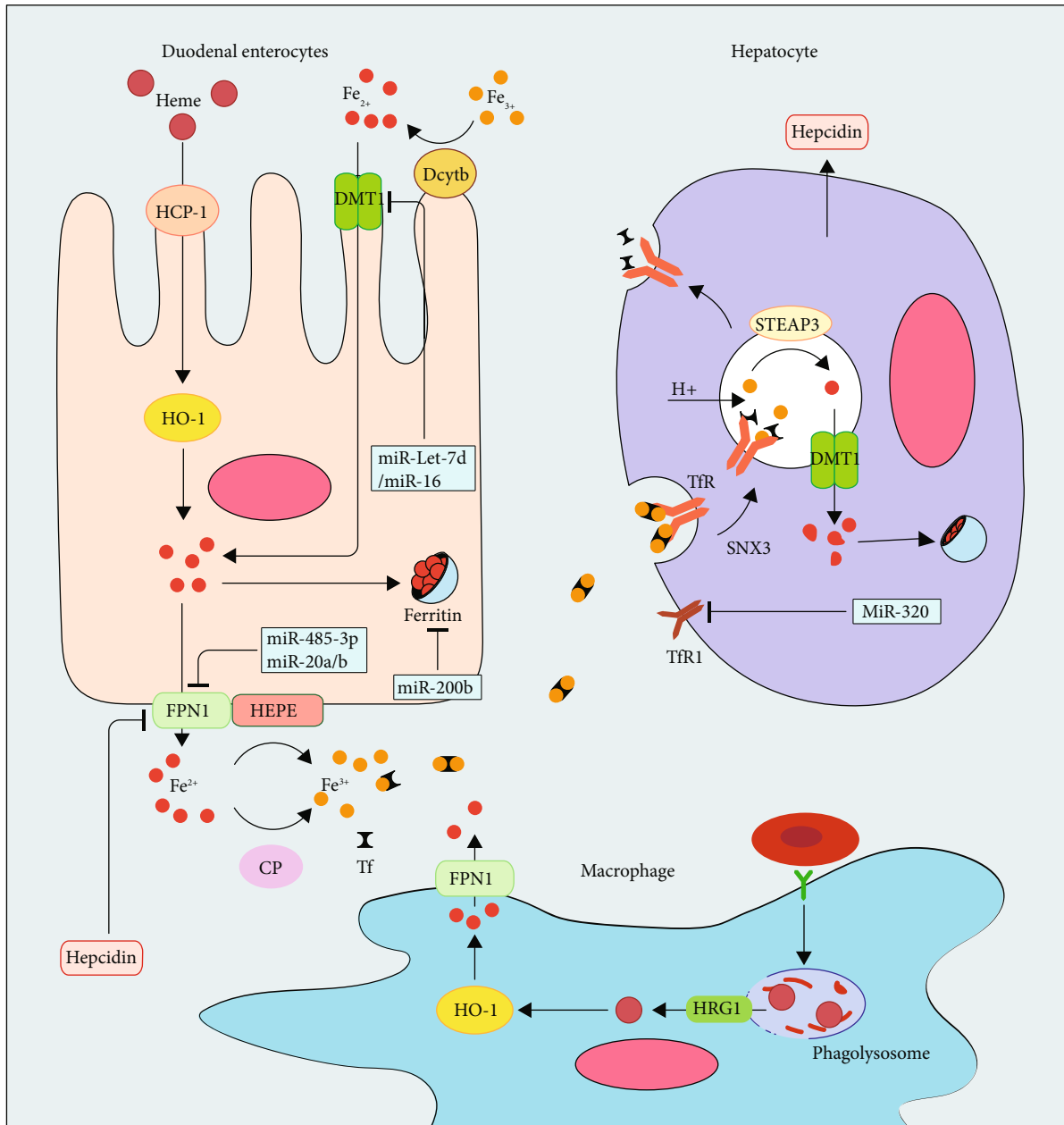


FIGURE 1: Systemic iron homeostasis.

receptor- (BMPR-) I/II complex [44, 45]. BMP6/HJV complex as a ligand combines with the BMPR I (Alk2 and Alk3) [46], and BMPR II (ActR2a and BMPR2) [47] promotes phosphorylation downstream BMP media such as SMAD1, SMAD5, and SMAD8 (SMAD1/5/8) [48]. Phosphorylated SMAD1/5/8 combines with the cytoplasmic SMAD4 as an active transcriptional complex and moves into the nucleus; the complex combines with the BMP reaction element (BMP-RE1 and BMP-RE2) and then activates transcription of the *HAMP* [49, 50]. MT-2 (matriptase-2, *TMPRSS6*, transmembrane protease serine 6) is ubiquitously expressed in the liver, invalid of MT-2 due to genetic mutation causes iron-refractory iron deficiency anemia (IRIDA) [51, 52], and MT-2 is also downregulated by iron and BMP6 [53, 54]. HJV is a glycosphosphatidylinositol- (GPI-) anchored protein

[55]; MT-2 cleaves the membrane HJV (m-HJV) to a form of soluble HJV (s-HJV) to decrease the affinity for BMP6 [56]; thus, the MT-2 expression increases during iron deficiency [57]. However, recent research shows that MT-2 independently cleaves HJV to regulate hepcidin expression, and it also cleaves other components in the BMP/SMAD pathway other than HJV [58]. The furin family of proprotein convertases expressed in the liver also produces s-HJV by cleaving the HJV, but different with MT-2; sHJV generated by furin negatively regulated BMP while the MT-2 only reduces the combination [56]; this process is regulated by iron deficiency or hypoxia [59]. Others like endofin, ATOH8, and SMAD7 also affect the signal transduction of the BMP/SMAD pathway [60–62], which is the perceptron and messenger of iron concentration.

pathway. HIF promotes MT2 and furin to cleavage HJV, and miR-210 inhibits it to reduce hepcidin expression. Iron increases BMP6 expression.

In inflammation, IL-6 combines with its receptor IL-6R to activate the JAK, triggering the phosphorylates of STAT3 that forms as a complex move into the nucleus and promotes the transcription of *HAMP*. IL6 increases the BMP/SMAD pathway by promoting ALK3.

2.3. Role of Inflammation, Hypoxia, and MicroRNA in Iron Regulation. Infection and inflammation induce hepcidin production [74], which inhibits iron efflux from intestinal and promotes iron chelation in macrophages, thus reducing the concentration of blood iron [75]. During inflammation, the secretion of proinflammatory cytokines (such as IL-6) increases. Interleukin-6 (IL-6) is one kind of cytokine that regulates the transcription of hepcidin [76]. It combines with the IL-6 receptor (IL-6R) on the membrane, then activates JAK and phosphorylates STAT3 protein in hepatocytes. The phosphorylated STAT3 protein moves into the nucleus, regulating the expression of *HAMP* by binding to the STAT3-specific site [77]. IL-6 not only affects hepcidin expression through the JAK/STAT3 pathway but also combines one of the BMPR I receptor Alk3 [78]; this indicates that the JAK-STAT3 pathway has cross action with the BMP/SMAD pathway [79]. In acute inflammatory condition, the stimulation of Toll-like receptor reduces FPN1 in macrophages, blocking the iron excretion from macrophages which is recovered from red blood cells and rapidly induced hypoferrremia [80]. Then, the heme, required by the proerythroblast to complete its terminal differentiation stage, is exported from macrophages by FLVCR1 [81]. High hepcidin lowers the pathogens available in iron; it is a strategy to starve the pathogens to limit their growth [82]. But as one of the defensin-like peptide hormones, the innate immunity functions of hepcidin have a connection to antimicrobial peptides and inflammation; perhaps, the role of hepcidin in immunity could bypass iron and be directly related to hosting defense (Figure 2).

The body compensates for the oxygen content by intensifying the erythropoiesis when hypoxia, blood loss, or the other causes. In response to the erythropoiesis, erythropoietin (EPO) is secreted by the kidney. According to the severity of hypoxia, EPO has a hundred times of differing in serum [83], it controls iron absorption, erythroid progenitor cell proliferation, maturation, and survival [84, 85]. Erythroferrone (ERFE) is a soluble protein released by EPO-stimulated erythroid precursors; it suppresses the expression of hepcidin [86]. EPO and ERFE suppress the expression of hepcidin by BMP/SMAD pathway target genes [87–89]. But in the IRIDA, due to the MT-2 restriction, the EPO/ERFE-mediated hepcidin downregulation in the BMP/SMAD pathway is obstructed, the blocked signal transmission leads both the EPO and the ERFE, and hepcidin simultaneously maintained elevated levels even in the patients with anemia [90]. The hypoxia-inducible factor (HIF) is a transcription factor of EPO, and the content of the EPO is completely dependent on HIF-2 α [91]. HIF-2 α promotes erythropoiesis, including increases in the production of EPO, which enhances iron uptake and utilization [92]. Therefore, hypoxia increases

the demand for iron and reduces the expression of hepcidin by HIF and EPO [93]. Hepcidin promoter contains several HIF1 and HIF2 sites, regulating the hepcidin by the hypoxia-oxygen-sensing regulatory pathway [94]. Besides that, HIF participates in the BMP/SMAD pathway by affecting the MT-2 and increasing the furin mRNA level [95, 96] (Figure 2).

MicroRNAs are a class of small noncoding RNAs (~22 nt) that bind to the 3' untranslated region (3'UTR) of the target messenger RNA (mRNA), thereby negatively regulating gene expression, and many miRNAs are involved in posttranscriptional regulation of iron. miR-485-3p and miR-17 seed family member miR-20a and miR-20b, as the concurrent modulator to regulate the expression of FPN1 [97–99]. miR-Let-7d and miR-16 family (miR-15b, miR-16, miR-195, and miR-497) bind the 3'UTR of *DMT1*-IRE mRNA then decrease DMT1 expression levels, causing iron accumulation in the endosomes, or hoarded in ferritin or used for iron-related proteins [100–102]. MiR-320 is another microRNA related to cellular iron uptake, which inhibits TfR1 expression and prevents cell proliferation [103], and miR-200b induces downregulation of ferritin [104]. In the BMP-SMAD signaling, ALK2 as primary endogenous BMP type I receptors is involved in systemic iron regulation; miR-130a targets 3'UTR of *ALK2* to inhibit BMP-SMAD signaling and the expression of hepcidin; it was upregulated in the iron deficiency mice [105].

In the regulation of hypoxia, *HIF-1 α* hypoxia response element-binding site was identified in the promoter of miR-210; the miR-210 is specifically induced by HIF-1 α during hypoxia [106]. Iron-sulfur cluster scaffold protein (ISCU) is an iron homeostasis essential molecule; iron deficiency induces miR-210 expression through HIF-1 α , and miR-210 directly inhibits ISCU and TfR to maintain the systemic iron homeostasis [107]. miR-122 is a very important microRNA that is selectively expressed in the liver and participates in a variety of regulation, including maintaining iron homeostasis. It controls hepcidin mRNA transcription by inhibiting the expression of *Hfe*, *Hjv*, and *Bmpr1a* in the liver, thereby preventing iron deficiency [108], thus activating *Hamp* mRNA expression. miRNAs related to iron regulation are summarized in Figures 1 and 2.

2.4. Diseases Related to Disorders of Iron Metabolism

2.4.1. Iron Overload Causes Cell Oxidative Damaged-Ferroptosis. Ferroptosis is a form of regulated cell death; unlike other forms of regulated cell death, ferroptosis is unnecessary for the caspases [109]. Ferroptosis is characterized by the overwhelming iron-dependent oxidative injury and accumulation of lipid hydroperoxides to lethal levels. The excessive iron produces ROS (reactive oxygen species) by Fenton reaction in cells. In cells, the ROS has multiple sources; iron and its derivatives are essential for the ROS-producing enzymes.

Ferroptosis is related to amino acid metabolism. Glutathione (GSH) protects cells from oxidative stress damage, but the availability of cysteine limits the GSH biosynthesis [110]; therefore, the cysteine is contributed to protecting cells

TABLE 1: Genetic mutation causes iron metabolism disorders.

Protein	Gene	Mutation site	Downstream effect	Phenotype	Reference
HFE	HFE	C282Y	Iron concentration perception	Regulation hepcidin expression by binding TfR	[133]
TfR2	TFR2	Y250X	Tf, HFE receptor	C282Y homozygote modifier	[144]
HJV	HJV	G320V, etc.	Activate BMP-SMAD	Regulation hepcidin expression	[134]
MT2	TMPRSS6	A736V	Cleavage HJV	Determining protease activity, influences the hepcidin response to iron	[140]
FPN1	SLC40A1	C326S	Cellular iron effluxion	Resistance combine hepcidin	[145, 146]

from oxidative stress. Cysteine is produced by the reduction of cystine which is transported into cells by the cystine/glutamate reverse transport system xc⁻, then for the GSH synthesis. Cells not only rely on the system xc⁻ to import cystine but also bypass the system xc⁻ by the transsulfuration pathway to biosynthesize the cysteine from methionine.

The depletion of GSH inactivation of the GSH peroxidase 4 (GPX4) ultimately causes the ferroptosis. Erastin, an oncogenic RAS-selective lethal small molecule [111], induces ferroptosis by inducing GSH depletion and inactivation of the phospholipid peroxidase GPX4 and inhibits import of cystine [112]. So amino acid metabolism is closely linked to ferroptosis [113]; furthermore, studies on the association of ferroptosis and various diseases have provided a new perspective and have become a new research aspect, such as Parkinson's disease, Alzheimer's disease, Huntington's disease, stroke, apoplexy, ischemia-reperfusion injury, cardiopathy, carcinogenesis, periventricular leukomalacia, and brain injury [110].

2.4.2. Parkinson's Disease. Parkinson's disease (PD) is a progressive neurological disorder, primarily from the death of dopaminergic neurons in the substantia nigra [114]. Studies have shown that Parkinson's disease is caused by biochemical abnormalities, including oxidative stress and mitochondrial dysfunction [115, 116], and in recently, some studies have also shown the correlation between PD and ferroptosis [117].

Iron accumulation in neurons induces oxidative stress by Fenton's reaction generating ROS. ROS induces iron release from mitochondrial iron-sulfur cluster protein and other iron storage proteins; it leads the further ROS generation through Fenton's reaction [118], then the ROS damage DNA and mtDNA by epigenetic mechanism and oxidize protein [118–120]. The most significant characteristic of Parkinson's disease is the progressive degeneration in the substantia nigra, but current research is still incomprehensible why neurodegeneration only exists in certain nuclei while the other iron-accumulation tissue remains unaffected and the mechanism of neurotoxicity [121].

Mitophagy, the spontaneous and selectively autophagic elimination of damaged or dysfunctional mitochondria, is regulated by accumulation of iron, Parkin, and PINK1 (PTEN-induced putative kinase protein 1) and mediated by autophagosomes. There are reports that show the loss of iron in neuronal triggering mitophagy in a PINK1/Parkin-independent manner [122, 123], and in contrast, the accumulation of cellular iron obstructed the mitophagy, so that the

cells unable to eliminate the damaged mitochondria to maintain normal physiological status.

PINK1 is stably localized on damaged mitochondria with low membrane potential [124], and the Parkin, an E3 ubiquitin ligase, is selectively recruited from cytosol to dysfunctional mitochondria [125] and liberates the activity of the E3 by the PINK1-dependent mitochondrial localization [124], then Parkin ubiquitination outer mitochondrial membrane proteins to trigger mitophagy [126]. So, the PINK1 and Parkin together sense the distress of mitochondria and selectively target them for degradation [127], and the mutations of PINK1 or Parkin fail to clear damaged mitochondria [128, 129], causing neuronal damage [130], leading to Parkinson's disease [131].

2.4.3. Hereditary Iron Disease. Hereditary hemochromatosis (HH) mainly in Western populations causes iron overloaded. HH is caused by multiple genetic defects like *HFE*, *TfR2*, *HJV*, *TMPRSS6*, *FPN1*, and *HAMP*. According to different mutant genes, HH is divided into HFE hemochromatosis (type1), juvenile hemochromatosis (type 2), TfR2 hemochromatosis (type 3), and ferroportin hemochromatosis.

The majority of the HH is typ1 and typ2; it is due to the homozygosity for the C282Y mutation in the *HFE* and G320V, etc. in the *HJV* genes [132–135]. *HFE* and *HJV* mutations alone or simultaneously affect the expression of hepcidin through the BMP/SMAD pathway. In type 3 HH, the mutation was identified on human chromosome 7q22 homozygous recessive Y250X in *TfR2* [136]; type 3 HH is less severe than typ1 and typ2 HH. Type 3 HH pathogenesis is demonstrated in the mutation experiment of mice; the mutation of TfR2 caused the inability of TF and HFE to bind to it, weakened the signal transmission, and resulted in the down-regulation of hepcidin expression [137], which ultimately caused iron overload in multiple organs. As a receptor for hepcidin, *FPN1* has C326 residue and is necessary for the binding of hepcidin [138]. Ferroportin hemochromatosis is associated with the mutation of C326 residue, it is an autosomal dominant genetic disease with similar clinical and phenotypic features to other HH, and the mutation of C326 suffices to cause FPN1 resistance of hepcidin [138, 139]. The loss-of-function mutation of *TMPRSS6* causes IRIDA, and its molecular basis was first identified in 2008 [140, 141]. Microcytic hypochromic anemia, low Tf saturation, and excessive hepcidin are the main characteristic of IRIDA; however, oral iron supplementation is futile in relieving the symptoms. In the IRIDA, the most frequent mutation is S304L; besides that, 40 different mutations in the *TMPRSS6*

gene have been described including *K225E*, *K253E*, *G228D*, *R446W*, *V736A*, and *V795I* [142], but the latest research shows that *ALK2* gene mutation is also involved in the IRIDA [143]. Including the gene mutations mentioned above, we summarized the various genetic variations that caused hereditary iron disease in Table 1.

2.4.4. Perspectives. As one of the most important elements in the body, after the decades of research, we have been clear about the effect of the liver on iron metabolism and regulation, but we are still constantly discovering new methods to affect iron metabolism directly or indirectly. As the secretory organ of hepcidin, the study of microRNA and gene mutations has opened a new horizon for iron regulation in hepatocyte. The discovery of more potential regulators raises more awareness of iron metabolism, and more drugs can be developed to treat iron-related diseases, such as inhibitors or agonist of key genes. Due to the importance of iron in the body, the molecular mechanism of iron sensing and regulation and its interaction needed to fully comprehend.

Conflicts of Interest

The authors declare no conflict of interest, financial, or otherwise.

Acknowledgments

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