Title

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Journal

The FEBS Journal, 286(4)

ISSN

1742-464X

Authors

Zhang, Jin

Chen, Xinbin

Publication Date

2019-02-01

DOI

10.1111/febs.14638

Peer reviewed

HHS Public Access

Author manuscript

FEBS J. Author manuscript; available in PMC 2020 February 01.

Published in final edited form as:

FEBS J. 2019 February ; 286(4): 620–629. doi:10.1111/febs.14638.

p53 Tumor Suppressor and Iron Homeostasis

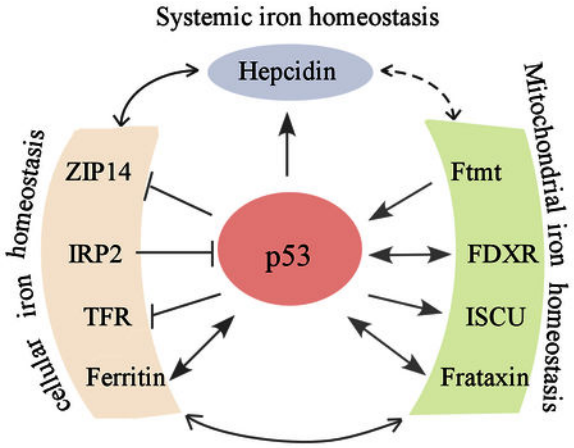
Jin Zhang[*] and **Xinbin Chen**[*]

Comparative Oncology Laboratory, School of Veterinary Medicine and Medicine, University of California at Davis, Davis, CA

Abstract

Iron is an essential nutrient for all living organisms and plays a vital role in many fundamental biochemical processes, such as oxygen transport, energy metabolism, and DNA synthesis. Due to its capability to produce free radicals, iron has deleterious effects and thus, its level needs to be tightly controlled in the body. Deregulation of iron metabolism is known to cause diseases, including anemia by iron deficiency and hereditary hemochromatosis by iron overload. Interestingly, dysregulated iron metabolism occurs frequently in tumor cells and contributes to tumorigenesis. In this review, we will discuss the role of p53 tumor suppressor in iron homeostasis.

Abstract



P53 tumor suppressor plays a critical role in maintaining the genome integrity. Recent studies show that p53 is instrumental in regulating iron homeostasis by modulating several iron regulators. Some iron regulators also form a feedback regulatory loop with p53. Thus, the crosstalk between p53 and the iron regulators may shed a light on the mechanisms by which iron metabolism is altered in cancers.

Keywords

Iron homeostasis; tumor suppression; mitochondrial iron homeostasis; p53; IRP1/2; FDXR

[*]Corresponding to Dr. Jin Zhang: jinzhang@ucdavis.edu, Dr. Xinbin Chen: xbchen@ucdavis.edu.

Introduction

Iron is essential for many cellular processes including cell growth and proliferation. The most important feature of iron is that it mediates electron transfer by interchanging between ferrous (Fe(II), Fe^{2+}) and ferric (Fe(III), Fe^{3+}) states. Iron acts as an electron donor in the ferrous state but as an electron acceptor in the ferric state. Consequently, iron plays a vital role in many fundamental biochemical activities, such as oxygen transport, energy metabolism, and DNA synthesis [1]. However, iron can be highly toxic due to its capability to participate in Fenton reaction. Ferrous iron donates an electron in a reaction with hydrogen peroxide to generate the hydroxyl radical, a reactive oxygen species (ROS), which leads to oxidative stress, lipid peroxidation, and DNA damage. Thus, the uptake, storage, and usage of iron need to be tightly controlled. Indeed, all organisms have developed sophisticated mechanisms to modulate iron homeostasis.

Systemic iron homeostasis

Circulating iron in the body is controlled by four main cell types: enterocytes in the duodenum to absorb dietary iron; erythrocyte precursors in the bone marrow to incorporate iron into hemoglobin; macrophages in the liver, spleen, and bone marrow to recycle iron; and hepatocytes in the liver to store iron. The control of circulating iron is mediated by factors that can sense the iron level and subsequently, regulate the expression of genes necessary for iron homeostasis. One of the major regulatory mechanisms is the hepcidin-ferroportin (FPN) axis (Fig. 1). FPN is a transmembrane protein that allows iron to be transported out of cells and into the bloodstream. High levels of FPN are found in enterocytes, macrophages, and hepatocytes. The role of FPN in iron export has been demonstrated in mouse models. Loss of FPN leads to embryonic lethality in mice, suggesting a critical role of FPN in development [2]. Interestingly, conditional deletion of FPN in mouse intestine leads to accumulation of iron in duodenal enterocytes and these mice become severely anemic within weeks [2]. FPN-mediated iron efflux is negatively controlled by hepcidin, a 25-amino acid peptide hormone produced by hepatocytes [3, 4]. Circulating hepcidin inhibits iron export from macrophages, enterocytes, and hepatocytes and thereby regulates the amount of iron in the bloodstream [5–7]. Mechanistically, hepcidin binds to the extracellular domain of FPN and induces its endocytosis and subsequent degradation [5, 8, 9], leading to reduced export of cellular iron. The importance of the hepcidin-FPN axis in systemic iron homeostasis is exemplified by several iron disorders. For example, decreased FPN activity, led by high levels of hepcidin, is found in iron-restriction syndromes, including iron-refractory iron deficiency anemia (IRIDA) [10] or anemia of inflammation [11], in which iron accumulates in recycling macrophages and enterocytes, but may become insufficient in other tissues. By contrast, hyperactive FPN, usually as a result of hepcidin deficiency, is found in hereditary hemochromatosis [12] or β-thalassemia intermedia [13], in which excessive iron absorption and toxic iron deposition are found in hepatocytes and other parenchymal cells, but relative iron depletion occurs in macrophages.

Cellular iron homeostasis

Cellular iron homeostasis is regulated via iron uptake, trafficking and export (Fig. 2). These processes are tightly controlled by iron regulatory protein 1 (IRP1) and IRP2 (also known as ACO1 and IREB2, respectively) [14, 15]. IRPs are RNA-binding proteins and interact with conserved cis-regulatory hairpin structures known as IREs (iron-responsive elements), which are present in the 5' or 3'untranslated regions (UTRs) of target mRNAs. Generally, IRPs inhibit the translation of mRNAs that contain an IRE in their 5'UTRs and increase the stability of mRNAs that contain an IRE in their 3'UTRs. For example, IRPs suppress the translation of FTH1, FTL, and FPN1 mRNAs via binding to an IRE in their 5'UTRs. By contrast, IRPs stabilize mRNAs of TFR1 and DMT1 via binding to an IRE in their 3'UTRs [16, 17]. Interestingly, the activity of IRPs is controlled by iron. When intracellular levels of iron are low, IRPs are active and stabilize mRNAs for proteins involved in iron uptake but repress the translation of mRNAs for proteins involved in iron storage and export. In iron-replete cells, IRP1 functions as an aconitase but not a RNA-binding protein whereas IRP2 undergoes iron-dependent degradation. As a result, both IRPs are inactive and thus unable to increase the level of proteins involved in iron uptake or decrease the level of proteins involved in iron storage and export. The biological significance of IRPs in regulating cellular iron homeostasis has been confirmed in mouse models. Genetic ablation of both IRPs in the mouse leads to embryonic lethality [18, 19], suggesting a critical role of iron homeostasis during development. However, mice deficient in IRP1 or IRP2 are viable and fertile, indicating a redundant function between these two IRPs. Notably, IRP2 deficiency leads to abnormal body iron distribution, a mild microcytic anemia, and neurodegeneration [20, 21]. IRP1-KO mice were initially found to be asymptomatic, suggesting that IRP1 is not necessary in iron metabolism [22]. Later, it was found that IRP1 plays an essential role in regulation of systemic iron homeostasis and erythropoiesis [23, 24]. Additionally, it was found that overexpression of IRP1 reduces, whereas overexpression of IRP2 promotes, tumor growth in vivo [25–28]. These data suggest that IRP1 and IRP2 are not functionally redundant and may have different impacts in the content of cancer.

Mitochondrial Iron homeostasis

Mitochondria play a central role in energy production, oxygen transport, and deoxynucleotide synthesis. Mitochondria are also essential for iron metabolism (Fig. 2). Intracellular iron can be transported to mitochondria, where it is utilized to synthesize essential cofactors for a number of proteins. Indeed, the mitochondrion is the only site where heme is synthesized. Heme is a prosthetic group for proteins involved in cellular respiration, oxygen transport/storage, and enzymatic functions [29], such as hemoglobin, myoglobin, and cytochrome c. A multi-step reaction is necessary for heme biogenesis, which is catalyzed by eight enzymes [30, 31]. The first rate-limiting step occurs in mitochondria and is mediated by δ-aminolevulinic acid synthase (ALAS1/2) to form δ-aminolevulinic acid (ALA). ALA is exported to the cytosol and converted to coproporphyrinogen III (CPgenIII), which is then transported back to mitochondria and converted to protoporphyrin IX (PPIX). The final step is mediated by ferrochelatase (FECH), which inserts ferrous iron into PPIX to form heme. Defective heme synthesis is associated with sideroblastic anemia [32], in which erythroblasts cannot make enough hemoglobin due to disrupted heme production. Consistently, patients with sideroblastic anemia were found to have hereditary gene

mutations in ALAS2 and FECH, both of which are known to be required for heme synthesis [33, 34].

Mitochondria are the major site to produce iron sulfur clusters (ISCs), which are cofactors essential for proteins involved in mitochondrial respiration, DNA replication/repair, and enzymatic functions [35, 36]. The initial stage of ISC assembly is carried out by a multimeric protein complex [37, 38]: 1) cysteine desulfurase (NFS1) which provides sulfur by removing it from cysteine residues; 2) ISD11, a binding partner to stabilize NFS1; 3) ISCU (iron-sulfur cluster assembly enzyme), a scaffold protein that supplies the backbone structure to synthesize the nascent Fe-S cluster; and 4) Frataxin that supplies the source of iron [39]. In addition, ferredoxin reductase (FDXR) and ferredoxins 1 and 2 (FDX1/2) provide an electron that reduces sulfane to sulfide in order to achieve an appropriate electronic configuration for a given ISC [40]. Once the nascent Fe-S cluster is formed, it is transferred to recipient apo-proteins, thereby converting them to their holo-forms. Importantly, genetic mutations of the genes involved in ISC biosynthesis have been identified in neurodegenerative and metabolic diseases associated with mitochondrial iron overload [38]. For example, reduced expression of frataxin due to homozygous unstable GAA trinucleotide expansion in the FXN gene can result in Friedreich's ataxia (FA), an autosomal recessive disease characterized by severe neurodegeneration and cardiomyopathy [41]. Consistent with this, mice deficient in frataxin are embryonically lethal whereas conditional loss of frataxin in neuron/cardiac muscle phenocopies the pathophysiological and biochemical features of the human FA [42]. Mutation of NFS1 leads to infantile mitochondrial complex II/III deficiency, an autosomal recessive disease characterized by hypotonia, lactic acidemia, and multisystem organ failure [43]. Moreover, loss of function of ISCU due to splicing mutation leads to ISCU myopathy, a disease leading to severe exercise intolerance in skeletal muscles [44, 45]. Furthermore, biallelic mutations in FDX2 are found in patients with mitochondrial muscle myopathy [46]. Recently, two groups discovered that FDXR mutations are found in patients with auditory neuropathy, optic atrophy, and other neurological signs of mitochondriopathy [47, 48].

Iron homeostasis and cancer

Deregulation of iron metabolism has been implicated in several types of cancer with abnormal iron uptake, utilization and storage [49]. Cancer cells often have an increased expression of iron importers and decreased expression of iron exporters. For example, FPN expression is reduced in breast cancer along with increased levels of the labile iron pool and enhanced tumor growth [50]. Similarly, FPN was found to be decreased in prostate cancer and ovarian cancer [51, 52]. By contrast, hepcidin, the negative regulator of FPN, was found to be increased in patients diagnosed with prostate cancer, breast cancer, hepatocellular carcinoma, and ovarian cancer [53–56]. Additionally, ferritin, TfR, and STEAP3, a metalloreductase that converts iron from an insoluble ferric (Fe^{3+}) to a soluble ferrous (Fe^{2+}) form, were found to be highly expressed in cancer cells to increase iron intake [57–59]. Recently, it was found that NFS1, a regulator of ISC assembly, promotes lung cancer by regulating iron homeostasis [60]. It is suggested that iron promotes tumor formation as an essential growth factor. Indeed, iron is necessary for the function of many enzymes involved in DNA synthesis and cell cycle [61]. By contrast, iron depletion inhibits cell proliferation

by decreasing cyclin D1 and Cdk2 expression [62, 63]. Additionally, iron can function as a tumor promoter by generating reactive oxygen species via the Fenton reaction. This reaction not only damages lipids and proteins, but also causes oxidative damage to DNA, including DNA base modifications and DNA strand breaks [64, 65], which can be mutagenic [66, 67].

The crosstalk between tumor suppressor p53 and iron regulators

The tumor suppressor p53 is often referred to as the “guardian of the genome” [68, 69]. p53 is the most commonly mutated gene in human cancer and loss of p53 is known to play a central role in tumor development [70]. The importance of p53 in tumor suppression is underscored by its ability as a transcription factor to regulate a series of target genes necessary for cell survival and death [71]. Recent studies suggest that p53 plays a role in iron homeostasis and conversely, p53 is also regulated by several key regulators in iron metabolism (Fig. 3).

p53 expression is modulated by both iron overload and iron deficiency.

Upon treatment with iron chelators, p53 expression is increased and then induces growth inhibition by activating its targets such as p21 [72–75]. The enhanced expression of p53 by iron chelators is likely due to the increased p53 protein stability by hypoxia-inducible factor 1 alpha (HIF1α) [76]. HIF1α is activated in response to iron-deprived conditions [77, 78]. Conversely, p53 expression is decreased upon exposure to excess iron or iron overload via heme-p53 interaction [79]. Consistently, p53 expression is decreased in $Hfe^{-/-}$ mice that exhibit hereditary hemochromatosis, an iron overload disease [80]. Mechanistically, heme interacts with p53 DNA-binding domain, which promotes p53 export out of the nucleus through CRM1 and subsequently, p53 degradation [79]. However, p53 is also found to be upregulated upon exposure to excess iron but downregulated upon iron depletion via MDM2 [81]. It is not clear why two opposing observations were obtained in response to iron alterations. One possibility is that different cell types, e.g., cancer cells [72–75] vs. hepatocytes [81], were used in these studies. Thus, a systemic study is warranted to determine how p53 expression is altered by iron chelation or depletion.

p53 plays a role in iron homeostasis by modulating iron regulators.

C57BL/6 mice fed a high-iron diet show a decrease in p53 protein levels in the liver [79]. Consistent with this, loss of p53 leads to increased levels of serum iron in mice fed with excess dietary iron [82]. As a master regulator, p53 is likely to regulate expression of key iron sensors to control intracellular iron pool. Indeed, the promoter of HAMP, the gene encoding hepcidin, contains a putative p53-responsive element and can be activated by p53 but decreased when p53 is silenced [83]. It is suggested that an increased level of hepcidin by p53 plays a role in the pathogenesis of anemia, the most common haematological abnormality in cancer patients, whose p53 levels are often increased during cancer treatment. Additionally, it was found that ISCU is a target of p53 and the increased expression of ISCU by p53 protects cells from iron overload [82]. Thus, ISCU serves as a mediator of p53 to maintain the intracellular iron pool [82], consistent with the study that p53 is capable of increasing ferritin, but decreasing TFR1, expression [72]. Intriguingly, p53 appears to increase ferritin expression via a posttranscriptional mechanism [72]. However,

another study showed that p53 is recruited by NF-Y to the H ferritin promoter and subsequently, represses ferritin expression [84]. Moreover, the metal transporter ZIP14 was identified as a p53-regulated protein [85]. Knockdown of endogenous p53 increased ZIP14 expression and subsequently, cellular non-transferrin-bound iron (NTBI) uptake. Interestingly, p53 appears to modulate ZIP14 expression through interaction with ZIP14, subsequently preventing ZIP14 from degradation.

p53 plays a role in mitochondrial iron homeostasis.

p53 is found to modulate several mitochondrial proteins involved in iron metabolism. For example, ferredoxin reductase (FDXR) is identified as a target of p53 [86, 87]. FDXR is the sole human ferredoxin reductase involved in the biosynthesis of ISCs and heme. Mice deficient in FDXR are embryonically lethal, likely due to iron overload in developing embryos [88]. It is suggested that p53-mediated FDXR expression plays a role in mitochondrial iron homeostasis and subsequently, modulates ISC or heme synthesis [89]. In addition, frataxin, a key regulator of ISC synthesis, is regulated by p53 [90, 91]. Notably, frataxin expression was found to be associated with p53 status and the promoter of the FXN gene contains a putative p53-responsive element [90]. Nevertheless, the biological significance of p53-mediated frataxin expression remains to be elucidated.

Multiple feedback loops between p53 and iron regulators.

Feedback regulation is involved in many cellular processes. Since p53 regulates several key iron regulators, it is likely that some of these regulators in turn modulate p53 expression. Indeed, our laboratory showed that FDXR is necessary for p53 expression [88]. Specifically, we showed that loss of FDXR reduces, whereas ectopic expression of FDXR increases, p53 expression. Mechanistically, FDXR signals through ferredoxin 2, a substrate of FDXR, which subsequently activates IRP2 to decrease p53 mRNA translation. As a result, mice heterozygous in Fdxr had a short life span and were prone to spontaneous tumors and liver abnormalities [88]. In addition, knockdown of frataxin induces cell death in human astrocytes, which is accompanied with a significant up-regulation of p53 and p21 [92]. Similarly, it was found that silencing of frataxin expression triggers p53-dependent apoptosis in human neuron-like cells [93]. Consistent with this, high levels of p53 protein were expressed in B cells derived from Friedreich’s ataxia patients, suggesting that frataxin deficiency activates p53 expression [94]. Moreover, ferritin, an iron storage protein, was found to activate p53 expression under oxidative stress [95]. Specifically, ferritin binds to p53 and subsequently, increases the transcriptional activity of p53, which is independent of the ferroxidase activity of ferritin. Consistent with this, knockdown of ferritin alleviates induction of p53 target genes upon treatment with hydrogen peroxide [95]. Similarly, it was found that mitochondrial ferritin (Ftmt), a mitochondrial iron storage protein, activates p53 expression along with its target p21, leading to growth suppression [96].

p53 and ferropotosis

Ferroptosis is an iron-mediated, caspase-independent, cell death pathway that requires the accumulation of lipid hydroperoxides [97] and recent studies suggest that ferroptosis may be a new option for cancer therapy [98]. Recently, it was found that ferropotosis is a crucial component of p53-mediated tumor suppression [99]. p53 induces ferroptosis at least in part

via transcriptional repression of SLC7A11, a component of system xc−, a cystine/glutamate antiporter [99]. Additionally, p53 mediates ferroptosis by activating GLS2 and SAT1 [100–102]. Intriguingly, it was found that p53 inhibits ferroptosis by inhibiting dipeptidyl-peptidase-4 (DPP4) activity in a transcription-independent manner in human colorectal cancer cell lines [103]. In another study, it was found that p53 decreases system xc− activity, and simultaneously reduces the sensitivity of cells to metabolic stress-mediated ferroptosis [104]. These apparently opposing observations are likely due to different settings. For example, basal p53 was found to induce ferroptosis [100–102], whereas stress-induced p53 was found to inhibit ferroptosis [103, 105]. Nevertheless, a comprehensive understanding of how p53 modulates ferroptosis is needed, which would be beneficial for developing cancer therapies targeting ferroptosis.

Conclusions and future directions

Emerging evidence suggests that dysregulation of iron metabolism contributes to tumorigenesis and many iron regulatory genes are found to be altered in cancers. Generally, cancer cells require high amount of iron for proliferation and thus, are vulnerable to iron deficiency. Thus, iron chelators are currently being tested for the treatment of several types of cancers including solid tumors and blood cancers [106–109]. For example, deferoxamine showed anti-tumor effect in patients with advanced HCC [110, 111]. In addition, iron chelator triapine showed promising results for patients with stage IB2-IIIB cervical cancer [112] and is currently being advanced to a phase II randomized trial for treatment of advanced cervical and vaginal cancers [113]. It is suggested that the anti-tumor effect of iron chelator is at least in part via activation of p53 or its downstream target, p21 [74]. Interestingly, p53 is not only necessary for inducing growth suppression upon iron depletion but also necessary for the maintenance of the intracellular iron pool. Thus, many questions remain unanswered. First, p53 is mutated in more than half of human cancers. Interestingly, it was found that ISCU expression was significantly lower in hepatocellular carcinoma tissues with mutant p53 as compared to those with wild-type p53 [82], suggesting a role of mutant p53 in deregulating iron homeostasis. Therefore, the role of mutant p53 in iron metabolism needs to be elucidated. Second, the genetic status of the p53 gene in tumors need to be determined when iron chelating agents are considered as a therapeutic strategy. Accordingly, the anti-tumor effect of iron chelator needs to be carefully examined in tumors with a mutant p53. Third, as p53 appears to modulate expression of genes involving in both systemic and cellular iron homeostasis, further studies are needed to determine how p53 cooperates with these iron regulators to modulate iron metabolism, which may shed a light to the role of p53 in diseases associated with aberrant iron homeostasis. Forth, several regulatory loops exist between p53 and mitochondrial iron regulators, such as FDXR-p53 and Frataxin-p53 loops. For example, FDXR is required for both wild-type and mutant p53 expression, thus, targeting FDXR may provide an ideal approach for tumors bearing a mutant p53 but not for the ones with wild-type p53. Thus, understanding the role of these feedback loops in cancer is required to target these loops as a cancer therapeutic strategy.

Aknowledgements:

This work is supported in part by NIH grants (CA224433, CA076069, CA081237, and CA195828)

Abbreviations:

IRP1	iron regulatory protein 1
IRP2	iron regulatory protein 2
IRE	iron-responsive elements
UTR	untranslated region
ALA	δ-aminolevulinic acid
ALAS1	δ-aminolevulinic acid synthase 1
CPgenIII	coproporphyrinogen III
PPIX	protoporphyrin IX
ISC	iron sulfur cluster
FDXR	ferredoxin reductase
FDX1/2	ferredoxins
FA	Friedreich's ataxia
Ftmt	mitochondrial ferritin
FPN	ferroportin

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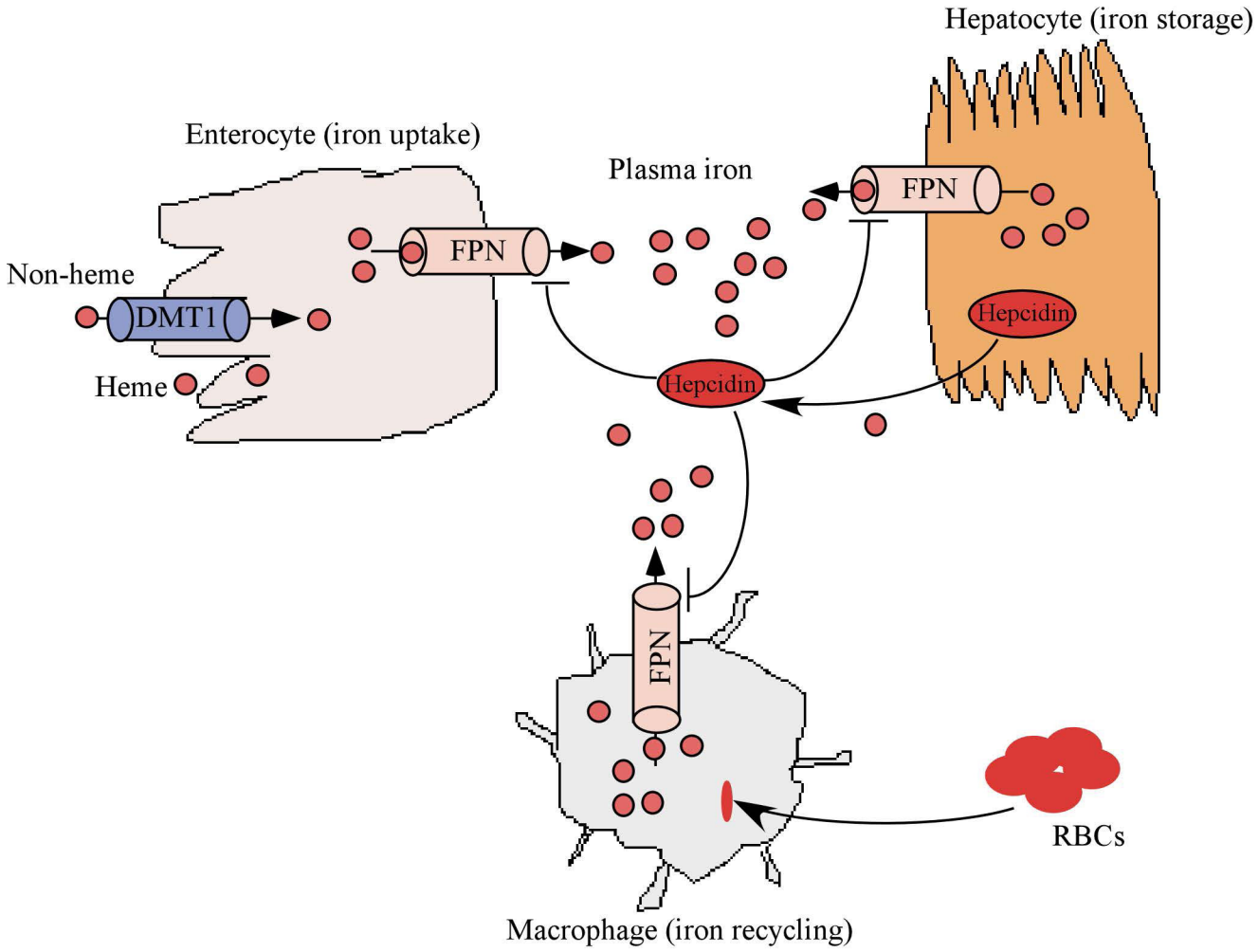

Figure 1.

Systemic iron homeostasis is controlled by the hepcidin-FPN axis. The peptide hormone hepcidin negatively regulates the expression of ferroportin (FPN), the major cellular iron exporter responsible for transporting iron from cell into plasma.

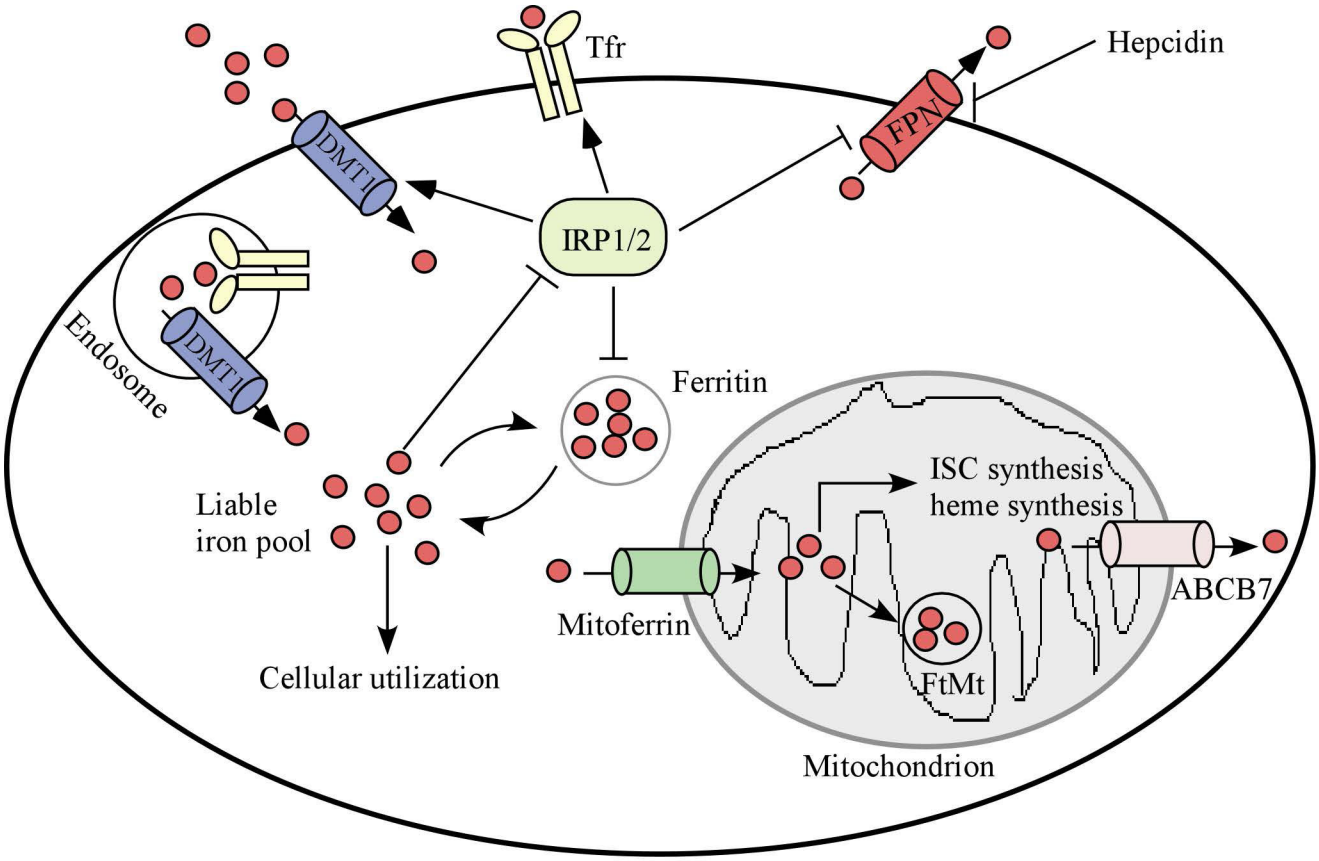

Figure 2.

Cellular and mitochondrial iron homeostasis. The cellular iron storage, uptake and export is controlled by iron regulatory proteins (IRP1/2). Mitochondria are a major site for ISC (iron sulfur cluster) protein synthesis as well as heme synthesis. The regulators of mitochondrial homeostasis include Mitoferrin (for iron delivery), FtMt (ferritin mitochondrial, for iron storage) and ABCB7 (iron transporter).

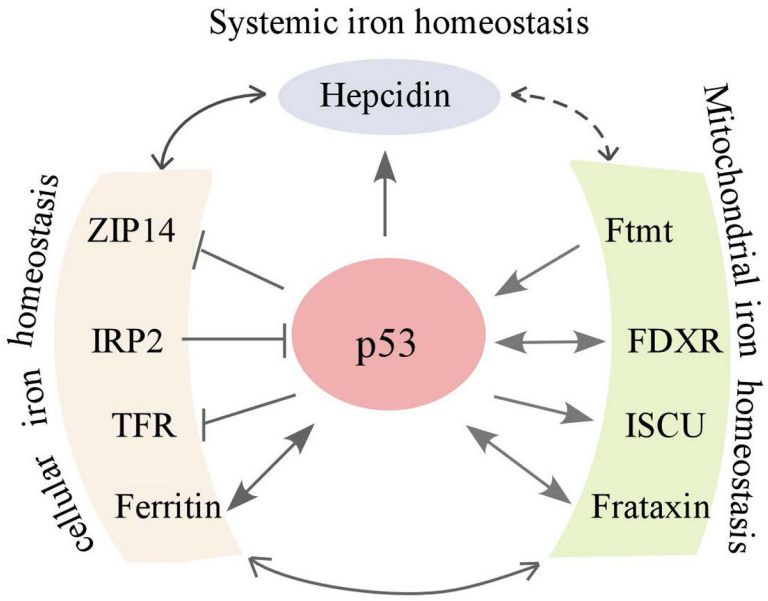

Figure 3.
Crosstalk between p53 and iron regulators. The crosstalk between p53 and various iron regulators involving systemic, cellular and mitochondrial iron homeostasis.