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Review

A Promising New Anti-Cancer Strategy: Iron Chelators Targeting CSCs

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Iron is a trace but vital element in the human body and is necessary for a multitude of crucial processes in life. However, iron overload is known to induce carcinogenesis via oxidative stress. Cancer cells require large amounts of iron for their rapid division and cell growth. Iron was recently found to play a role in cancer stem cells (CSCs); it maintains stemness during development. Iron also plays an important role in stemness by moderating reactive oxygen species. Thus, iron metabolism in CSCs is a promising therapeutic target. In this review, we summarize the roles of iron in cancer cells and CSCs. We also summarize anti-cancer therapeutic studies with iron chelators and describe our expectation of a new therapeutic strategy for CSCs on the basis of our findings.

Key words: cancer stem cell, stemness, iron, chelation, chemotherapy

In biological systems, iron exists in two main states, ferrous (+2) and ferric (+3), and plays an essential role in normal cell homeostasis. Iron orchestrates various crucial physiological processes in cells, such as cell respiration, oxygen metabolism, energy metabolism, and signaling. Iron also plays an active part in DNA synthesis and repair, cell growth, and differentiation [1,2]. However, iron is sometimes a double-edged sword. Iron overload can induce carcinogenesis via oxidative stress. More than 50 years ago, many types of compounds containing iron were reported to induce carcinogenesis [3-6].

Iron metabolism is different in cancer cells than in normal cells. Cancer cells require increasingly large amounts of iron to sustain their rapid division and cell growth [7]. Recent studies have hypothesized that cancer stem cells (CSCs) may be responsible for cancer recurrence and metastasis [8,9]. CSCs have self-renewal and differentiation abilities and may be a source of cancer. Recent studies have investigated new roles for iron in CSCs [10]. In this review, we provide an overview of iron's roles in cancer and CSCs and present our expectation of a new therapeutic strategy.

The Roles of Iron in Cancer Cells

Iron is a vital trace element in the body and is necessary to sustain life. Iron plays a pivotal role in cell cycle regulation, because it is integral to iron-containing ribonucleotide reductase, which is a rate-limiting enzyme in DNA synthesis [11]. In addition, iron plays an active part in various types of cell metabolism, especially in cellular respiration and energy metabolism, which provide cells with sufficient ATP primarily through oxidative phosphorylation and the citric acid cycle [12].

However, strict homeostasis is disrupted in malig-

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nant cells, and such disruption is thought to occur in connection with iron. A multitude of animal models have been made to elucidate the role of iron in carcinogenesis, and the results of studies with these models are consistent with those of epidemiological studies [3-6, 13]. Cancer cells require increasingly large amounts of iron to sustain their rapid division and cell growth. To meet their augmented iron requirement, malignant cells increase their uptake of iron from the microenvironment by upregulating pinocytosis and the expression of transferrin receptor 1 (TfR1) on the membrane. Cancer cells also secrete hepcidin (HP), which can suppress ferroportin (FPN) on the neoplastic cell membrane to reduce the export of intracellular iron [14-17] (Fig. 1). With an increase in available iron, ROS generation increases according to the Fenton reaction, which catalyzes Fe^{2+}, leading to DNA damage that increases mutations and malignancy [18, 19]. In addition, as mentioned above, cycle regulation and metabolism are enhanced, which promotes the growth and proliferation of tumors [20-22] by promoting ATP generation and mitochondrial oxygen consumption [23].

The malignant phenotype of cancer cells is regulated by oncogenes. Some oncogenes are associated with iron homeostasis. Myc family proteins, which are well-known transcription factors from oncogenes, are elevated in a wide variety of human cancers [24]. They contribute to several aspects of cellular metabolism, cell cycle regulation, and macromolecule biogenesis [25, 26]. Among them, c-Myc is firmly correlated with iron homeostasis. c-Myc increases the labile iron pool (LIP) via upregulation of iron regulatory protein 2

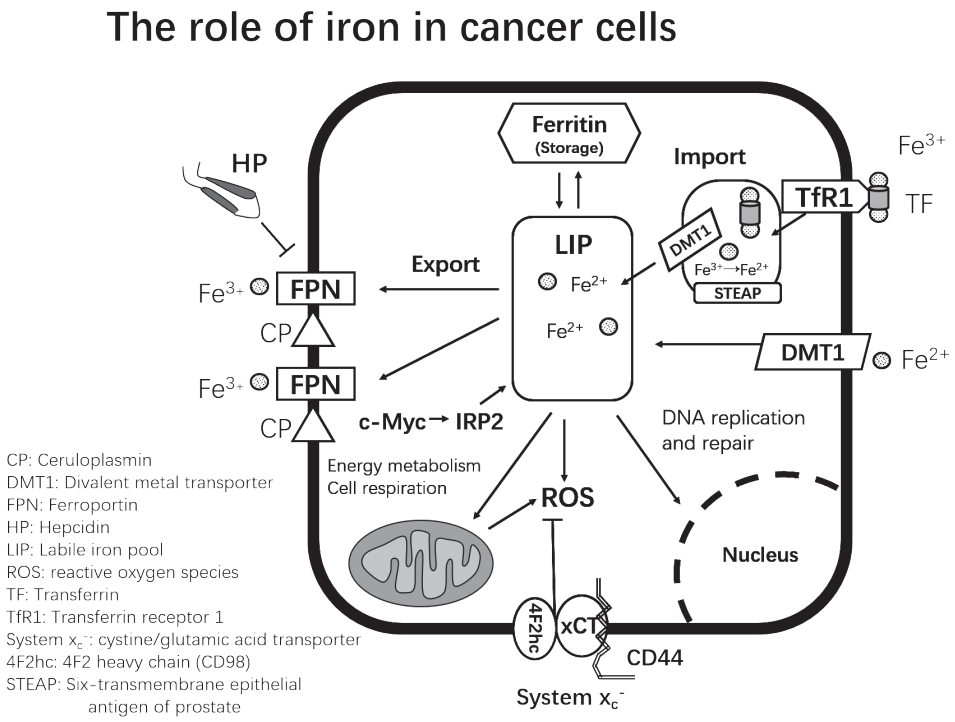

Fig. 1 The role of iron in cancer cells. In general, cancer cells show increased levels of intracellular iron compared to normal cells. Two methods are employed by cells to take up iron. 1) Ferrous iron (Fe^{2+}) is imported into cells directly by divalent metal transporter 1 (DMT1), especially in enterocytes. 2) Ferric iron (Fe^{3+}) is transferred by transferrin (TF) present in the circulation, combined with transferrin receptor 1 (TfR1), endocytosed via endosomes, reduced by the six-transmembrane epithelial antigen of prostate (STEAP), and exported through DMT1. The newly imported Fe^{2+} is added to the active labile iron pool (LIP) and utilized mainly by mitochondria and the nucleus for metabolic processes such as DNA replication and repair, energy metabolism, and cell respiration. LIP is also enhanced by upregulation of IRP2, which is regulated by c-Myc. Harmful reactive oxygen species are also generated by the increase in iron. Intracellular iron is stored in ferritin or exits the cell through ferroportin (FPN) and is oxidized by ferroxidase ceruloplasmin (CP) on the membrane. Hepcidin (HP), which is secreted by the liver, (the iron-sensing organ), acts as a negative regulator of FPN. ROS is downregulated by cysteine, an antioxidant molecule, via the cystine/glutamic acid transportation system (System x_c^-). System x_c^- consists of xCT and 4F2 heavy chain (CD98).

(IRP2), an iron-responsive protein that is a master regulator of intracellular iron homeostasis [7,27]. LIP is strongly increased in cancer cells compared to normal cells with overexpression of TfR and HP, low levels of FPN and ferritin (FT), or both [28].

These findings are supported by epidemiological data. Iron-rich foods such as red meat increase the risk of breast, colorectal, and lung cancers [29,30]. In short, iron plays many roles in cancer cells, from carcinogenesis to increasing the malignant phenotype.

The Role of Iron in CSCs

The theory of CSCs was proposed in the 1990s for acute myeloid leukemia based on experimental evidence [8,31]. Further research identified CSCs in solid tumors as well. CSCs are considered the main reason for the relapse and metastasis of cancer. CSCs are resistant to conventional chemotherapy and radiotherapy, and their presence is correlated with a poor clinical prognosis [32]. The functions of CSCs are related to iron metabolism. Recent studies revealed that iron induces not only carcinogenesis but also the stem cell phenotype in cancer cells. Iron increases sphere formation ability, which reflects self-renewal ability [33,34]. The expression of TfR1 is higher in breast CSCs than in cancer cells [35] (Fig. 2). CSCs are protected against ROS and maintain lower levels of intracellular ROS [36]. Considering that ROS accumulation induces carcinogenesis via oxidative stress, these findings indicate that CSCs can be thought of as ROS-generated cancer cells that are strongly protected from ROS.

Iron also plays an important role by moderating ROS in stemness, which is a main feature of CSCs. ROS moderates the redox balance and redox signaling. The redox balance affects self-renewal ability [37].

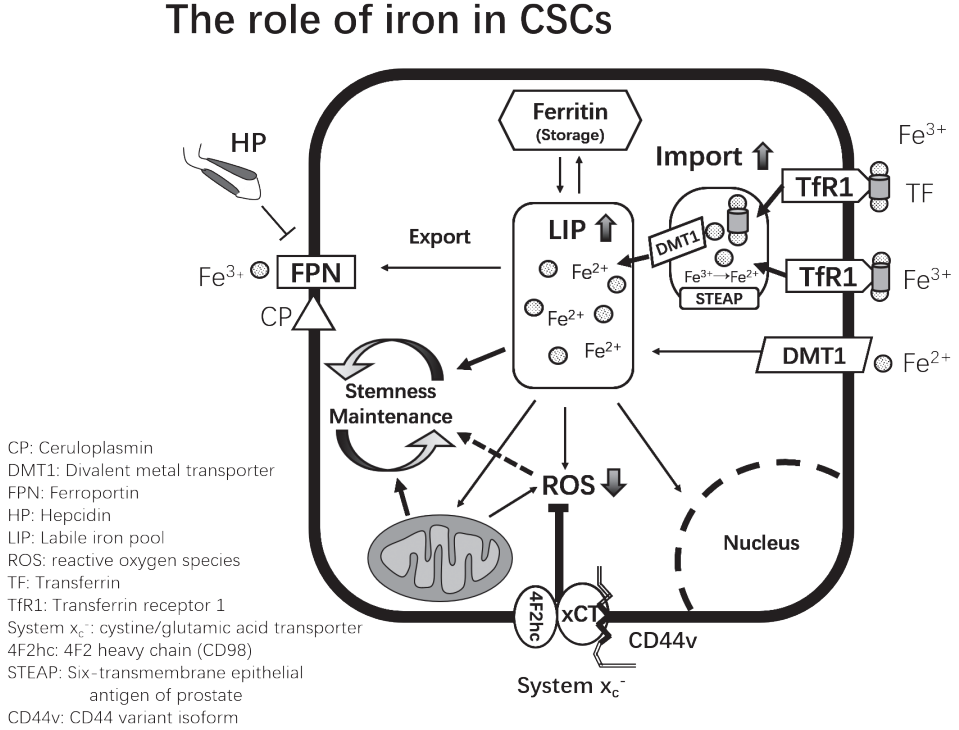

Fig. 2 The role of iron in CSCs. CSCs feature augmented dependence on iron and a higher accumulation of the labile iron pool (LIP) for active proliferation and stemness maintenance compared to normal cancer cells. The increase in ferrous iron (Fe^{2+}) enhances the expression of stem cell markers. To increase LIP, CSCs express high levels of transferrin receptor 1 (TfR1) and downregulate the expression of ferroportin (FPN), increasing the import and decreasing the export of iron. In addition, hepcidin (HP) is also elevated to suppress FPN export by triggering degradation and internalization. With the increase in intracellular iron, ROS increases. CSCs have a strong antioxidative mechanism mediated by the CD44 variant isoform (CD44v). CD44v stabilizes xCT and increases intracellular cysteine, an antioxidative substance, and maintains the low level of intracellular ROS. Compared to normal cancer cells, CSCs with fewer intracellular ROS and more LIP proliferate and are more difficult to eliminate.

Redox signaling affects self-renewal and the differentiation status of stem cells [38]. Stemness markers are often used to determine the stemness status and the existence of CSCs. Several markers are related to CSCs, such as CD44, CD133, Nanog, Epithelial cell adhesion molecule (EpCAM), Leucine-rich repeat-containing G-protein-coupled receptor 5 (LGR5), and Aldehyde dehydrogenase (ALDH) [39,40]. These markers are related to poor prognosis in clinical-pathological examinations [41-45]. A CD44 variant, which is a well-known CSC marker, works as an antioxidant molecule by enhancing the expression of cystine/glutamic acid transporter (system x_c^-). The CD44 variant stabilizes xCT, a key molecule of system x_c^-, increases intracellular cysteine, an antioxidative substance, and maintains a low level of intracellular ROS, which is thought to be a reason why CSCs can maintain lower levels of intracellular ROS. Moreover, some stemness markers promote a metastatic phenotype that is regulated through ROS [45,46]. Together, these recent studies have shown new roles for iron in CSCs and have revealed that ROS induction is a possible type of CSC therapy.

Iron Metabolism As a Therapeutic Target in CSCs

Iron metabolism has been targeted in cancer therapy. Phlebotomy was first considered to decrease internal iron levels as a cancer therapy [47,48]. Iron chelators also have been proposed as anti-cancer drugs that target iron metabolism [49-52]. Many kinds of iron chelators, such as deferaxamine, deferasirox, tachpyridine, di-2-pyridylketone-4,4-dimethyl-3-thiosemicarbazone, and super polyphenol, have shown anti-cancer effects [51-57]. These iron chelators also suppress metastasis [51,58]. In hepatocellular carcinoma, deferaxamine showed a clinically significant effect in some cases [59]. However, no iron chelation treatment for cancer has been established, and there may be several plausible reasons for this: many other strong anti-proliferative drugs have been developed that are not iron chelators; iron chelators have side effects because normal cells also use iron; and the complicated roles of iron chelators in cancer cells and the microenvironment have not been completely elucidated. However, recent progress in molecular biology has suggested a new use for iron chelators combined with molecular targeting drugs to treat intractable cancer [60-63]. Moreover, progress in stem cell research and an increased understanding of iron's role in CSCs have provided new insight in this field. We found that iron chelators suppress stemness in a CSC model derived from mouse-induced pluripotent stem cells [64] (Fig. 3). A similar phenomenon was confirmed in cholangiocarcinoma, esophageal cancer, and pancreatic cancer cell lines with stemness potential [34,65]. Although the expectation of iron chelators as a new therapeutic modality for CSCs is increasing, the underlying mechanism is still debatable. Iron chelators generally induce apoptosis in cancer cells. Some iron chelators induce another type of cell death, called ferroptosis. Sulfasalazine, a traditional iron chelator, induces ferroptosis in CSCs via suppression of xCT. Salinomycin is also an iron chelator that induces ferroptosis by sequestering iron in lysosomes and inducing ROS generation [35]. However, it remains to be determined which iron chelator and which mechanism are most important for CSC targeting therapy. Tumor heterogeneity may affect the results [66]. Further studies are needed to establish CSC targeting therapy using iron chelators.

Iron was present when the earth was formed. Since all living things evolved in the presence of iron, it is not surprising that iron is essential for the maintenance of stemness. Adequate control of iron homeostasis will contribute to establishing CSC targeting therapy.

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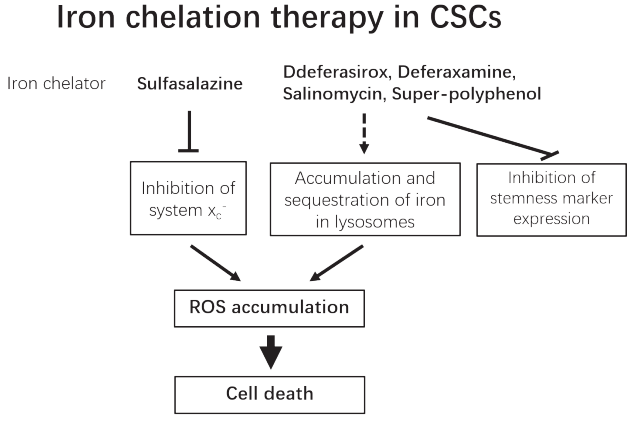

Fig. 3 Iron chelation therapy in CSCs. Iron chelators are reported to be effective in CSCs. Although CSCs are strongly protected from ROS, both sulfasalazine and other iron chelators induce ROS accumulation and cell death in CSCs. The detailed mechanism is known to be different.

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