

Iron metabolism and its contribution to cancer (Review)

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Abstract. Iron is an essential element for biological processes. Iron homeostasis is regulated through several mechanisms, from absorption by enterocytes to recycling by macrophages and storage in hepatocytes. Iron has dual properties, which may facilitate tumor growth or cell death. Cancer cells exhibit an increased dependence on iron compared with normal cells. Macrophages potentially deliver iron to cancer cells, resulting in tumor promotion. Mitochondria utilize cellular iron to synthesize cofactors, including heme and iron sulfur clusters. The latter is composed of essential enzymes involved in DNA synthesis and repair, oxidation-reduction reactions, and other cellular processes. However, highly increased iron concentrations result in cell death through membrane lipid peroxidation, termed ferroptosis. Ferroptosis, an emerging pathway for cancer treatment, is similar to pyroptosis, apoptosis and necroptosis. In the present review, previous studies on the physiology of iron metabolism and its role in cancer are summarized. Additionally, the significance of iron regulation, and the association between iron homeostasis and carcinogenic mechanisms are discussed.

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1. Introduction

As a fundamental inorganic nutrient in the human body, iron serves an important role in numerous biological processes, including DNA and RNA synthesis, oxygen transport, cellular respiration, the activity of numerous enzymes, heme synthesis, detoxification processes, and immune function and metabolism (1). Iron homeostasis is tightly regulated in healthy cells by balancing absorption, systemic transportation, and cellular uptake and storage (2). However, dysregulation of this balance may increase the risk of cancer and has been associated with carcinogenesis (3,4). Numerous studies have investigated iron regulation pathways and examined the association between increases in iron concentration and enhanced tumor growth (5-7). For instance, high-iron clusters were observed in macrophage deposits in mammary tumors, lung metastases and brain metastases with the accumulation of hemosiderin (8).

Iron is an indispensable element for the synthesis of iron sulfur clusters, which are versatile and used by enzymes for vital cellular processes in normal and cancer cells (9). However, a high concentration of oxygen makes iron sulfur clusters susceptible to oxidation and Fenton reactions resulting in DNA damage (10,11). Increasing intracellular labile iron pools, using iron sucrose, may be applied to enhance the toxicity of pharmacological ascorbate in human colon cancer cells by increasing the generation of H₂O₂ (12). Additionally, iron excess in tumor cells, due to an excessive dietary intake and/or genetic factors, makes iron deprivation a principal strategy of chemotherapy for multiple types of human cancer (13,14). However, despite great progress, the association between iron metabolism and cancer has yet to be fully elucidated. The present review summarizes recent studies on novel processes and mechanisms of iron transport into cells, which could promote cancer cellular proliferation. The concepts discussed in the present study may provide a novel approach to cancer prognosis and therapy.

2. Iron absorption

Iron is not synthesized during physiological processes. Therefore, iron concentrations must be maintained through nutrition. Iron from food is primarily absorbed by duodenum enterocytes (90%). The stomach does not contribute much in the assimilation of iron, as its absorption is $\leq 2\%$ of the total intake (15). There are two types of dietary iron that may be

absorbed: Heme iron, from the breakdown of hemoglobin and myoglobin in red meat, or non-heme inorganic iron, which is predominantly released from foods, including vegetables and cereals (16,17).

Dietary iron is present in the ferric form (Fe^{3+}). Prior to absorption, Fe^{3+} is reduced to ferrous iron (Fe^{2+}) by duodenal cytochrome b (Dcytb), a brush border membrane ferrireductase (Table I). Fe^{2+} is subsequently transported across the apical membrane of enterocytes through divalent metal transporter 1 (DMT1; Table I). Hemoglobin and myoglobin are more bioavailable compared with inorganic iron (18). Researchers studied young iron-deficient piglets to investigate the pathways of heme iron absorption and to determine the efficacy of oral heme iron supplementation (16). The stomach and duodenum degrade hemoglobin to heme prior to absorption by the proximal part of the duodenum. Intact heme is transported to the enterocyte interior via heme carrier protein 1 and heme responsive gene-1 (HRG1) importers. There are two separate pathways involved in the absorption of heme iron. The first pathway involves heme oxygenase-1 (HO-1) catabolizing intracytoplasmic heme into ferrous ion, which follows the fate of inorganic dietary iron ions. The second pathway involves heme iron being transported across the basolateral membrane by feline leukemia virus subgroup C cellular receptor 1 and captured by hemopexin in plasma to form a heme-hemopexin complex (Hpx-heme). Subsequently, Hpx-heme is transported into various sites in the body via prolow-density lipoprotein receptor-related protein 1 (19).

In the cytosol, iron is neutralized by ferritin (a multimeric iron-storage protein) (Table I) and weakly bound together to form a pool of iron termed the cytoplasmic labile iron pool (cLIP) (20). The cLIP supplies iron to a number of cytoplasmic enzymes, in addition to mitochondria for heme and iron sulfur cluster synthesis. Ferroportin (FPN) (Table I), the iron transporter at the basolateral membrane of intestinal enterocytes, is the principal cellular iron exporter and transfers duodenal iron out of cells into circulation; this is the principal way for iron to enter systemic circulation (21). The released iron is reduced to ferrous ions by membrane-bound hephaestin or ceruloplasmin in plasma. These enzymes oxidize Fe^{2+} to Fe^{3+} and load Fe^{3+} onto transferrin (Tf) in the blood (22). Subsequently, Tf combines with the transferrin receptor (TfR) on cytomembranes. Hepcidin (Hep), a protein secreted by hepatocytes, binds to FPN, ceasing cellular iron export (Table I) (23-32).

Ferric ions are reduced by Dcytb and subsequently enter enterocyte epithelial cells via DMT1. Some of the iron is stored in ferritin and some passes through FPN into the plasma. In specific cases, Hep may prevent FPN from releasing the iron. Tf takes the released iron to TfR on the cell surface, the ion is then used by the cells. Other specific proteins are involved in iron intake, including zinc transporter (ZIP)14, ZIP8, transient receptor potential cation channel 6 (TRPC6), L-type calcium channels (LTCCs) and T-type calcium channels (TTCCs; Fig. 1).

Dcytb. As a member of the cytochrome b561 family, Dcytb serves a vital role in the ascorbate-dependent reduction of inorganic iron in duodenal enterocytes. Besides Dcytb, there are additional members of the cytochrome b561 family,

including stromal cell-derived receptor 2, cytochrome b ascorbate-dependent protein 3 and cytochrome b561 domain-containing protein 2 (33,34). Dcytb reduces extracellular ferric iron to ferrous ion (24,35). The expression of Dcytb may be modulated by the iron regulatory protein 1-hypoxia-inducible factor 2 α axis (24,36).

DMT1. DMT1 is well known for its involvement in ferric iron influx into the duodenum cytoplasm. In erythroid precursors, hepatocytes and macrophages, DMT1 is the principal contributor in iron transport, transporting iron out of the endosome and into the cytosol (37). DMT1 is also expressed in other tissues, including the kidneys, liver, brain and heart (25). When animals exhibit iron deficiency, the expression of DMT1 is increased in the duodenum to elevate iron absorption (38). This process is regulated by an iron responsive element (IRE) at the 3'-untranslated region of DMT1 (37,39).

Ferritin. Ferritin forms a hollow shell that may bind $\leq 4,500$ atoms of iron. Ferritin consists of 24 subunits, and has a combination of a heavy (H) chain and light (L) chain ferritin types (40). H-type ferritin ferroxidase quickly oxidizes iron to Fe^{3+} following Fe^{2+} incorporation into ferritin, whereas, L-type ferritin may be responsible for the electron transfer across the globular protein cage (41). Since free iron is toxic inside the cells, ferritin stores excess iron and is ligated in labile cellular iron to protect cells from iron toxicity. Ferritin stores are subsequently exported as ferrous ions to the plasma via FPN, or utilized when cells are subjected to iron deficiency. Ferritin is not only detected intracellularly, it is also located extracellularly in the serum, cerebrospinal fluid and synovial fluid. Serum ferritin is associated with inflammation and body iron load in patient populations (42). The expression of ferritin may be modulated by the iron regulatory protein 1 (IRP)-IRE system at the post-transcriptional level.

FPN. FPN, encoded by SLC40A1 (additionally termed SLC11A3, MTP1 or IREG1), is the only known cellular iron exporter in mammals and is highly expressed in spleen macrophages, the liver, and the basolateral membranes of enterocytes and erythroid precursors (43,44). Macrophages, liver cells and enterocytes export Fe^{2+} to the blood via FPN. Subsequently, hephaestin or ceruloplasmin oxidizes Fe^{2+} to Fe^{3+} in order to bind Tf. FPN may be inhibited by Hep binding to cell surface-localized FPN (Fig. 1A), which leads to FPN internalization and degradation, and consequently to the loss of iron export capacity (45).

Tf and TfR. Tf is the primary extracellular iron transport protein in blood. Tf possesses a single chain bilobal protein. Each lobe has a high affinity for Fe^{3+} (45). The combination of Tf- Fe^{3+} is reversible, thus making it a convenient method to deliver iron to cells. Tf has two conformations: Apo Tf (the iron-free form of Tf) and holo Tf (the iron-saturated form), of which the latter buries iron deeply within each lobe (46). Tf is secreted by the liver and under normal circumstances 20-30% of Tf is bound to iron. If circulating iron levels exceed the binding capacity of Tf, toxic non-Tf-bound iron may accumulate, leading to various diseases (47). TfR mediates cellular iron uptake by binding and internalizing Tf. TfR expression is tightly regulated by iron levels in the cLIP inside cells.

Table I. The characteristics of protein associated with iron.

Protein	Human chromosome	Location	The content of iron in cytoplasm	Refs.
Dcytb	2	Duodenal enterocytes	$\text{Fe}^{2+} \rightarrow \text{Fe}^{3+}$	(24)
DMT1	12	Enterocytes surface and endosome	$\text{Fe}^{3+} \uparrow$	(25)
Ferritin	H chain 11 L chain 19	Cytoplasm	Store iron	(26)
Ferroportin	2	Cell membrane	$\text{Fe}^{3+} \downarrow$	(27)
Hepcidin	19	Plasma great secretion majority by liver	$\text{Fe}^{3+} \uparrow$	(28)
ZIP14	8	Basolateral membrane	$\text{Fe}^{2+} \uparrow$	(29)
ZIP8	4	Apical membrane	$\text{Fe}^{2+} \uparrow$	(30)
TRPC6	11	Cell membrane	Fe^{2+} and $\text{Fe}^{3+} \uparrow$	(31)
LTCCs and TTCCs	1, 3, 12, X and 16, 17, 22	Cell membrane	$\text{Fe}^{2+} \uparrow$	(32)

H, heavy; L, light; Dcytb, duodenal cytochrome b; DMT1, divalent metal transporter 1; ZIP, zinc transporter; TRPC6, transient receptor potential cation channel 6; LTCCs, L-type calcium channels; TTCCs, T-type calcium channels.

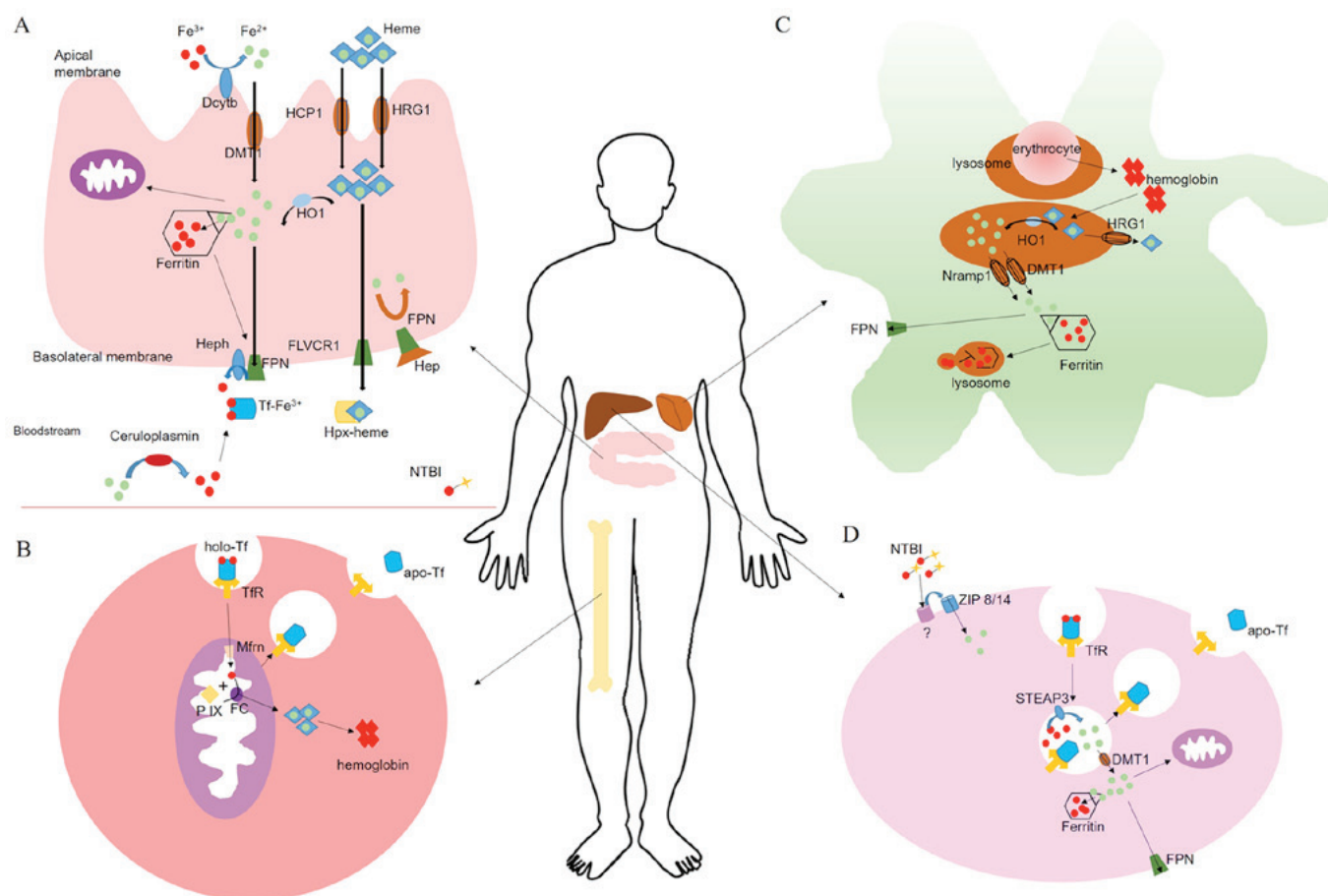


Figure 1. Overview of iron homeostasis in the human body. Iron homeostasis in a (A) duodenal enterocyte, (B) erythrocyte, (C) macrophage and (D) liver tissue cell.

Hep. *Hep* (also termed liver-expressed antimicrobial peptide 1) is a peptide comprising 25 amino acids encoded by *HAMP*, and is predominantly expressed in the liver, and to a lower extent, in the heart. Additionally, *Hep* may be secreted by macrophages, lymphocytes, adipocytes, pancreatic β -cells, neutrophils and renal cells (48). *Hep* regulates cellular iron

export and regulates the iron concentration of plasma by binding to FPN, thus triggering the internalization and degradation of FPN (49). The storage of systemic iron is closely associated with the synthesis of *Hep*. When plasma iron is deficient, *Hep* transcription is decreased in the liver. As the plasma iron concentration increases, the *Hep* expression

level increases. However, a high concentration of Hep in the blood negatively regulates iron absorption, and consequently, the release of iron into the plasma is decreased (50).

3. Iron distribution and excretion

Iron is transported in a cycle of Tf-bound and non-Tf-bound iron (NTBI) forms. In steady state conditions, iron is loaded onto Tf. Iron distribution is achieved using primary pathways: Iron utilization in erythropoiesis, erythrocyte recycling by macrophages and iron uptake into tissue (Fig. 1B-D). In total, ~24 mg of iron is utilized at erythropoiesis (the process that generates erythrocytes) per day. Macrophages phagocytose aged erythrocytes to recycle iron (51). For humans, there is no biological mechanism for the excretion of iron. Healthy adults lose ~5% of plasma iron through gastro-intestinal tract lining desquamation, skin or blood loss (37,52).

Iron and erythropoiesis. Erythropoiesis is characterized by three progressive stages from progenitor cells to precursor cells and, ultimately, to mature RBCs in bone marrow (53). Erythroid progenitors (burst forming unit-erythroids and colony forming unit-erythroids) have the capacity to differentiate to proerythroblasts, basophilic erythroblasts, polychromatophilic erythroblasts, orthochromatic erythroblasts, reticulocytes and mature erythrocytes (53). Maturation and proliferation of early erythroid progenitor cells depends on erythropoietin, which is a cytokine produced by the kidneys (54).

The body produces ~200 billion erythrocytes every day. Erythropoiesis is the largest consumer of iron in the body (>80% of plasma iron). Macrophages phagocytose senescent erythrocytes and release hemoglobin-derived iron into the blood. Hemoglobin-derived iron is the primary source of RBC regeneration. Erythrocytes contain hemoglobin, which are functionally responsible for transporting oxygen. Iron is the active site of hemoglobin binding oxygen. When heme synthesis and Fe-S cluster biogenesis occur, the iron demand increases. To meet this demand, transferred iron is delivered to the mitochondrial matrix by mitoferrin and the insertion of Fe²⁺ into protoporphyrin IX is catalyzed to make heme by ferrochelatase, which is exported to the cytoplasm (Fig. 1B) (55).

Macrophage and erythrocytes. Iron homeostasis is regulated by circulating erythrocytes. Macrophages remove senescent erythrocytes through erythrophagocytosis (56). The majority of aged or damaged erythrocytes are removed to release iron for the production of novel RBCs. Red pulp splenic macrophages and the Kupffer cells (specialized macrophages) in liver sinusoids are primarily responsible for erythrophagocytosis. When the tissue microenvironment is triggered by iron instability, monocyte-derived macrophages are recruited to the liver, forming a liver-specific phenomenon (57).

Heme degradation is catalyzed by HO-1 in macrophage lysosomes. Prior to degradation, a part of heme is exported from the lysosome to the cytosol by HRG1. Fe²⁺ is exported from the lysosome to the cytoplasm by DMT1 and natural resistance-associated macrophage protein 1 (58). Subsequently, the iron is released into blood or accumulated by ferritin (Fig. 1C) (59).

Iron uptake into tissue. Iron is transported in the Tf cycle normally; however, iron additionally exists in the state of NTBI in iron loading conditions. TfR is expressed ubiquitously on the surface of the majority of cells and combines with holo Tf to form a complex, which is swallowed by the cells as an endosome. When the complex enters a cell, ferric ions are dissociated from Tf by acidification. At that time, apo-Tf remains bound to TfR; apo-Tf is released once the complex is transferred to the cell surface (60,61). The ferrireductase protein, six-transmembrane epithelial antigen of prostate 3 (STEAP3), subsequently reduces Fe³⁺ to Fe²⁺ within the endosome. Fe²⁺ enters the cytoplasm of cells via DMT1.

The uptake of NTBI may be associated with ZIP8 and ZIP14 (Table I), which belong to the ZIP family of metal-ion transporters (62,63). TRPC6, LTCCs and TTCCs (Table I) additionally serve a role in NTBI uptake. The ability of TRPC6 was first postulated in previous a study using PC12 cells (31). LTCCs and TTCCs are pore-forming voltage-gated calcium channels, and are associated with NTBI transport (64). Under NTBI circumstances, iron appears in plasma bound to acetate, citrate, albumin or other organic anions of intermediary metabolism (65). NTBI accumulation is a principal cause of iron toxicity in organs leading to oxidative stress and cellular damage (66). NTBI clearance is primarily performed by hepatocytes, which makes hepatocytes the first target of iron toxicity. However, other organs, including the hypophysis, pancreas or heart, are additionally influenced by NTBI uptake and accumulation (Fig. 1D) (51).

Redundant plasma iron, which is bound by ferritins, is stored in hepatocytes (54). High expression levels of FPN have been detected on cell surfaces (in particular, the highest expression was detected in cells of the periportal areas) that export large quantities of iron into the bloodstream (67). Spleen macrophages phagocytose erythrocytes to release iron from hemoglobin. In the pancreas, ferritin is segregated in lysosomes of acinar cells, and iron deposits are discrete and only in B cells (68). Iron is principally bound to Tf, whereas, a very small amount binds to other filterable iron-binding proteins, including neutrophil gelatinase-associated lipocalin, myoglobin, albumin, lactoferrin, hemoglobin and Hep (69). However, the mechanism of filtering iron by human kidney requires further investigation. In the distal and proximal tubules, iron is reabsorbed almost entirely. Resorbed iron may be utilized by mitochondrial proteins of the renal tubular epithelium or exported into blood or the interstitium via the basolateral membrane of tubular epithelial cells (70). Cardiomyocytes express relatively increased FPN and Hep; however, do not serve a role in systemic iron regulation (71).

4. Iron and various cancers

In 1959, an animal study first demonstrated that repeated intramuscular injections of iron dextran were able to induce malignant tumors (72). Over time, accumulating research demonstrated that the injection of iron preparations caused serious side effects, such as sarcomas, and exacerbated diseases (73,74). Supersaturation ferric ion or iron exposure may increase cancer risk (75). Iron-status biomarkers are Tf saturation, the total iron binding capacity of Tf and the serum iron concentration, which are regulated by dietary iron intake,

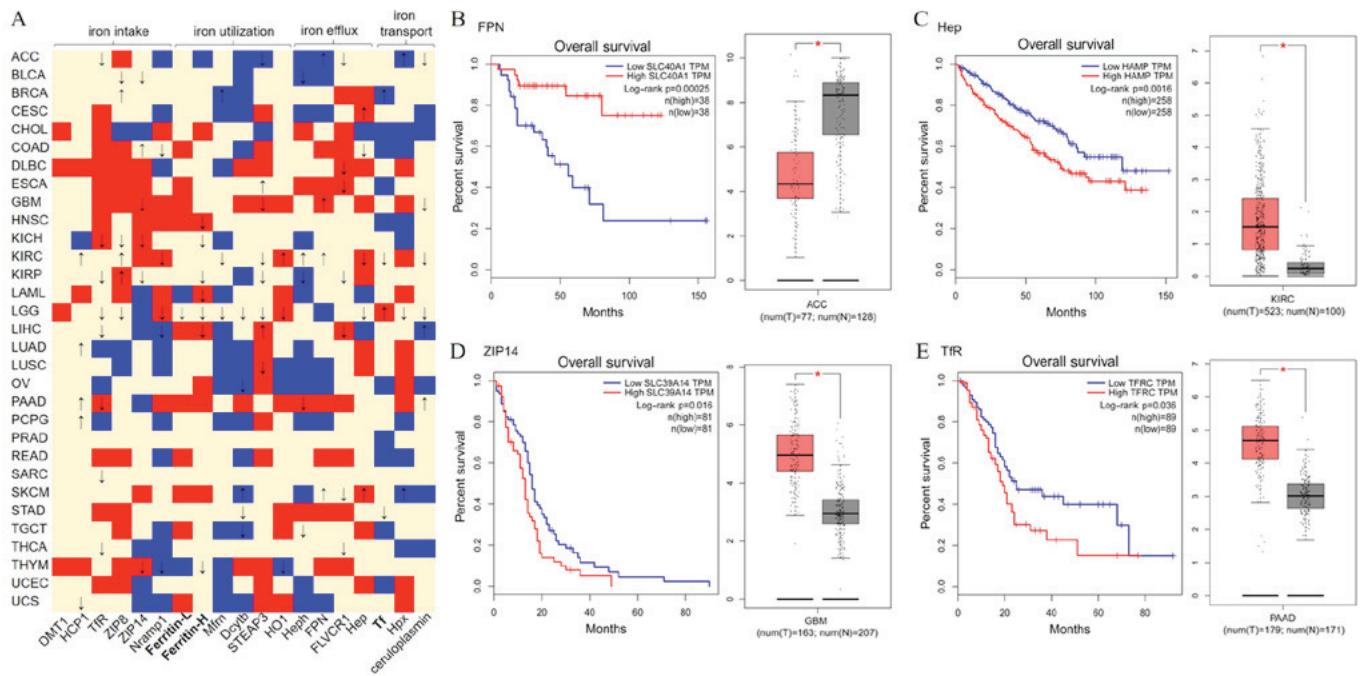


Figure 2. Iron metabolism-associated regulators in cancers. (A) Significantly upregulated (red) and downregulated (blue) expression of iron metabolism genes in 31 tumor samples with potential effects on either improving (↑) or shortening (↓) the OS of patients with cancer compared with controls. The comprehensive OS (left) and altered gene expression (right) of iron regulators for (B) FPN, (C) Hep, (D) ZIP14, (E) TfR. OS data was analyzed using Log-rank test (also known as the Mantel-Cox test). Altered gene expression data were compared with controls using one-way analysis of variance (\log_2 fold change Cutoff: 1; P-value Cutoff: 0.01). ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangio carcinoma; COAD, colon adenocarcinoma; DLBC, lymphoid neoplasm diffuse large B-cell lymphoma; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LAML, acute myeloid leukemia; LGG, brain lower grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; TGCT, testicular germ cell tumors; THCA, thyroid carcinoma; THYM, thymoma; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma; OS, overall survival. FPN, ferroportin; Hep, hepcidin; ZIP14, zinc transporter 14; TfR, transferrin receptor.

gene status and iron overload disease (76). Accumulating evidence suggests that iron excess is closely associated with tumorigenesis in multiple types of human cancer.

Iron metabolism-associated proteins and cancer. To evaluate the contribution of iron metabolism to tumorigenesis, the expression of iron metabolism-associated genes and clinical datasets were retrieved from The Cancer Genome Atlas projects and mined using GEPIA online tools (version 2017; <http://gepia.cancer-pku.cn>), which processed high-throughput transcriptomic data using standard pipeline (77). As presented in Fig. 2A, for the 31 cancer types, 19 genes involved in iron intake, utilization, efflux or transport were identified, demonstrating either upregulated or downregulated expression in tumor samples compared with normal control samples. To test the hypothesis, the overall survival (OS) data from these patients were analyzed using Log-rank test (also known as the Mantel-Cox test). Altered gene expression data of these patients were compared with controls using one-way analysis of variance (\log_2 fold change Cutoff: 1; P-value Cutoff: 0.01). Considering the patients' OS percentage, it was also observed that specific cancer types exhibit frequent poor or good survival rates, particularly for kidney chromophobe (KICH), kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP), brain lower grade glioma (LGG) and liver

hepatocellular carcinoma (LIHC). The majority of proteins expressed at high levels expression predicted a poor OS for these patients. However, high HCP1, ZIP8, HO-1, Heph and FPN expression demonstrated a good OS in patients with KIRC. Additionally, high Zip8 expression, high Tf expression, and high STEAP3 and ceruloplasmin expression demonstrated a good OS in patients with KIRP, LGG and LIHC, respectively. The survival rates associated with these cancers may be partially due to interrupted iron metabolism in liver and kidney tissues. As presented in Fig. 2B-E, in patients with adrenocortical carcinoma, low FPN expression demonstrated a lower survival rate (Fig. 2B), whereas, high Hep expression predicted a poor OS in patients with KIRC (Fig. 2C). In addition, the high expression of ZIP14 in patients with glioblastoma multiforme or TfR expression in patients with pancreatic adenocarcinoma predicted a poor OS (Fig. 2D and E). Notably, FPN had been demonstrated to transport iron between the inside and outside of the cell, whereas, Hep stops the transit (49). ZIP14 and TfR transfer iron from outside to inside of the cell, which increases the intracellular iron concentration. Supporting the hypothesis that iron-excess contributes to tumorigenesis (29,60).

Colorectal cancer. Colorectal cancer is the third most common cancer in men and second in women worldwide (78). With the exception of hereditary factors, lifestyle factors, including

physical activity, obesity, smoking and alcohol consumption are closely associated with colorectal cancer (79). The correlation between excess iron and colorectal cancer risk has been examined in numerous previous studies (80-82), and iron overload associated with the H63D mutation and C282Y in *HFE* may increase the risk for developing colorectal cancer (83-85).

Preoperative anemia is a common phenomenon in patients with colorectal cancer and iron supplementation is the most common therapy (86). However, an analysis of previous studies investigating ingested iron as treatment of anemia identified it as potentially detrimental and hazardous for human colorectal cancer risk (87-89). Recent studies demonstrated that compared with oral iron, intravenous iron therapy is more effective in anemic patients with colorectal cancer with higher Tf and lower ferritin levels (90,91).

Liver cancer. Liver cancer is one of the most common malignancies in numerous countries worldwide and hepatocellular carcinoma is the most frequent type of global cancer mortality rates (92). A number of factors, including hepatitis B virus, hepatitis C virus, alcohol, tobacco, aflatoxin and chronic inflammation are associated with hepatic carcinogenesis (93). Iron overload is a significant risk for hepatocellular carcinoma as the liver is the main organ for iron storage.

Excessive iron accumulation may cause hepatocellular injury. Oversaturated ferritin subunits result in ionic iron releasing into hepatocyte cytoplasm when iron is overloaded (74). If iron stores are excessively overloaded in the liver, the lobules may develop fibrosis. Hereditary haemochromatosis (HH), an inherited iron metabolism disorder, and excess dietary iron are associated with hepatic iron overload. HH induces hepatic fibrosis and cirrhosis when treatment is not timely and appropriate (94). Patients with HH possess C282Y mutations on *HFE* (95). C282Y homozygosity has been correlated with an increased risk of hepatocellular cancer in men (85).

Breast cancer. Breast cancer is the most commonly diagnosed cancer in women, and the number of cases of breast cancer is still increasing (96). It was identified that the development of breast cancer is associated with protein tyrosine phosphorylation (97). Tyrosine phosphorylation is regulated by a careful balance of activity of tyrosine kinases and tyrosine phosphatases, which may activate or inactivate oncogenic pathways in human breast cancer cells (98). Iron chelator aurointricarboxylic acid may inhibit tyrosine phosphatases (99).

A number of genes serve important roles in breast cancer progression through increased iron content in cells. Histone-lysine N-methyltransferase EHMT2 regulates breast cancer growth by modulating iron homeostasis through the repression of ferrooxidase hephaestin (100). Dcytb is an important predictor of outcome and is associated with the response to therapy in patients with breast cancer (101).

A mammogram is a test performed to check whether women have breast cancer using x-rays, which subjects the body to radiation. At present, with advances in technology, iron imaging may identify macrophage hemosiderin deposits in metastatic breast cancer (8). Recently, superparamagnetic iron oxide based nanoprobe as multifunctional theranostic agents were applied to breast cancer imaging and therapy (102).

Lung cancer. Lung cancer is the most common leading cause of mortality in cancer during the past several decades (103). There are two types of lung cancer: Non-small cell lung cancer (NSCLC) and small cell lung cancer. Accumulating evidence suggests that iron overload is associated with lung cancer (104). WNT, MYC and hypoxia-inducible factor signaling pathways may be activated by iron (105,106). Subtoxic concentrations of iron induce cellular hydroxyl radicals, affecting cancer stem cell-like subpopulations of human NSCLC cells, which is important for aggressive cancer behaviors and metastasis via transcription factor SOX9 upregulation (107).

Air pollution, particularly particulate matter (PM), increases the risk of respiratory morbidity and mortality, and even lung cancer (108). In PM, iron components have anti-apoptotic effects, which activate nuclear factor erythroid 2-related factor 2-dependent antioxidant processes (109). This previous study provided insight for the development of lung cancer caused by PM pollution; it was hypothesized that a nearby iron foundry may influence the physical condition of local residents. Another study demonstrated that men (aged <75 years), but not women, residing within 800 m of the iron foundry coke oven had a high lung cancer risk (110).

Other cancers. In multiple myeloma, iron metabolism remains unclear. Serum ferritin may serve as a negative prognostic indicator (111,112). Decreased FPN leads to an intracellular iron overload and promotes myeloma cell growth (113). In gastric cancer, iron chelators induce gastric cancer cell apoptosis, involving endoplasmic reticulum stress formed by reactive oxygen species (ROS) and c-Jun N-terminal kinase activation (114).

5. Mechanisms of iron-mediated proliferation of tumor cells

Cancer cells have a strong ability to proliferate and metastasize, requiring higher levels of environmental nutrients compared with their healthy counterparts (115). As proliferation is closely associated with the vast biosynthesis of nucleic acids and proteins, the acquisition of energy is particularly vital. Mitochondria are essential organelles for cells, which generate energy and contain diverse enzymes involved in the synthesis (116). Iron is a crucial element of these enzymes and has an important function in the synthesis of these enzymes (117) (Fig. 3).

Mitochondria are one of the principal ancient endomembrane systems and have a circular genome of ~16 kb. The numbers of mitochondria are associated with the vitality of cell types in different tissues (118). Recently, the association between mitochondria and iron was identified. Apart from classic pathways, including β -oxidation of fatty acids and the tricarboxylic acid cycle, mitochondria are the principal organelles for the metabolism of iron (119). There are three metabolic pathways of mitochondrial iron: Iron-sulfur cluster biogenesis, heme synthesis and iron storage (120). Macrophages store large amounts of iron and serve an important role in tumor progression.

Iron-sulfur cluster. Iron-sulfur cluster biogenesis and mitochondrial iron transport are complex, and includes 16 genes, including *SFXN1* and *SFXN5* (121). There are

numerous biological processes that require Fe-S proteins, including the mitochondrial respiratory chain, DNA replication and repair, and RNA modification (122). As a source of energy, the mitochondrial respiratory chain depends on specific Fe-S cluster-containing enzymes, including NADH-ubiquinone oxidoreductase [additionally termed Complex I (CI)], Rieske iron-sulfur protein (RISP) and subunits of succinate dehydrogenase (SDH, additionally termed succinate-coenzyme Q reductase or respiratory Complex II) (123). A high concentration of iron and these enzymes promote cellular growth significantly in tumors.

CI is one of largest membrane-bound enzymes in the cell and is the largest complex of the mitochondrial respiratory chain. The primary function of CI is ATP production, which drives protons across the inner membrane by reducing the potential of NADH. In total, CI is responsible for ~40% of ATP synthesis. There are three subcomplexes of CI: An iron sulfur protein fraction, a flavoprotein fraction and a hydrophobic fraction. The electron transfer centers of CI are associated with redox reactions, which includes eight iron-sulfur clusters, a flavin mononucleotide and ubiquinone (124). CI is indispensable in healthy cells. However, in cancer cells, CI serves an important role in proliferation (125). Small molecular inhibitors serving through CI have been identified as anticancer agents. For example, rotenoids, polyphenols AG311, metformin, BAY 87-2243, fenofibrate, canagliflozin and kalkitoxin offer potential anticancer treatment (126,127).

RISP is an essential subunit of mitochondrial complex III. The progression of the electron transfer reaction requires RISP to dock to the quinol oxidation site; the electron transfer reaction serves a crucial role in the synthesis of ATP (128). A previous study demonstrated that knocking down RISP of mitochondrial complex III in human cancer cells decreased their invasive potential (129). Atovaquone, as a oxidative phosphorylation inhibitor, has been observed to target mitochondrial complex III to eliminate cancer stem cells (130).

SDH is composed of four subunits: A flavoprotein (SDHA), an iron-sulfur protein (SDHB), a cytochrome b560 subunit (SDHC) and cytochrome b small subunit (SDHD). There are three iron-sulfur clusters of SDHB: [2Fe-2S], [4Fe-4S] and [3Fe-4S]. SDH is a key respiratory enzyme complex in the citric acid cycle that converts succinate to fumarate and is also involved in the mitochondrial electron transport chain (131). SDH transfers electrons from the [Fe-S] clusters to ubiquinone (132). SDH has been proposed as a target for cancer therapy. As an inhibitor of SDH, lonidamine provides novel approaches for the treatment of cancer (133). Vitamin E analogues, 3-Bromopyruvate, Malonate, 3-nitropropionic acid, Thenoyltrifluoroacetone and Troglitazone were identified as anticancer agents targeting SDH (134).

Macrophages, iron and tumor cells. The traditional role of macrophages for tumor clearance has been challenged, as it was demonstrated that macrophages have pro-tumor properties. Over the course of cancer progression, tumor cells secrete various mediators to construct their own niche in order to adapt to the surrounding environment (135). It was even observed that tumor-infiltrating macrophages helped tumor cells. Tumor-associated macrophages are principal suppliers of cytokines, proteases and growth factors, such as cysteine

cathepsin proteases, which enhance tumor progression and the therapeutic resistance of different cancer types (136,137). For example, in hepatocellular carcinoma and gastric cancer, tumor-associated macrophages promote tumor growth and invasiveness via C-C motif chemokine 22-induced epithelial-mesenchymal transition and the activated nuclear factor- κ B signaling pathway (138,139). Furthermore, growing cancer cells demand plenty of iron. Therefore, how tumor cells obtain iron from their microenvironment requires further study.

For the tumor itself, iron may be increased by upregulated expression of iron import and storage proteins, including TfR and ferritin, and downregulated expression of iron export proteins, including FPN (140). In the tumor microenvironment, macrophages secrete lipocalin2 (LCN2), which increases tumor intracellular iron concentration (141,142). LCN2 is a member of the lipocalin superfamily and functions as a carrier protein whose structural feature is a β -barrel (143). LCN2 is able to bind to iron-loaded siderophores. As a result, tumor-infiltrating macrophages release unlimited iron for tumor cells. A previous study observed that iron in super paramagnetic iron-oxide nanoparticles may target tumor-associated macrophages, which may be used for cancer therapy (144).

6. Ferroptosis: Iron-dependent cancer cell death

Ferroptosis, as a novel form of iron-dependent programmed cell death characterized by the accumulation of lipid peroxides, is genetically and biochemically different from pyroptosis, apoptosis and necroptosis (145). Ferroptosis may be triggered by erastin, sorafenib and sulfasalazine (5,146). The accumulation of iron, through the Fenton reaction, generates lipid peroxides and ROS, leading to the occurrence of erastin-induced ferroptosis (147). A number of cancer types exhibit sensitivity to ferroptosis inducers, including large B-cell lymphoma, cervical carcinoma, renal cell carcinoma, osteosarcoma, prostate adenocarcinoma, liver cancer, ovarian carcinoma, pancreatic carcinoma and carcinoma of the lungs (148-151). Notably, ferroptosis inhibitors, such as Liproxstatin-1, may reduce ischemia/reperfusion-induced hepatic damage in Gpx4^{-/-} mice (152). Other molecular mechanisms of ferroptosis have been identified (153,154).

Erastin inhibits the cystine/glutamate antiporter (system x_c⁻), which imports cystine from the extracellular matrix (155,156). Cysteine is transported into the cell by system x_c⁻ for the synthesis of glutathione (GSH). Catalyzed by glutathione peroxidase 4 (GPX4), GSH is oxidized to glutathione disulfide, and GPX4 inhibits lipid hydroperoxides (lipid ROS) (157,158). Specific lipid ROS are generated from iron involved in the Fenton reaction. In the absence of GPX4, large amounts of lipid ROS accumulate in cells, which leads to ferroptosis (159-161) (Fig. 4).

Intracellular iron may regulate the sensitivity of cells to ferroptosis. Enhanced intracellular iron promotes erastin-induced ferroptosis; conversely, reduced intracellular iron diminishes ROS, thus suppressing ferroptosis (146). Although ROS induction and iron deprivation therapy may be examined as a possible therapeutic intervention in a variety of cancer types (13,14), the optimal therapeutic strategies have yet to be identified. Therefore, novel therapies, termed ferroptosis therapy, have emerged. Fenton-reaction-acceleratable magnetic

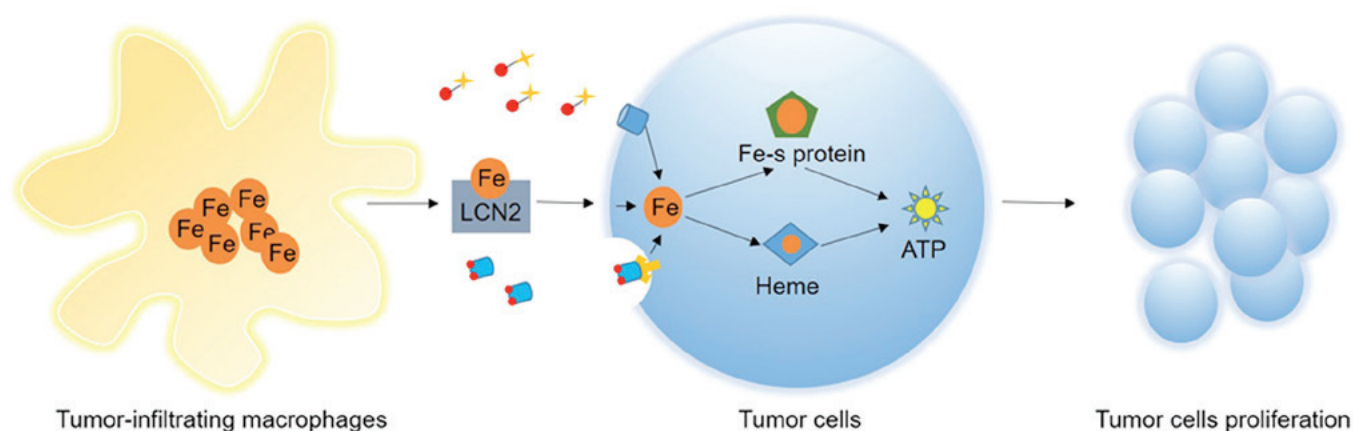


Figure 3. Iron-mediated proliferation mechanisms in tumor cells. LCN2, lipocalin2.

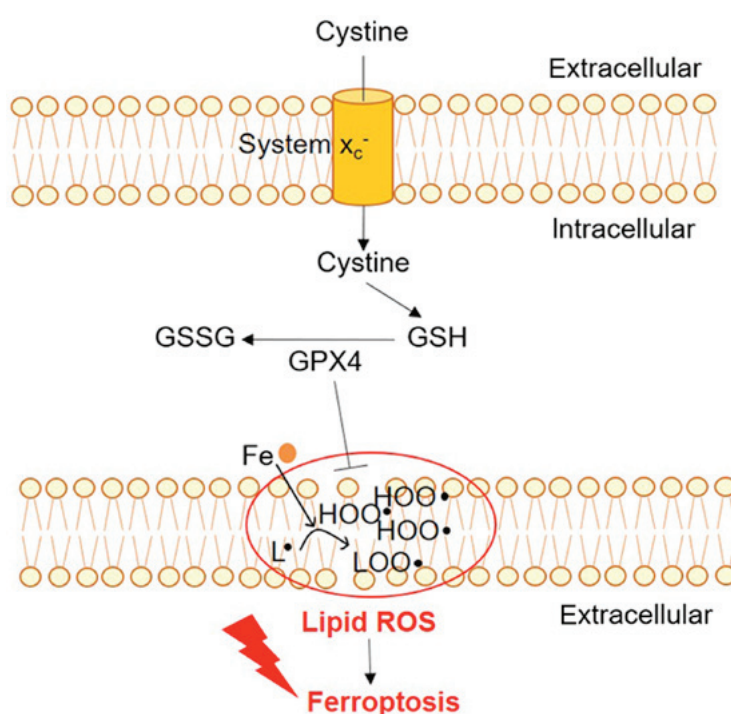


Figure 4. Ferroptosis mechanism. GSH, glutathione; ROS, reactive oxygen species; GPX4, glutathione peroxidase 4; system x_c^- , cystine/glutamate antiporter; GSSG, glutathione disulfide.

nanoparticles (FeGd-HN@Pt@LF/RGD2) significantly inhibit tumor growth by delivering Fenton reaction reactants to the tumor site (162). Furthermore, two studies examined tumor suppression mediated by a direct interaction between heme and p53 in iron deprivation (163,164). p53 downregulating metabolic stress-induced ferroptosis in tumors (164) demonstrated that this well-known tumor-suppressor gene is associated with iron metabolism, in addition to cancer cell proliferation and death. In summary, there is great potential for the development of ferroptosis-based effective treatments for iron metabolism-associated diseases and cancer.

7. Conclusions

Iron is essential for numerous vital metabolic processes in mammalian systems. The present review focused on the

importance of iron regulation, and the association between iron homeostasis and carcinogenic mechanisms, summarizing the progression of research on tumors. Altering iron homeostasis in various cancers may influence patient outcome. Ferroptosis, a unique form of regulated cell death, may serve as a tumor-suppressor for cancer therapy. Taken together, future studies are required to develop novel methods to disturb iron-induced activation, and the resulting signal transduction cascades leading to carcinogenesis and progression.

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Authors' contributions

YY, CG and ZF were involved in the conception of the review. CG and YC were involved in the writing of the article. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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