

REVIEW

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# Therapy-resistant nature of cancer stem cells in view of iron metabolism

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## Abstract

Due to increased resistance to standard chemo/radiotherapies and relapse, highly tumorigenic cancer stem cells (CSCs) have been proposed as a promising target for the development of effective cancer treatments. In order to develop innovative cancer therapies that target CSCs, much attention has focused on the iron metabolism of CSCs, which has been considered to contribute to self-renewal of CSCs. Here, we review recent advances in iron metabolism and conventional iron metabolism-targeted cancer therapies, as well as therapy resistance of CSCs and potential treatment options to overcome them, which provide important insights into therapeutic strategies against intractable cancers. Potential treatment options targeting iron homeostasis, including small-molecule inhibitors, nanotechnology platforms, ferroptosis, and 5-ALA-PDT, might be a focus of future research for the development of innovative cancer therapies that tackle CSCs.

**Keywords:** Cancer stem cell, Iron metabolism, Iron chelator, Nanotechnology, Ferroptosis, 5-ALA-PDT

## Background

Due to increased resistance to standard chemo/radiotherapies and relapse, highly tumorigenic cancer stem cells (CSCs) have been proposed as a promising target for the development of effective cancer treatments [1]. Iron is critical for cancer progression and recurrence, and a variety of iron metabolism-related proteins is abnormally regulated in CSCs, implicating that an augmented accumulation of intracellular iron and iron-dependency are one of metabolic hallmarks of CSCs [2]. In order to develop innovative cancer therapies that target CSCs, much attention has focused on the iron metabolism of CSCs, which has been considered to be important for self-renewal of CSCs [3–5]. Thus, targeting iron metabolic pathways in CSCs represents a valuable strategy which impairs therapy-resistant nature of CSCs and thereby inhibiting the cancer recurrence. However,

resistant mechanisms of CSCs on iron metabolism-targeted cancer therapy remain to be fully elucidated. Here, we review the mechanisms underlying therapy resistance of CSCs particularly by focusing on the iron metabolism and potential strategies to overcome them.

## Main text

### Iron metabolism in CSCs and non-CSCs

Dysregulated iron homeostasis has been considered as a metabolic hallmark of CSCs, in which some alterations of iron trafficking have been identified compared to cancer cells (Fig. 1) [6]. These changes clearly indicated that an augmented accumulation of intracellular iron is associated with iron-dependent maintenance and expansion of CSCs, resulting in therapy resistance of bulk tumors [2]. Transferrin (TF) binding to transferrin receptor 1 (TFR1) is a major starting point of the way to increase iron uptake [7]. Recent studies revealed that TF protein is upregulated in glioblastoma and ovarian CSCs than non-CSCs [3, 8]. It has been observed that expression levels of *Tfr1* gene are increased in the CSCs of breast, prostate, and cholangiocarcinoma, suggesting that CSCs exhibit an enhanced iron uptake [4, 8, 9]. Ferroportin 1

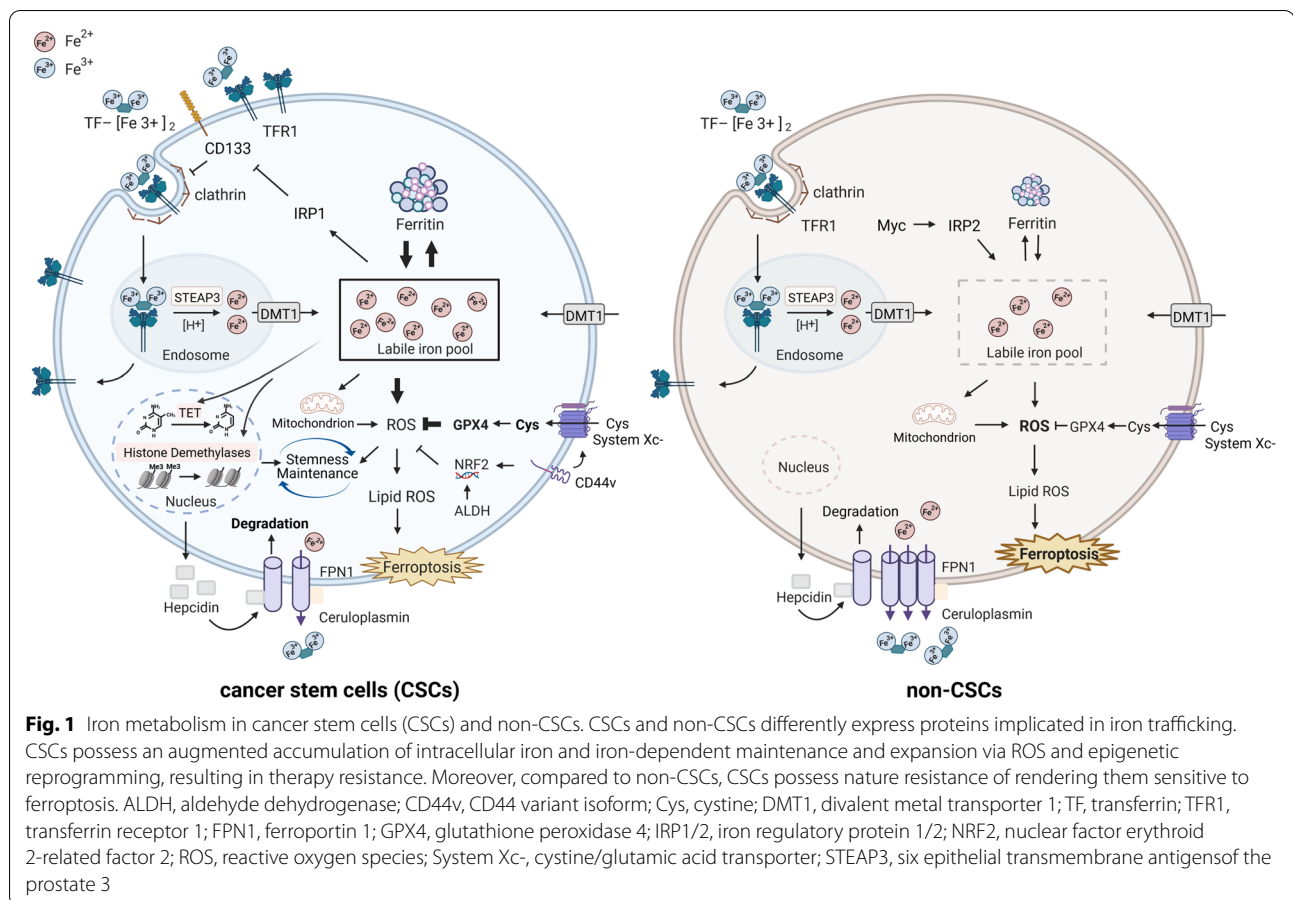
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(FPN1) is the sole cellular iron exporter, and hepcidin induces FPN1 internalization and degradation, thereby inhibiting iron efflux [6]. The expression levels of *Fpn1* gene are downregulated in ovarian and cholangiocarcinoma CSCs [3, 10]. There is increasing evidence indicating that patients of multiple tumor types have high levels of serum and tumor hepcidin, although the levels of hepcidin in CSCs remain to be fully investigated [11, 12]. Ceruloplasmin, a ferroxidase involved in iron transport that facilitates iron flux from cells, is found to be reduced in CSCs as an additional mechanism of iron retention [7]. Along with internalization of iron-TF by endocytosis, iron is reduced by six-transmembrane epithelial antigen of the prostate 3 (STEAP3) in the endosome and is subsequently exported by divalent metal transporter 1 (DMT1) into the cytoplasmic labile iron pool (LIP). Cellular iron homeostasis is post-transcriptionally regulated by iron regulatory proteins, IRP1 and IRP2, which are RNA-binding proteins that bind to iron-responsive elements (IREs) of the major proteins of iron metabolism [13]. LIP is enhanced in non-CSCs by upregulation of IRP2, which is regulated by proto-oncogene and proliferation gene *c-Myc* [14]. IRP1, which is the regulator of

iron metabolism-related gene expression, binds to IREs of some stem cell genes including CD133 to inhibit their translation or degradation [15]. CSCs have enhanced iron uptake and reduced iron efflux, which collectively lead to high intracellular iron. A forced increase in intracellular iron promotes metastatic spread of ovarian CSCs through the expression of matrix metalloproteases and synthesis of IL-6 [16]. The majority of cytoplasmic iron is stored in ferritin, which increases in glioblastoma stem-like cells compared to non-CSCs [3]. Recent studies show that high heavy-chain ferritin (H-ferritin) expression seems to relate closely with CSC features in breast and cholangiocarcinomas [8, 9]. However, except for TFR1, levels of proteins involved in iron trafficking are still disputed between CSCs and non-CSCs in different cancers (Fig. 1). The CSC addiction to iron might result in part from the role of iron in stemness maintenance, as iron activates self-renewal and influences the differentiation status of CSCs via mitochondrial reactive oxygen species (ROS) and epigenetic reprogramming such as DNA and histone demethylation [6, 17]. The important role of iron in stem cell dynamics is its essential function as a co-factor of epigenetic enzymes including TET

enzymes and JmjC domain-containing proteins. CSCs alter the canonical Notch, Wnt, and hedgehog signaling pathways for CSC maintenance and self-renewal ability by iron-mediated epigenetic mechanisms [18, 19]. Taken together, some of the major proteins in iron metabolism might have therapeutic potential for CSC treatment, such as iron transporter TF and its receptor, iron storage protein ferritin, iron exporter FPN1, iron regulator hepcidin, and epigenetic enzymes.

#### Current cancer treatments targeting iron metabolism

Recent studies depicting the molecular characterization of alterations of iron homeostasis aimed at maintaining the high iron demand of CSCs [20] offered support to the use of iron chelators as anti-tumor drugs [21]. Iron chelators work by firmly sequestering iron and preventing it from being used in cellular activities, resulting in a decrease in intracellular iron levels and a slowing of cellular metabolism. Iron chelators have been shown to reduce chemoresistance and the possibility of tumor cell progression by inhibiting the expression of stemness-related markers such as OCT4, SOX2, KLF4, NANOG, and SALL4 [22]. Iron chelators have also been shown to block DNA and histone demethylation enzymes including TET enzymes and JmjC domain-containing proteins, which are iron-dependent oxygenases involved in transcriptional control and DNA repair [23, 24]. Numerous Food and Drug Administration (FDA)-approved iron chelators, such as deferoxamine (DFO), deferiprone (DFP), and deferasirox (DFX), in vitro have been promising in cancers, including leukemia, hepatoma, neuroblastoma, prostate, and breast cancer [25–30]. Some compounds with iron-chelating properties have been reported to be used for cancer therapy. Di-2-pyridylketone-4,4,-dimethyl-3-thiosemicarbazone (Dp44mT) exhibits anti-proliferative activity both in vitro and in vivo in models of pancreatic, neuroblastoma, and lung cancers [31–33]. Curcumin, derived from the plant *Curcuma longa*, has also iron-chelating ability and shows efficacy against colon, duodenal, stomach, esophageal, and oral cancers [34]. However, iron chelation treatment has been not yet approved for clinical cancer treatment, due to dose-limiting toxicities, lack of tumor cell selectivity, and ineffective intratumoral concentrations [35–38].

Targeting iron metabolism-related proteins has been developed into a promising avenue of cancer therapy. Although several clinical trials have been conducted on antibodies against TFR1 and show anti-tumor efficacy, immunogenicity of therapeutic protein remains a major concern directly related to patient safety [39]. TFR1-targeted delivery systems could circumvent systemic toxicity, and preliminary results are promising. MBP-426, a Tf-conjugated oxaliplatin-liposome, treats gastric and

esophageal adenocarcinomas in a phase II clinical trial (NCT00964080). SGT-53 and SGT-94, targeting to TFR on cancer cells via a TFR1-scFv to deliver the plasmid DNA into cells, are currently under clinical evaluation (NCT02340117, NCT01517464). In addition to TFR1, targeting downregulation of ferritin light chain (FTL) protein by miR-133a increased sensitivity of breast cancer cells to chemotherapy drugs [40]. Although cancer therapies targeted at iron metabolism have manifested a certain level of success in some malignancies, the overall effectiveness is far from satisfactory partly due to adaptive resistance of CSCs.

#### Iron-buffering abilities of CSCs in therapy resistance

Abnormal metabolism of iron in CSCs reveals the direct driving force of CSC tumorigenicity and therapeutic resistance. Due to adaptive resistance of CSCs, recent studies suggest CSCs possess iron-buffering capacity to maintain iron homeostasis under iron deficiency. It is reported that glioblastoma and breast CSCs express higher levels of TFR1 than non-CSCs [3, 4]. During incubation with iron chelator, glioblastoma CSCs could increase iron uptake by upregulating TFR1, thus responding to iron deficiency [3]. Breast CSCs trigger the degradation of ferritin into lysosomes replying to iron depletion [4]. In addition, stem cell marker has been demonstrated as an alternative pathway in iron acquisition of CSCs by mediating iron endocytosis. CD133 is regulated by iron and its expression has been linked to endocytosis of Tf/TFR1 or iron uptake suggesting the existence of CD133-Tf-iron network [15]. CD44 itself is transcriptionally regulated by mediating iron endocytosis, suggesting this pathway represents a powerful alternative to maintain iron homeostasis of CSCs [41]. These results demonstrate that the higher needs of iron in CSCs might trigger iron endocytosis pathway to maintain basal level of cellular iron (Fig. 1). Moreover, treatment of breast cancer cells with the iron chelator DFO might cause epigenetic reprogramming and decrease the expression of histone demethylases [42]. CpG island methylation is exhibited in the FPN1 gene promoter; hypermethylation of FPN1 promoter results in decreased FPN1 expression in basal breast cancer cells [43]. However, epigenetic reprogramming of CSCs in maintaining iron homeostasis remains to be clearly defined.

In the recent study, a small-molecule chelator of iron, fluorescent labeling of a clickable surrogate of deferoxamine (cDFO), provides a means to target the nucleus iron of breast CSCs, suggesting iron homeostasis of CSCs could be targeted at the nucleus using small-molecule inhibitors [41]. Therefore, novel small molecule iron-scavenging agents are urgently required to be discovered and therapy resistance of CSC-driven

tumors needs to be resolved. Treatment of cancer cells with iron chelator induces increased accumulation of HIF-1 replying to iron deficiency [44, 45]. Lang et al. found that Tfr1-targeting liposomes could be employed to deliver DFO and the HIF1 $\alpha$  inhibitor YC1 to target pancreatic cancer cells [46]. HIF-1, as a vital molecule for maintenance of CSCs, participates in cancer recurrence, metastasis, and therapy resistance [47]. In addition, Imran ul-haq et al. found that hyperbranched polyglycerol (HPG)-conjugated DFO, which is nanopolymer-based chelating system, exhibited nontoxicity and longer half-life, but was not tested in tumors [48]. This co-delivery nanoparticle system and combination therapy lay the foundation for iron chelation of CSCs in future. Given that abnormal metabolism of iron in CSCs provides the buffer capacity in resisting, it is unlikely that current iron chelation therapy will be effective in CSC-driven cancers. Further understanding of resistant mechanisms of CSCs to iron chelation leads to the development of promising treatments that target the ability of a cell to control iron metabolism. Potential treatment options against regulators of iron metabolism, including small-molecule inhibitors and nanotechnology platforms, to some extent, exert their antitumor effects in CSC-driven tumors.

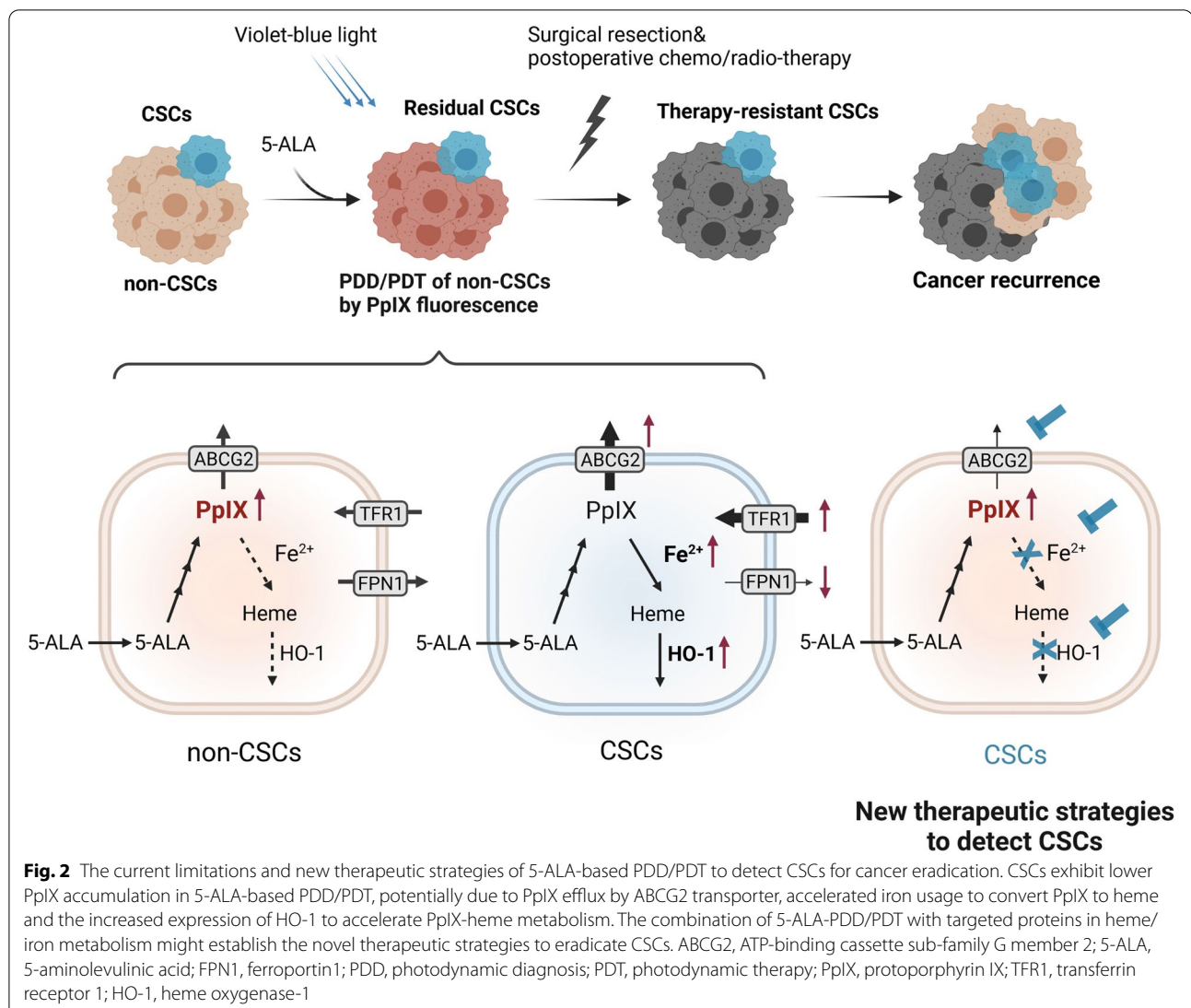
#### **New therapeutic strategies to tackle iron-adaptive CSCs**

High levels of free iron in cancer cells are associated with increased levels of the ROS production via Fenton reaction, which are more susceptible to lipid peroxidation-induced ferroptosis [49]. Ferroptosis is a specific type of cell death with distinct biochemical and genetic characteristics and differs from other forms of regulated cell death, including apoptosis, autophagy, and necrosis [50]. Since ferroptosis was discovered in 2012 as a novel iron-dependent type of regulated cell death triggered by ROS-induced lipid peroxidation, it is gaining a lot of attention as an important cell death pathway in various cancers [51]. However, CSCs possess nature resistance of rendering them sensitive to ferroptosis [52] (Fig. 1). Increased expression of ferritin in CSCs restrains ferroptosis by limiting the expansion of free iron pool, which might be protective mechanism against ferroptosis [53]. Mai et al. inhibits breast CSCs by salinomycin, which could induce the lysosomal degradation of ferritin and activate ferroptosis [4]. Recent studies have found there is the correlation between NRF2 expression and cell protection against ROS-induced ferroptosis [54]. CSC markers, including CD44 and ALDH, are found to be associated with elevated NRF2 expression, which suggests that NRF2 is a sensible target for eliminating CSCs via ferroptosis

[55, 56]. In the lipid peroxidation process, lipid hydroperoxides are important intermediates. The glutathione peroxidase 4 (GPX4) transforms lipid hydroperoxides to lipid alcohols, which avoids the generation of iron-dependent lipid ROS. Dysfunctions in cysteine metabolism influence GPX4, and inhibiting GPX4 activity causes lipid peroxidation, which can lead to ferroptosis [57]. Cystine is uptaken by Xc<sup>-</sup> system for the synthesis of glutathione, which further enhances the anti-ferroptosis activity of GPX4. The expression of CD44 variant isoform (CD44v) suppresses ferroptosis by interacting with Xc<sup>-</sup> system [58]. The results from studies concluded that interference with GPX4 pathways results in ferroptotic death in CSCs, which presents as a novel strategy to counteract tumor relapse [59, 60]. CD44v-targeting drugs like salazosulapyridine, whose effect is considered to be ROS production, are still in phase I trials for gastric cancer and non-small-cell lung cancer, suggesting that CSCs have dual capabilities, not only to scavenge ROS but also even in the presence of ROS, to exploit it to enhance CSC activity [61, 62]. As a result, the therapy of ROS-inducible CSCs by blocking anti-oxidant molecules like Cys and Xc-system should be more deeply considered. Understanding the mechanistic regulation of ferroptosis could open an additional opportunity to target CSCs.

Photodynamic diagnosis (PDD) and therapy (PDT), which utilize photosensitizers for fluorescence detection or photochemical therapeutic strategy, are promising non/minimally invasive approaches for cancer diagnosis and treatment [63]. 5-ALA is a crucial precursor in the heme biosynthesis pathway, where it is converted into the photosensitizing intermediate protoporphyrin IX (PpIX). PpIX is predominantly accumulated in cancer cells following 5-ALA treatment compared to normal cells, providing the foundation for the use of 5-ALA-based PDD and PDT in cancers [64, 65]. 5-ALA-based PDD and PDT are commonly used in the treatment of skin tumors and also have been employed for treatment of various tumors, such as bladder cancer, gastric cancer, head and neck cancer, T cell leukemia, and malignant glioma [66]. However, due to insufficient and heterogeneous PpIX accumulation, non-dermatologic applications of 5-ALA-based PDD and PDT have not moved beyond initial clinical trials. Recent studies demonstrate CSCs accumulate less PpIX, and thus, they might be resistant to 5-ALA-PDT [5]. The crucial parameters associated with CSC resistance to 5-ALA-PDT are abnormal expression of major proteins in iron metabolism of CSCs (Fig. 2). High ATP-binding cassette sub-family G member 2 (ABCG2) expression plays a pivotal role in regulating PpIX accumulation, and CSCs are enriched in the ABCG2-high ALA-expelling





population [67, 68]. Kawai et al. demonstrate that CSCs could be targeted by the combination of 5-ALA-PDD/PDT with an ABCG2 inhibitor Ko143 in the gastrointestinal cancer cell lines [69]. CSCs have high intracellular iron due to upregulation of TFR1 and downregulation of FPN1 [3, 4, 8–10], and iron is the substrate for conversion of PpIX to heme by ferrochelatase (FECH). Previously, we found that reduced amounts of iron by DFO lead to enhanced PpIX accumulation in glioma CSCs. Meanwhile, we also observed that HO-1 is upregulated in them, which might accelerate the PpIX/heme metabolic pathway, leading to the poor 5-ALA-mediated accumulation of PpIX. Moreover, high expression of HO-1 predicts human glioma malignancies [5]. Therefore, HO-1 could be a reasonable target to enhance 5-ALA-based PDD and PDT in glioblastoma CSCs. Moreover, we found there is no significant difference

of FECH expression between GBM and normal tissues, and its expression is not correlated with the prognosis of GBM patients [5]. However, Fujishiro et al. found that there is a significant upregulation of FECH and ABCG2 in human GBM cell line A172-derived CSCs, suggesting that glioma CSCs could be targeted by the combination of 5-ALA-PDD/PDT with FECH or ABCG2 inhibitors [70]. These results indicate that mechanisms of CSC resistance to 5-ALA-PDT might be diverse depending on the types of tumor cells, and the combination of 5-ALA-PDD/PDT with targeted proteins in heme/iron metabolism might establish the novel therapeutic strategies to eradicate CSCs.

## Conclusion

In this review, we briefly summarize current knowledge on iron metabolism in CSCs and their resistance to conventional cancer therapies, as well as the potential treatment options targeting iron/heme metabolism, especially focusing on ferroptosis and 5-ALA-PDT, which provide important insights into therapeutic strategies targeting CSCs. Although our knowledge about resistant mechanisms of CSCs in view of iron metabolism needs to be improved, potential treatment options targeting iron homeostasis, including small-molecule inhibitors, nanotechnology platforms, ferroptosis, and 5-ALA-PDT, might be a focus of future research for development of innovative cancer therapies against CSCs.

## Abbreviations

ABCG2: ATP-binding cassette sub-family G member 2; 5-ALA: 5-Aminolevulinic acid; ALDH: Aldehyde dehydrogenase; CD44v: CD44 variant isoform; cDFO: Clickable surrogate of deferoxamine; CSCs: Cancer stem cells; Cys: Cystine; DFO: Deferoxamine; DFP: Deferiprone; DFX: Deferasirox; Dp44mT: Di-2-pyridylketone-4,4,-dimethyl-3-thiosemicarbazone; DMT1: Divalent metal transporter 1; FDA: Food and Drug Administration; FECH: Ferrochelatase; FPN1: Ferroportin 1; FTL: Ferritin light chain; GPX4: Glutathione peroxidase 4; HO-1: Heme oxygenase-1; IREs: Iron-responsive elements; IRP2: Iron regulatory protein 2; LIPS: Labile iron pool; NRF2: Nuclear factor erythroid 2-related factor 2; PDD: Photodynamic diagnosis; PDT: Photodynamic therapy; PpIX: Protoporphyrin IX; ROS: Reactive oxygen species; STEAP3: Six-transmembrane epithelial antigen of the prostate3; System Xc-: Cystine/glutamic acid transporter; TF: Transferrin; TFR1: Transferrin receptor 1.

## Authors' contributions

WW, KT, and TT wrote the manuscript and finalized it. The authors read and approved the final manuscript.

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## Availability of data and materials

Further information and requests for resources and reagents should be directed to the authors: Tetsuya Taga ([taga.scr@mri.tmd.ac.jp](mailto:taga.scr@mri.tmd.ac.jp)) and Kouichi Tabu ([k-tabu.scr@mri.tmd.ac.jp](mailto:k-tabu.scr@mri.tmd.ac.jp)).

## Declarations

### Ethics approval and consent to participate

Not applicable to this review manuscript.

### Consent for publication

Not applicable to this review manuscript.

### Competing interests

The authors declare that they have no competing interests.

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