·Review·

Advancement of the study on iron metabolism and regulation in tumor cells

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[**Abstract**] As an essential metal for sustaining life, iron is involved in a number of metabolic processes, including DNA synthesis, electron transport, oxygen delivery, and so on. Iron metabolism involves the absorption, transport, and use of iron and is strictly regulated. Numerous studies have found a positive correlation between iron storage and the risk of tumors, such as colorectal carcinoma, hepatic cancer, renal carcinoma, lung cancer, and gastric cancer. In tumor cells, iron metabolism changes by several mechanisms, such as regulating the growth of tumor cells by transferrin, accelerating the uptake of iron by the overexpressions of transferrin receptors 1 and 2 (TfR1 and TfR2), synthesizing or secreting ferritin by some malignant tumor cells, and upregulating the level of hepcidin in patients with cancer. Some advances on diagnosis and treatment based on iron metabolism have been achieved, such as increasing the transfection and target efficiency of transferrin-polyethylenimine (PEI), inducing cell apoptosis by β-guttiferin through interacting with TfR1.

Key words: Iron metabolism, tumor, ferritin, transferrin receptor, transferrin, hepcidin

As an essential element for human life and the richest transient metal, iron is widely involved in many important metabolic processes, such as DNA synthesis, electron transport, and oxygen delivery. Additionally, about half of the enzymes and coenzymes participating in the tricarboxylic acid cycle involve or require iron. Similar to other essential metals, iron metabolism includes absorption, transport, and utilization. The human body possesses a strict regulation mechanism of iron metabolism, and needs a dynamic balance of iron between intestinal absorption and the bodily requirement. The intestinal absorption of iron increases if there is a lack (or requirement) of iron, while it decreases if there is an redundance of iron. Recently, it has been considered that high iron content is a risk factor of tumorigenesis. Through studying different races, researchers found that the storage of iron was related to the risk of certain cancers, such as rectal cancer, hepatic cancer, renal carcinoma, lung cancer, and gastric cancer[1].

Normal iron metabolism

In humans, iron is only absorbed in the small intestine, stored in the liver and the reticuloendothelial (RE) system, and is mainly use in bone marrow. Intestinal absorption of iron depends on 4 types of proteins of iron metabolism: duodenal cytochrome b (Deytb), divalent metal transporter 1 (DMT1), ferroportin 1 (FP1) and hephaestin (Hp). Deytb and DMT1 are located on the lateral membrane of intestinal epithelial cells, while FP1 and Hp are located on other lateral membranes. Deytb first reduces free ferric to ferrous iron, and then ferrous iron moves to the epithelial cells mediated by DMT1. With pH > 7 and the synergism of amino acids and carbonates, intestinal iron binds with transferrin (Tf), and moves to the liver through a portal system, where most are recognized by two kinds of transferrin receptors (TfR), TfR1 and TfR2 on the surface of hepatocytes to mediate the uptake of transferrin-bound iron. Part of this iron reaches the bone marrow through the bloodstream. Bone marrow is the site for erythrocyte formation and heme synthesis, and is also the main site for iron utilization. Reticulocyte phagocytizes transferrin-bound iron to synthesize heme through TfR on the membrane. Ferritin (Fn) and hemosiderin are the main form of iron storage in the mononuclear macrophage of the bone marrow, liver, and spleen. Under iron homeostasis, little iron enters and leaves the storage pool each day. Large amounts of iron are excreted through

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gastrointestinal epithelial cells and bile, while a small amount of iron is released through the urogenital tract, the skin, sweat, and exfoliated cells. Aging erythrocytes are phagocytosed by macrophages and the released heme iron can be reused. Further studies are needed to explore the mechanism of heme iron absorption by the intestinal epithelial cells.

Iron metabolism and regulation in tumor cells

Transferrin (Tf)

Tf is the carrier protein of plasma iron, a β2 globulin synthesized by the liver, composed of a single peptide, and transfers the iron absorbed by the intestinal mucosa to the bone marrow for hemaglobin formation in normoblasts[2]. Tf binds with two Fe^{3+} in the peripheral blood and combines with TfR on the surface of the cells, and then transfers iron into the cells. This process has been confirmed both in normal cells and in tumor cells. Due to the many intracellular enzymes, such as ribonucleotide reductase for DNA synthesis, that require iron as a cofactor, energy pathways for life-sustaining as well as electron transport need iron. Thus, Tf is essential for the growth and survival of cells.

Tf is a growth factor of all proliferated and cultured cells. A large number of studies indicate that free serum Tf can replace the growth factor[3]. In some tumor tissue, Tf is also synthesized for its own specific proliferation and differentiation. A factor secreted by breast cancer cell (BCC) line MCF-7 is similar to Tf in immunology, and serves as an autocrine factor to accelerate the proliferation of BCCs and the growth of tumor cells in less vascularly distributed regions through selective advantage. Park *et al.*[3] found that both exogenous and endogenous Tf regulated the growth of MCF-7 cells. Interleukin-18 (IL-18) is the inducer of endogenous Tf expression in BCCs, and MAPK pathway is correlated to Tf induced by IL-18.

According to the study on Tf, Farias-Eisner *et al.*[4] considered that using apolipoprotein-1 (ApoA-1), prealbumin (TTR), and Tf as diagnostic markers enhanced the diagnostic rate of ovarian cancer. Regarding treatment, Liu *et al.*[5] introduced exogenous genes to target cells by Tf- polyethylenimine (PEI) binding with TfR to significantly enhance the transfection and targeting efficiency and increase the efficacy of cancer gene therapy.

Transferrin receptor 1 (TfR1)

Iron metabolism alters greatly in tumor cells, and the upregulation of TfR1 on the cell surface is the most well known alteration. TfR1 is a glycoprotein expressed in all nucleated cell membranes, and plays an important role in iron absorption. Tumor cells with higher expressions of TfR1 compared to normal cells, show a faster rate of iron absorption and its high frequency of proliferation is related to the high expression of TfR1[6]. In vitro experiments showed that anti-TfR1 monoclonal antibodies blocked the growth of tumor cells in the blood system[7].

As shown by Hänninen *et al.*[8], mRNA expression of TfR1 was high in the medulla oblongata and the hippocampus, and low in the cortex, thalamus, and cerebellum. No differences were shown in TfR1 mRNA expression between normal and tumor tissues. However, TfR1 expression in astrocytoma cell lines was higher than in brain tumor cells. In the malignant transformation process of Barrett's esophagus to adenocarcinoma, cellular iron import proteins (TfR1, DMT1, and Deytb) and iron storage protein H-Fn are overexpressed[9].

In human B lymphocytes, TfR1 is a critical downstream target of oncogene c-myc[10]. TfR1 expression is related to c-myc expression in mouse lymphoma models. All these results suggest that TfR plays an important role in c-myc-regulated target gene networks. C-myc activates TfR1 to induce cell proliferation and tumorigenesis. TfR1 is overexpressed in all 5 cases of diffuse large B cell lymphoma, while poorly expressed in both 5 cases of small lymphocytic lymphoma and 5 cases of follicular lymphoma. All 5 cases of mantle cell lymphoma express TfR, however, the number of TfR positive cells and the intensity of TfR labeling are variable[11].

The efficacy of p53 gene therapy mediated by the transferrin receptor single-chain antibody fragment (TfRscFv) immune complex was detected in human breast cancer metastasis nude mice models, and the results showed that the TfRscFv-targeted cationic immune complex enhanced the binding ability, increased the release and transfection efficiency of target genes, and extended the survival time of nude mice[12].

β-guttiferin induces cell apoptosis indirectly through TfR1[13]. As a commonly used anticancer drug, anthracycline interacts with cellular iron pools and plays important roles in producing cardiac toxicity and inducing cell apoptosis[13]. Thus, it is very important to explore the interference mechanisms of iron metabolism affected by anthracycline drugs for heart protection. Xu *et al.*[14] has discovered the effect of doxorubicin (DOX) on iron metabolism through detecting TfR1 expression under DOX treatment. In SK-Mel-28 cells, DOX serves as an iron-chelating agent to increase TfR1 mRNA expression with a highest concentration of 2 μmol/L, which was confirmed in 4 other cell lines (SK-N-MC, MCF-7, DMS-53, and IMR-32) with different doses and regulatory effects. Other anthracycline drugs, such as daunorubicin and epirubicin, also elevate TfR1 and Ndrg1 mRNA expression in a dose-dependent manner[14]. Typical iron-chelating agents upregulate TfR1 mRNA expression through iron-regulatory proteins (IRPs)-iron-sensitive elements. Anthracycline drugs, as an atypical iron-chelating agent, play roles in cellular iron metabolism and iron-regulated genes, including the downstream targets (Ndg1 and Fn) of TfR1 and N-myc[14].

Transferrin receptor 2 (TfR2)

A newly discovered TfR is called TfR2, is located on chromosome 5. Different from TfR1, TfR2 does not have an iron response element (IRE), and its expression is not regulated by cellular iron, but related to the cell cycle. IRE encodes cell division cycle 14A (CDC14A). However, whether CDC14A takes parts in cell division is still controversial. CDC14A IRE binds with IRP1 and IRP2, and its mRNA expression is regulated by iron repression[15], indicating that its regulatory mechanism is related to IRE/IRP and iron metabolism may be associated with the cell cycle.

TfR2 is expressed in tumor cells but not in normal cells.

Particularly frequent is its expression in ovarian cancer, colon cancer, and glioblastoma cell lines, and less frequent is its expression in leukemic and melanoma cell lines[6]. Calzolari et al. analyzed TfR2 expression in solid tumors and leukemic cell lines by flow cytometry and Western blot analysis, and high levels of TfR2 mRNA have been detected in HepG2 (human hepatoma), K562, and HEL-R (both human erythroleukemic) cell lines. The human lymphoid cell lines Raji and MOLT-16 and human myeloid cell lines U937, NB-4, HL-60, KCL22, and KG-1 expressed low or undetectable levels of TfR2 mRNA[6]. All these results suggest that TfR2 expression is different in different tumor cells, which provides helpful information for studying primary tumors. Hänninen found that TfR2 mRNA expression appeared in some brain tumor tissues, but not in astrocytoma cell lines [8]. TfR2 expression is modulated by iron through different biochemical mechanisms in tumor cells, and the molecular basis remains to be determined.

Experiments of in-vitro iron loading or iron deprivation provide evidence that TfR2 is modulated in cancer cell lines according to cellular iron levels following two different mechanisms: (i) in some cells, iron loading causes a down-modulation of total TfR2 levels; and (ii) in other cell types, iron loading leads to a down-modulation of membrane-bound TfR2, without affecting the levels of total cellular TfR2 content. Iron deprivation causes in both conditions, the opposite effect compared to iron loading[6].

In humans, mutations of TfR2 cause type 3 hemochromatosis and a deficient mutation in mice leads to iron overload with a similar phenotype[16]. The results suggest that TfR2 not only takes part in iron homeostasis at present, its function still requires further study.

Currently, we know little about TfR2. Only mRNA expression of TfR2 has been proved in tumor cells, and little evidence about the protein expression of TfR has been discovered[17].

Ferritin (Fn)

Many solid tumor cells synthesize or secrete Fn, such as hepatic cancer, lung cancer, leukemia in remission, and breast cancer recurrence or metastasis, and the serum Fn of patients increases significantly. Thus, Fn is not only an iron storage indicator, but also a malignant tumor marker. Despite an increase in iron storage, serum ferritin has been observed to be elevated in most patients with tumors[18]. Li *et al.*[19] detected sFn, CEA, CA19-9, CA15-3, and SCC in 111 patients with lung cancer, and found that the positive rate of sFn was the highest. The positive rates of sFn in hepatic cancer, lung cancer, leukemia, and erythroleukemia in patients are 66.6%, 7.2%, 62.5%, and 5.8% respectively[20].

sFn markedly elevates in neuroblastoma (NB) at stages III and IV, but not in stages I and II, thus, it is suggested that sFn served as a prognostic indicator, with high level of sFn indicating a poor prognosis and low levels of sFn indicating a good prognosis. NB cells contain more Fn, and Fn increases significantly in the advanced stages of tumor cells. Fn divides into a heavy chain (H-Fn) and a light chain (L-Fn), and they play different roles. H-Fn represses the immune response, while L-Fn carries iron and promotes tumor cell proliferation. L-Fn is the main form of Fn secreted by NB cells, and serves as an iron source for other NB cells. The reasons for Fn secretion in tumor cells need to be further studied, and Fn may serve as an autocrine growth factor.

Some oncogenes repress Fn synthesis. E1A inhibits Fn expression on a transcriptional level, and c-myc represses H-Fn and activates IRP2. The overexpression of H-Fn reduces cell proliferation. p53 upregulates Fn expression by decreasing IRP binding, but not by activating the transcription of Fn. p53 induces alterations of Fn and TfR expression to inhibit cell growth, indicating that iron utilization plays an important role in modulating tumor cell proliferation.

H-Fn and L-Fn are overexpressed in p53-transfected NSCLC H129 cells. To further confirm that p53 induced Fn expression, Fn expression is detected in human colon cancer cell line HCT116 and it has been observed that H-Fn is overexpressed in p53 expressed cells. However, H-Fn mRNA does not respond to p53, and p53 decreases the binding of IRE and IRPs, indicating that p53 regulates Fn expression through IRPs, and IRP1 is the most remarkable one[21].

Fn binds with the anti-angiogenic region of cleaved high molecular weight kininogen (HKa) to block anti-angiogenesis induced by HKa, which is proved in an angiogenesis model of injecting prostate cancer cell line PC3 into the ribs of nude mice. In addition, Fn inhibits anti-angiogenesis caused by HKa at multiple levels, suggesting that Fn directly binds with the anti-angiogenic region of HKa[22].

Hepcidin

Patients with cancer usually manifest high levels of serum hepcidin [23]. Hepcidin is a peptide synthesized and secreted by the liver, through decreasing the uptake of iron by the small intestine and reducing the deprivation of iron by the reticuloendothelial system to negatively regulate iron homeostasis, and plays regulatory roles in iron metabolism[24]. In the process of iron deprivation regulated by hepcidin, except for acting on intestinal epithelial cells, hepcidin also acts on macrophages and hepatocytes by the same mechanism[18]. Hepcidin has a single hairpin structure composed of 8 cysteine residues. HNF3β, C/EBPβ, NFκB, and other transcription factors located upstream of hepcidin. Precursors of hepcidin consist of 84 amino acids and produce different bioactive peptides by degradation with 2 predominant forms as 20 and 25 amino acids. Both have original microbial activity. Hepcidin is located on chromosome 19 in human, and on chromosome 7 in mice. Both are composed of 3 exons and 2 introns, and the third exon encodes the amino acid sequence of hepcidin. Humans only have 1 hepcidin gene, and mice have 2: hepcidin1 and hepcidin2, and the hepcidin1 is similar to the human gene.

The decrease in survival time for patients with renal cell carcinoma is related to hepcidin mRNA overexpression, which is lower in tumor tissue than in nontumor tissue, and serum hepcidin-25 is higher in patients with renal metastasis than in patients with primary renal cell carcinoma. mRNA expression of hepcidin in patients with renal cell carcinoma may be associated with metastasis, but not related to differentiation or tumor stage. No correlation appears between hepcidin-25 and hepcidin mRNA expression [25]. Hepcidin mRNA expresses in 34% of colorectal

cancer tissue and relates to iron deficiencies[26]. While in patients with hepatoma patients, the expression level is lower compared to nontumor tissue. The inhibition of hepcidin expression is not associated with TfR1 and TfR2. The obvious associations are observed between serum hepcidin-25 and serum iron, hepcidin-25 and Fn, and hepcidin and total iron binding capacity. However, the mechanism of hepcidin mRNA reduction has not been identified. Due to the requirement of iron in tumor cell proliferation, the transcriptional inhibition of hepcidin contradicts iron homeostasis [27]. In TfR2-knockout mice, hepcidin is repressed, which suggests that TfR2 is the upstream gene of hepcidin[28].

It has been reported that IL-6 induces hepcidin expression[29]. In addition, C-reactive protein (CRP) relates to renal cell carcinoma stage and prognosis [30,31], and the increased level of CRP is first caused by IL-6 overexpression. IL-6 and CRP are associated with tumor stage and metastasis [25]. However, the relationship between IL-6, CRP, tumors, and hepcidin remains to be further studied.

The tumor suppressor gene p53 inhibits tumor cell growth and promotes cell apoptosis and DNA repair in the transcriptional process[32]. Inhibition of the p53 pathway is also a marker in most human cancers. It has been found that hepcidin promoters involved a p53RE in HepG2 cells, and p53 binds with p53RE and activates p53-induced hepcidin expression. Inactivated p53 results in decreasing hepcidin expression in human hepatic tumor cells, speculating that increased hepcidin is a part of the antitumor defense mechanism, which is consistent with other studies [33]. Therefore, iron deprivation treatment is a new antitumor strategy. However, recent studies concerning the regulation of hepcidin were only performed at the mRNA level, further receaches should be conducted at the protein level.

Conclusion

Many proteins of iron metabolism show a high degree of expression in tumor cells, indicating that iron plays an important role in tumorigenesis and development. However, regulatory factors of iron metabolism and their mechanisms remain to be studied. New treatment strategies may be developed by combining imaging agents or targeted drugs with proteins related to iron metabolism, and specifically transferring to tumor cells through the latter. Recently, magnetic nanoparticles carrying chemotherapeutic drugs provide a new thinking for solid tumor targeted therapy. For example, combining magnetic nanoparticles Fe_3O_4 with cisplatin (DDP) is used to reverse DDP resistance of the human ovarian cancer cell line SKOV3/DDP through increasing intracellular drug concentrations, and promoting cell apoptosis by reducing mRNA expression of the antiapoptosis genes bcl-2 and survivin[34].

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