

Iron metabolism and the tumor microenvironment: A new perspective on cancer intervention and therapy (Review)

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Received September 9, 2024; Accepted October 29, 2024

DOI: 10.3892/ijmm.2024.5480

Abstract. Iron metabolism plays a crucial role in the tumor microenvironment, influencing various aspects of cancer cell biology and tumor progression. This review discusses the regulatory mechanisms of iron metabolism within the tumor microenvironment and highlights how tumor cells and associated stromal cells manage iron uptake, accumulation and regulation. The sources of iron within tumors and the biological importance of ferroptosis in cancer were explored, focusing on its mechanisms, biological effects and, in particular, its tumor-suppressive properties. Furthermore, the protective strategies employed by cancer cells to evade ferroptosis were examined. This review also delves into the intricate relationship between iron metabolism and immune modulation within the tumor microenvironment, detailing the impact on tumor-associated immune cells and immune evasion. The interplay between ferroptosis and immunotherapy is discussed and potential strategies to enhance cancer immunotherapy by modulating iron metabolism are presented. Finally, the current ferroptosis-based cancer therapeutic approaches were summarized and future directions for therapies that target iron metabolism were proposed.

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Key words: iron metabolism, ferroptosis, tumor microenvironment, cancer immunotherapy, cancer therapy

1. Introduction

Iron is an essential metal in the human body, serving as a crucial component for the synthesis of hemoglobin and myoglobin. In addition, iron plays vital roles in cellular vitality and is involved in a wide range of biochemical and physiological processes, including oxygen storage and transport, mitochondrial respiration, DNA synthesis and repair, and enzymatic reactions within cells (1). However, excess iron can exert toxic effects on the human body due to its active redox capacity (2), making free iron readily accept and donate electrons, leading to its involvement in various pathological mechanisms.

Iron plays a crucial role in cells, and its normal accumulation and regulation are essential for the survival of cells (3). In tumor cells, a series of gene expressions and molecular mechanisms facilitate the acquisition of sufficient iron to meet the high demands of growth and metastasis (4). Various organelles, including mitochondria (5) and lysosomes (6), probably participate in regulating iron metabolism and redox imbalance. However, when iron excessively accumulates, disrupting the balance of supply and demand, it can have the opposite effect, inhibiting normal cell growth (7).

A critical analysis of current research is required to understand the molecular regulation of iron metabolism systematically, ranging from its physiological implications to its therapeutic potential. For instance, the role of ferroptosis in tumor cells has been validated using ferroptosis-inducing drugs (8), underscoring its potential as a novel target for anti-cancer therapies. Focusing on the process of iron accumulation, regulation and ferroptosis, the following content will primarily discuss iron metabolism and its roles in tumor cells. Building on previous research, the potential of cancer therapies will be further explored based on the regulation of iron and the activation of ferroptosis.

Given the crucial role of iron in the growth and division of various cell types, it is important not only to discuss its impact on tumor cells themselves but also to broaden the perspective to include the entire tumor microenvironment, with a particular focus on its effects on immune cells. According to existing research, iron can exert varying degrees of influence on a wide range of immune cells (9), thereby directly affecting the growth and development of tumor cells. This provides a new perspective on the role of iron metabolism in tumors, warranting systematic exploration and further investigation.

Understanding the intricate mechanisms and regulatory pathways of iron in the tumor microenvironment, exemplified by the process of ferroptosis, provides insight into potential therapeutic strategies targeting ferroptosis in cancer treatment.

This review's body is organized into four key chapters, focusing on the multifaceted role of iron metabolism in cancer biology, particularly ferroptosis and its therapeutic implications: i) The Accumulation and Regulation of Iron in Tumor Cells: This chapter delves into how tumor cells take up and regulate iron, emphasizing the roles of various transporters and regulatory factors. It will be analyzed how the availability of iron influences tumor growth and survival, revealing changes in iron homeostasis within the tumor microenvironment and their impact on cancer cells. ii) The occurrence of ferroptosis in tumor cells: This chapter discusses the mechanisms and biological significance of ferroptosis, elucidating how this unique form of regulated cell death functions in cancer. A focus was placed on the potential of ferroptosis to inhibit tumor growth, as well as how cancer cells respond to the challenges posed by ferroptosis. iii) Regulation of immune cells in the tumor microenvironment by iron: This chapter examines how iron metabolism influences the function of immune cells within the tumor microenvironment, discussing how iron regulates immune cell behavior and impacts immune evasion mechanisms and the effectiveness of immunotherapy. iv) Targeting iron metabolism for cancer treatment: Finally, this chapter explores emerging therapeutic strategies that target iron metabolism and ferroptosis, emphasizing the potential of combination therapies to enhance treatment efficacy and overcome resistance.

2. Accumulation and regulation of iron in tumor cells

Impact of tumor-environment interactions: Study of several specific tumors as examples. Cancer can strategically control body systems, such as the neuroendocrine and immune systems, to reset homeostasis in a way that promotes its own growth, often at the expense of the host's well-being (10), highlighting the intricate relationship between tumors and their environmental influences. In general, cancer not only evades the body's regulatory mechanisms but also acquires the ability to influence both local and systemic homeostasis. In this section, several typical cancers were used as examples to demonstrate the validity of existing research that observes cancer development from the perspectives of metabolism and the body's environment. The present review's focus on iron metabolism arises from this very logic.

Melanoma. Melanomagenesis is influenced by various environmental and internal factors, including genetic predisposition and epigenetic changes. Exposure to solar radiation is a significant risk factor, particularly for cutaneous melanomas, while acral melanomas, which occur in areas not directly exposed to sunlight, primarily affect darker-skinned populations (11). The tumor microenvironment, characterized by local neuroimmune interactions and systemic factors, plays a crucial role in disease progression.

Hepatocellular carcinoma (HCC). HCC is the most common type of primary liver cancer, characterized by a multifactorial etiology that includes genetic, environmental and behavioral influences (12). Several environmental factors,

particularly copper and iron metabolism, play important roles in the progression and treatment resistance of HCC. For instance, elevated ceruloplasmin levels further enhance hypoxia-inducible factor (HIF)1 α expression by decreasing iron availability, creating a positive feedback loop that sustains the cancer cells' survival (13). The interplay between copper and iron homeostasis, mediated by copper metabolism MURR1 domain 10 and HIF1 α , highlights a critical link between environmental factors and the molecular mechanisms underlying HCC progression and therapy resistance. This understanding opens up potential therapeutic avenues aimed at disrupting these metabolic pathways to improve treatment outcomes.

Iron uptake and accumulation mechanisms. Cancer cells require abundant iron to sustain their rapid proliferation and metabolic demands. Cells of tumors often exhibit high iron metabolic activity, which supports their rapid proliferation and survival. Iron metabolism disorders are also common in cancers. Both iron overload and deficiency can affect disease progression and be linked to tumorigenesis. The complexity of iron metabolism in the tumor microenvironment lies in its multifaceted interplay with cancer cells and surrounding tissues. Cancer cells exhibit dynamic adaptations to fluctuations in iron availability, finely tuning the expression of key iron metabolism proteins to sustain their proliferation and survival. Meanwhile, the tumor microenvironment, characterized by hypoxia and inflammation, further modulates iron metabolism through the activation of the secretion of iron-binding proteins. These mechanisms highlight the sophisticated strategies employed by cancer cells to ensure an adequate supply of iron. Cancer cells could effectively increase their iron uptake and retention, creating an iron-rich environment that supports their aggressive growth and survival through comprehensive approaches, including overexpressing transferrin (TF) receptor 1 (TfR1), upregulating six-transmembrane epithelial antigen of the prostate (STEAP) protein and downregulating ferroportin (FPN).

Overexpression of TfR1. Iron is primarily absorbed by the divalent metal transporter protein 1 (DMT1) on the intestinal wall and it is transported to various tissues with the assistance of TF, which carries trivalent iron. And iron is mainly taken up by cells through endocytosis. TfR1 interacts with Tf proteins to form endocytic vesicles that facilitate the absorption of iron. Although TfR1 is generally expressed at low levels in most normal cells, its expression is significantly elevated in rapidly proliferating cells, such as those found in tumors (14,15), the basal cell layer, intestinal epithelium and certain types of immune cells (16). It is well established that TfR1 plays a crucial role in cellular iron uptake and homeostasis (17).

TfR1 expression is precisely regulated at multiple levels, including transcriptional and post-transcriptional mechanisms, to meet cellular iron demands and prevent disruptions in iron homeostasis, which can be detrimental to the cell (18). The primary regulatory mechanism involves IRPs, specifically IRP1 and IRP2, which will be elaborated on in the following chapters. Other regulatory factors include oncogenes such as c-MYC, which directly binds to a conserved E box in intron 1 of TFRC (19), and HIF-1, which activates TFRC expression under specific conditions, such as iron-deficient conditions, by binding to an upstream hypoxia response element (20). For

instance, in breast cancer, the SRC oncogene (sarcoma gene) encodes a tyrosine kinase that phosphorylates TfR1, enhancing cancer cell survival and inhibiting apoptosis. The loss of SIRT3, a mitochondrial deacetylase, also upregulates TfR1 by increasing reactive oxygen species (ROS) production (21).

In cancer cells, TfR1 is significantly overexpressed to meet the increased iron requirements necessary for their rapid proliferation and biosynthesis. This overexpression supports enhanced iron uptake through TfR1-mediated endocytosis, which is crucial for DNA synthesis and cellular proliferation driven by ribonucleotide reductase, an iron-dependent enzyme that can be inhibited by maltose gallium (22). The phenomenon of 'iron addiction' actually underscores the higher dependency of cancer cells on iron compared to normal cells, making them more sensitive to iron deprivation targeting TfR1.

Elevated intracellular iron levels protect cancer cells from natural killer (NK) cell-mediated cytotoxicity and apoptosis induced by tumor necrosis factor (TNF) α by inhibiting ROS accumulation through ferritin. TfR1 can also interact with the inhibitor of NF- κ B kinase complex, enhancing NF- κ B signaling and promoting cancer cell survival. In addition, NF- κ B further upregulates TfR1 expression by regulating HIF-1 α levels, creating a feedback loop that sustains cancer cell growth (23). Moreover, TfR1 modulates mitochondrial respiration and ROS production, both of which are crucial for the growth and survival of malignant cells (24). For instance, in hepatocellular carcinoma in animals, TfR1 maintains the stemness of cancer stem-like cells and promotes malignancy by regulating iron accumulation (25).

Due to these multifaceted roles, TfR1 is overexpressed in various cancer types, often at levels significantly higher than in normal cells (23-25). This overexpression is associated with advanced stages and poor prognosis in cancers such as breast cancer (26,27), ovarian cancer (28), esophageal squamous cell carcinoma (29), pancreatic cancer (30), lung cancer (31), bladder cancer (32), cholangiocarcinoma (33), cervical cancer (34), osteosarcoma (35), adrenal cortical carcinoma renal cell carcinoma (36), hepatocellular carcinoma (37) and several other hematopoietic malignancies such as non-Hodgkin lymphoma (38) and chronic lymphocytic leukemia, as well as acute lymphoblastic leukemia (39). Of note, in HIV-infected patients, aggressive non-Hodgkin lymphoma shows even higher TfR1 mRNA levels compared to those in non-infected patients (40). Therefore, TfR1 overexpression is a hallmark of cancer biology, driving iron accumulation and supporting the aggressive and malignant behavior of cancer cells.

Downregulation of FPN. FPN is the sole known iron export protein in mammalian cells, responsible for transporting iron from the inside of the cell to the extracellular space. In tumor cells, the expression of FPN is often downregulated, leading to the accumulation of intracellular iron. Decreased expression of FPN results in iron retention within the cell, and may help to contribute to an iron-rich intracellular environment that favors cancer-cell growth and survival, and this process may be related to the action of hepcidin (41). By limiting the export of iron, cancer cells ensure a steady supply of this essential metal to support their heightened metabolic and proliferative needs. This mechanism of iron retention through FPN downregulation is a critical factor in the dysregulated iron homeostasis observed in numerous types of cancer.

Role of the STEAP protein family. The STEAP protein family consists of metalloreductases that facilitate the reduction of iron and copper, enhancing their bioavailability for cellular processes. The family includes STEAP1-4, all of which play significant roles in iron metabolism (42). These proteins are primarily localized in the endosomal and plasma membranes, where they reduce Fe(III) to Fe(II), which can then be transported by DMT1. What is notable is that STEAP proteins are often upregulated in cancer cells, thereby increasing the availability of reduced iron for cellular uptake. This upregulation correlates with enhanced cell proliferation, migration and tumor growth, underscoring the critical role of STEAP proteins in maintaining the iron homeostasis necessary for cancer-cell survival and proliferation.

STEAP1 is predominantly located on the cell membrane and is hypothesized to function as an ion channel or transporter within tight junctions, gap junctions or cell adhesion sites, facilitating intercellular communication. Overexpression of STEAP1 in cancer suggests its potential role in promoting cancer-cell proliferation and invasion. Blocking STEAP1 with specific monoclonal antibodies has been shown to increase cell death in LNCaP cells, suggesting that STEAP1 may support cancer-cell proliferation or inhibit apoptosis. STEAP1 also appears to facilitate cell growth by elevating intracellular ROS levels, indicating its involvement in both intra- and inter-cellular pathways (42). STEAP2 operates as a shuttle between the Golgi complex and the plasma membrane, participating in both endocytic and exocytic pathways. It may function as a receptor for endogenous and exogenous ligands or regulate protein delivery and sorting mechanisms. STEAP2's colocalization with TF and TfR1 suggests a role in the endosomal TF cycle of erythroid cells, aiding in the uptake of iron and copper by reducing Fe³⁺ to Fe²⁺ and Cu²⁺ to Cu⁺ (43,44). It has been proved that STEAP2 increases prostate cancer-cell proliferation by regulating genes involved in the cell cycle, causing partial cell-cycle arrest in G0/G1 phase, and this effect is mediated through the activation of the ERK pathway. Initially identified in studies on hypochromic microcytic anemia in nm1054 mouse mutants, STEAP3 plays a vital role in iron metabolism in erythroid precursors. Localization cloning confirmed that STEAP3 is the gene causing iron deficiency anemia in the mouse mutant nm1054; It encodes an iron and copper reductase, which is essential for the effective transport of TF iron (45). STEAP4 is crucial for cellular iron and copper uptake, significantly enhancing their absorption. It aids iron homeostasis through involvement in the TF cycle and response to inflammatory cytokines. In cancer, STEAP4 expression may increase iron uptake, supporting cancer-cell growth by meeting their high iron demands. Its role in inflammation could also influence the tumor microenvironment, affecting cancer progression (46).

In cancer, STEAP proteins are frequently upregulated, leading to increased iron levels that support cancer-cell proliferation, migration and tumor growth. This makes STEAP proteins significant for cancer research, as they provide potential therapeutic targets for disrupting iron homeostasis in cancer cells and inhibiting tumor progression.

Iron regulatory proteins (IRPs) and HIFs. Iron is essential for cancer cell growth and survival, while its excessive

accumulation can induce a series of unhealthy incidents including ferroptosis, leading to oxidative stress and cellular damage, affecting cancer-cell survival. Therefore, understanding the surrounding molecular mechanisms regulating iron metabolism is crucial for developing new cancer treatment strategies. For instance, animal cells, particularly cancer cells, regulate the expression of downstream proteins by synthesizing certain types of regulatory proteins, thereby ensuring an adequate supply of iron required for cellular metabolism. This allows them to adapt to fluctuations in environmental iron levels while avoiding the damage caused by excessive iron accumulation. Together, IRPs and HIFs orchestrate a complex regulatory network that ensures adequate iron supply in cancer cells. By regulating the transcription of key genes involved in iron metabolism, IRPs and HIFs enable cancer cells to adapt to varying iron levels and hypoxic stress in the tumor microenvironment.

Role of IRPs in gene transcription regulation. IRPs are critical regulators of cellular iron homeostasis. IRPs control the expression of genes involved in iron metabolism by binding to iron-responsive elements (IREs) located in the untranslated regions (UTRs) of target mRNAs. There are two main IRPs: IRP1 and IRP2. These proteins can respond to intracellular iron levels to either stabilize or degrade mRNAs encoding key proteins in iron metabolism (47).

When cellular iron levels are low, IRPs bind to IREs in the 5'-UTR of mRNAs, such as those of ferritin and ferroportin, inhibiting their translation and reducing iron storage and export. Conversely, IRPs bind to IREs in the 3'-UTR of mRNAs like TfR1, stabilizing the mRNA and promoting its translation, thereby increasing iron uptake (47,48). This regulation ensures that cells can adapt to fluctuations in iron availability, maintaining iron homeostasis. In cancer cells, the dysregulation of IRP activity can lead to altered expression of these iron metabolism genes, contributing to increased iron uptake and retention that supports tumor growth and survival.

Activation of HIF signaling pathways in hypoxic environments and their impact on iron metabolism. HIFs are transcription factors that play a central role in the cellular response to low oxygen levels (hypoxia), a common characteristic of the tumor microenvironment (48,49). HIFs are composed of an oxygen-sensitive α subunit (HIF-1 α , HIF-2 α) and a constitutively expressed β subunit (HIF-1 β). Under normoxic conditions, HIF-1 α is rapidly degraded via the ubiquitin-proteasome pathway. However, under hypoxic conditions, HIF-1 α is stabilized and translocates to the nucleus, where it dimerizes with HIF-1 β to activate the transcription of various genes involved in the adaptation to hypoxia (49,50).

HIFs significantly influence iron metabolism by upregulating the expression of genes that enhance iron uptake and utilization. For instance, as previously mentioned, molecules such as HIF-1 α can regulate downstream iron absorption by modulating the expression levels of TfR1 (51). Besides, HIFs also increase the expression of DMT1, which facilitates the transport of iron into the cytoplasm. In addition, HIFs can be used as a hypoxia signal, upregulating heme oxygenase-1 (HO-1), an enzyme that releases iron from heme, contributing to intracellular iron availability (52), which highlights the unique role of the HIF family in regulating iron metabolism.

In the context of cancer, activation of the HIF signaling pathways supports the increased iron demands of rapidly proliferating tumor cells. By enhancing iron uptake and utilization, HIFs help to sustain the metabolic and proliferative needs of cancer cells under hypoxic conditions. This adaptation not only promotes tumor growth but also contributes to the aggressive and treatment-resistant nature of hypoxic tumors (Table I; Fig. 1).

3. Occurrence of ferroptosis in tumor cells

Initially introduced in 2012, the term 'ferroptosis' denotes iron-dependent regulated cell death triggered by excessive lipid peroxidation and Fenton-like chemical reactions, which could lead to irreversible membrane rupture (53). Iron accumulation and lipid peroxidation are critical inducers of ferroptosis in various cell models (54,55). Ferroptosis represents an iron-dependent form of regulated cell death driven by lipid peroxidation and oxidative stress. Ferroptosis is a cell death mode closely related to iron metabolism. Its prerequisite is the massive accumulation of iron, which is particularly evident in various cancer cells. In the previous section, the conditions under which iron accumulates in cells were discussed. Due to the fact that iron itself is an essential component of cells, it is important to explore the specific situations and conditions that can induce ferroptosis, which makes the effect of iron on cells become negative.

Specific mechanisms of ferroptosis

Iron-dependent lipid peroxidation. Ferroptosis is fundamentally driven by iron-dependent lipid peroxidation. Iron, due to its redox-active nature, can catalyze the formation of ROS through Fenton reactions. These ROS, particularly hydroxyl radicals (OH $\cdot$), react with polyunsaturated fatty acids (PUFAs) in cell membranes, initiating a chain reaction of lipid peroxidation (53). ROS-induced lipid peroxidation is a crucial propulsive step in ferroptosis. The lipid peroxides formed are highly reactive and can further propagate the peroxidation chain reaction and promote more ROS production in different parts of cells, leading to the disruption of membrane integrity (56), DNA structure (57) and cell death. This process is central to ferroptosis, as it leads to the accumulation of lipid ROS that overwhelm the cell's antioxidant defenses.

Disruption of the xc-cystine/glutamate antiporter or glutathione peroxidase 4 (GPX4) system. Ferroptosis primarily involves balancing oxidative damage and antioxidant defenses. In fact, the destruction and failure of antioxidant mechanisms are crucial in the process of ferroptosis. The glutathione (GSH)-GPX4 antioxidant system plays a crucial role in protecting cells from iron-induced death (58). The xc-system imports cystine as a limiting substrate for GSH synthesis in exchange for glutamate (Glu). GPX4 utilizes GSH as a reducing cofactor to convert phospholipid hydroperoxides into non-toxic lipid alcohols, thereby inhibiting ferroptosis in tumor cells (58,59).

A key mechanism in ferroptosis is the disruption of the xc-cystine/glutamate antiporter or the GPX4 system (58). The xc-antiporter imports cystine into the cell in exchange for glutamate. Cystine is then reduced to cysteine, which is essential for the synthesis of GSH, the major cellular antioxidant.

Table I. Comparison of iron metabolism pathways in neoplastic and normal cells.

Pathway	Neoplastic cells	Normal cells	Canonical mechanism (TfR1)	Non-canonical mechanism (GPx)	(Refs.)
Canonical iron uptake	Overexpression of transferrins	Relatively low TfR1 expression	TfR1-mediated endocytosis increased	-	(10,14,15)
Canonical iron retention	Downregulated FPN	Normal FPN expression maintains iron homeostasis	Antagonism with FPN	-	(41)
IRPs	Dysregulated IRP activity; promotes increased iron uptake	Normal regulation of IRPs maintains iron homeostasis	IRPs bind to IREs in mRNAs to regulate TfR1 expression	Oxidative stress modulating IRP function	(47)
HIF signaling	Upregulated HIF-1 α enhances iron uptake	HIF activation is transient and regulated	HIF-1 α stabilizes and increases TfR1 and DMT1 expression	Oxidative stress affecting HIF regulation	(48-50)
STEAP proteins	Upregulated STEAP1, -2 and -4 enhance iron bioavailability	Normal expression, no significant role in iron uptake	STEAP proteins reduce Fe(III) to Fe(II) for uptake	Potential interaction with GPx for redox balance	(43,44)

DMT-1, divalent metal transporter 1; Tf, transferrin; TfR1, transferrin receptor 1; HIFs, hypoxia-inducible factors; IRPs, iron regulatory proteins; GPx, glutathione peroxidase; STEAP, six-transmembrane epithelial antigen of the prostate; FPN, ferroportin.

When the function of the xc-antiporter is inhibited, intracellular cystine levels drop, leading to a decrease in GSH synthesis. Without sufficient GSH, the activity of GPX4, an enzyme that reduces lipid hydroperoxides to non-toxic lipid alcohols, is compromised. This results in the accumulation of lipid hydroperoxides, which can then undergo iron-catalyzed decomposition to form toxic lipid radicals, further promoting ferroptosis.

Role of lipoxygenases (LOX) in the endoplasmic reticulum-associated compartment. LOX play a significant role in ferroptosis. LOX inhibitors, such as Baicalein and nordihydroguaiaretic acid, protect acute lymphoblastic leukemia cells from ferroptosis induced by GPX4 inhibition (60). Similarly, 12/15-LOX inhibitors and arachidonate 15-lipoxygenase (ALOX15) silencing reduce ferroptotic cell death in cancer cells, while ALOX15 overexpression enhances it (61). Lysyl oxidase is another molecule that plays a similar role to LOX, which promotes ferroptosis through ERK-dependent 5-lipoxygenase phosphorylation, leading to lipid ROS accumulation in neuronal cells (62). However, the role of LOX in ferroptosis may be more complex, as certain LOX inhibitors protect cells by acting as radical-trapping antioxidants rather than through LOX inhibition. While LOX activity may contribute to initiating ferroptosis, lipid autooxidation appears to drive the cell death process (63).

Interplay with other cellular systems. In addition to the primary mechanisms described, ferroptosis involves complex interactions with other cellular systems. For instance, the iron-sulfur cluster biosynthesis pathway and mitochondrial iron regulation are intimately linked with ferroptosis. Mitochondria, as major sites of iron metabolism and ROS production, contribute to the iron pool and oxidative stress that drive ferroptosis (64).

It is worth mentioning that multiple studies have shown that certain molecules can promote or inhibit ferroptosis

by regulating iron levels. This process occurs through the action on TfR molecules to modulate lipid peroxidation (65,66). For instance, Chen *et al* (65) clarified the characteristics of ferroptosis through the TfR1 mechanism when studying other molecular mechanisms. The actions of these molecules also make them key players indirectly related to the ferroptosis process. Molecules like ubiquinone (CoQ10) may play a role in this process. It is also universally acknowledged that ferroptosis suppressor protein 1 (FSP1) is another molecule which acts independently of GPX4. FSP1, when recruited to the plasma membrane through myristoylation, reduces lipid peroxidation by regenerating CoQ10 to its antioxidant form, ubiquinol, thus protecting against ferroptosis (67).

Other antioxidant systems, such as apoptosis-inducing factor mitochondria-associated 2-coenzyme Q10, tetrahydrobiopterin and the endosomal sorting complex required for transport III membrane repair system, counteract iron death in solid tumors. Furthermore, autophagy, particularly ferritinophagy (the autophagic degradation of ferritin), releases free iron within the cell, further promoting ferroptosis. Ferroptosis was initially considered autophagy-independent. Recent studies, however, have shown that excessive activation of selective autophagy promotes iron accumulation and lipid peroxidation, thereby inducing ferroptosis. Selective autophagy mechanisms include iron protein engulfment induced by nuclear receptor coactivator 4, molecular chaperone protein-dependent autophagy regulated by heat shock protein 90, lipid engulfment mediated by RAS oncogene family member RAB7A, member RAS oncogene family, and clock autophagy associated with sequestosome 1, selectively degrading iron proteins, GPX4 and lipid droplets to increase intracellular iron and free fatty acid levels, accelerating lipid peroxidation and promoting ferroptosis (68).

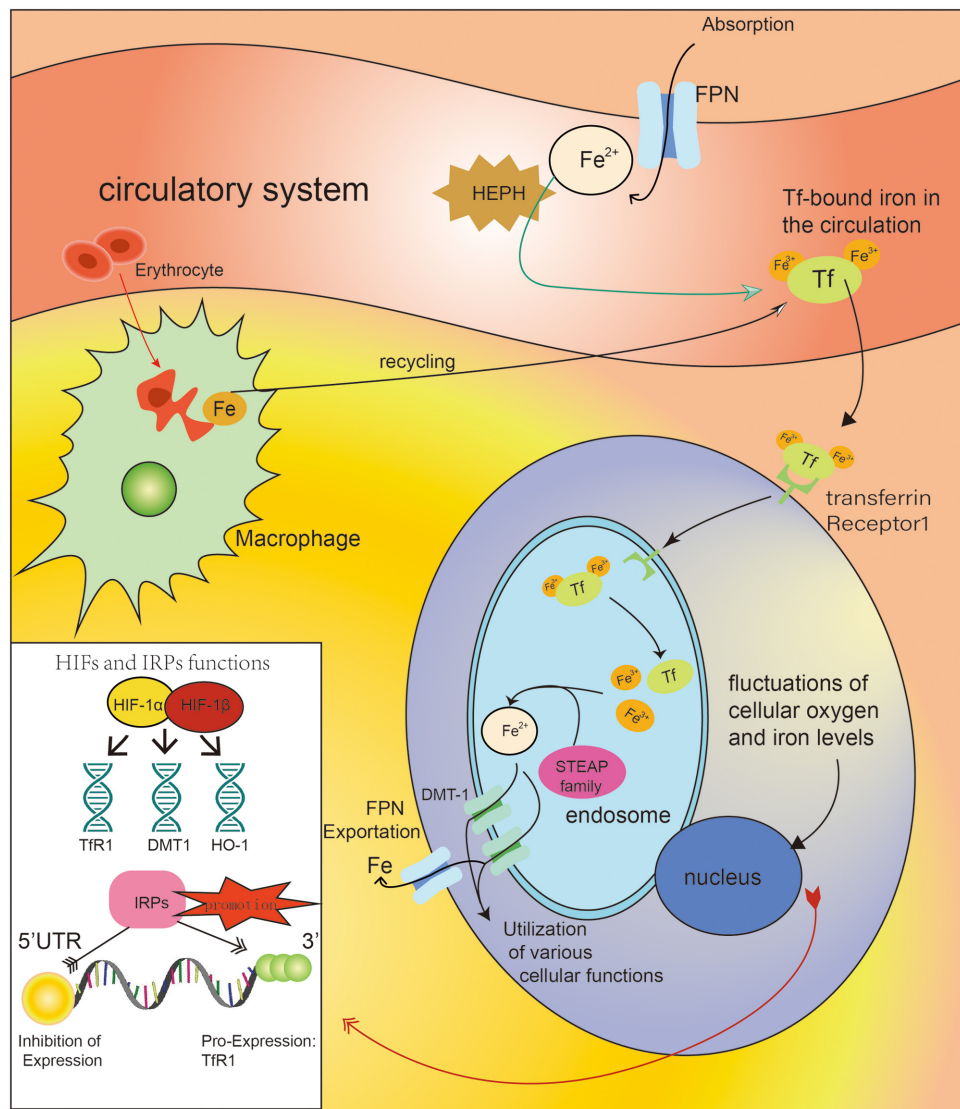


Figure 1. Diagram illustrating the mechanisms of iron accumulation and regulation in tissue cells. The circulatory system (e.g., blood circulation) acquires iron through two main pathways: Absorption from external sources (mediated by the FPN protein) and recycling. In the circulatory system, HEPH plays its roles in interacting with iron and altering its oxidation state. The iron is then converted to ferric iron and transported bound to Tf. Iron transport into cells requires the interaction between TfR1 and Tf, along with transmembrane transport by DMT-1. Tf carries iron into endosomes by binding to its specific receptor. After Tf releases the ferric ions (Fe^{3+}), the oxidation state of iron changes again and it can be transported into the cytoplasm via DMT-1. The STEAP protein family plays a role in converting the oxidation state of iron and promoting its utilization in specific cell types. In cancer cells, this process of iron accumulation is selectively enhanced. HIFs and IRPs are two key molecules in iron homeostasis regulation, interacting with genes and mRNA, respectively. Their different target sites result in varying downstream effects. Typical downstream molecules include TfR1, DMT-1 and HO-1, which influence the absorption and utilization of iron by tissue cells through various mechanisms, such as regulating iron uptake and affecting the release of iron from heme. DMT-1, divalent metal transporter 1; Tf, transferrin; TfR1, transferrin receptor 1; HIFs, hypoxia-inducible factors; IRPs, iron regulatory proteins; HO-1, heme oxygenase 1; HEPH, hephaestin (copper-dependent ferroxidase); FPN, ferroportin; STEAP, six-transmembrane epithelial antigen of the prostate; 5'-UTR, 5'-untranslated region.

Several oncogenic pathways closely relate to ferroptosis. For instance, numerous KRAS-mutated pancreatic cancers are sensitive to ferroptosis inducers such as Erastin (69). Furthermore, emerging evidence suggests that as a tumor suppressor gene, p53 inhibits cystine uptake and sensitizes cells to ferroptosis by downregulating the expression of the Xc system (70). However, studies also indicate that p53 can transcriptionally restrict Erastin-induced ferroptosis by blocking dipeptidyl peptidase 4 activity in a non-dependent manner (71).

These intricate molecular mechanisms underscore the complexity of ferroptosis and its regulation by various cellular pathways. Understanding these mechanisms provides a foundation for developing targeted therapies that can

modulate ferroptosis in cancer cells, potentially leading to novel anticancer strategies.

Protective mechanisms against ferroptosis in cancer cells. Under high demand for iron, cancer cells have a series of specific mechanisms to prevent ferroptosis. By listing and exploring these mechanisms, ferroptosis may be initiated by targeting key points in these mechanisms, providing new opportunities for cancer treatment.

Nuclear factor erythroid 2-related factor 2 (Nrf2) pathway. Nrf2 is a transcription factor that protects cells from toxic and oxidative damage by regulating the expression of a variety of genes. Under normal conditions, Nrf2 is continuously degraded

via the kelch like ECH associated protein 1 (Keap1)-mediated ubiquitin-proteasome pathway. Under conditions of cellular stress, the protein p62 can upregulate Nrf2 expression by inactivating Keap1, and the activation of the p62-Keap1-Nrf2 pathway helps protect cells from ferroptosis (72). Nrf2 also interacts with small Maf proteins to activate the transcription of antioxidant genes such as quinone oxidoreductase 1 and HO-1, contributing to iron homeostasis. Nrf2 regulates ferroptosis through the sigma-1 receptor (SIR), which is a ligand-regulated chaperone protein. SIR is overexpressed in certain cancer cells and helps protect against ferroptosis by upregulating ROS accumulation via the Nrf2 pathway (72,73). Inhibition of SIR can enhance ferroptosis by increasing Fe^{2+} , GSH and lipid peroxidation. Hence, targeting the Nrf2 pathway may be a potential strategy to induce ferroptosis in cancer cells.

Numerous studies have demonstrated that Nrf2 plays a protective role against chemical-induced carcinogenesis. For instance, Nrf2 knockout mice ($\text{Nrf2}^{-/-}$) are more susceptible to tumor formation in the stomach, bladder and skin when exposed to carcinogens (74). Nrf2-null mice showed increased gastric neoplasia after exposure to benzo(a)pyrene compared to wild-type mice. Higher tumor incidences were also reported in the intestines of Nrf2-deficient mice challenged with azoxymethane and dextran sodium sulfate, as well as in the bladder following exposure to N-nitrosobutyl (4-hydroxybutyl) amine, and in the skin after exposure to potent carcinogens such as dimethylbenz(a)anthracene and tetradecanoylphorbol-13-acetate. The protective mechanism of Nrf2 is attributed to its ability to reduce ROS and DNA damage in cells. In addition, mice with reduced Nrf2 expression due to a single-nucleotide polymorphism (SNP) in the Nrf2 gene promoter are more vulnerable to hyperoxia-induced lung damage (75). This protective role is supported by human studies where individuals with a similar SNP have lower Nrf2 mRNA levels and a higher risk of developing non-small-cell lung cancer.

Conversely, prolonged activation of Nrf2 is associated with the progression of various cancers, including lung, breast, head and neck, ovarian and endometrial carcinomas (76). High levels of Nrf2 in tumors are associated with poor patient prognosis, likely due to its role in enhancing cancer cell proliferation, chemoresistance and radioresistance. Elevated Nrf2 levels are observed in cancer cells resistant to chemotherapeutic agents, such as etoposide, carboplatin, cisplatin, 5-fluorouracil and doxorubicin. Silencing Nrf2 in these cells has been shown to restore drug sensitivity. Nrf2 also promotes cancer cell proliferation by activating genes involved in the pentose phosphate pathway (77) and other metabolic pathways, supporting glucose flux and generating purines necessary for DNA and RNA synthesis. In addition, Nrf2 helps maintain the redox balance and glutathione synthesis, further accelerating cancer cell proliferation. The dual role of Nrf2 in cancer underscores the complexity of its function (78). While transient activation of Nrf2 in normal cells is protective, constitutive activation in cancer cells enhances their survival and progression. Therefore, selectively targeting Nrf2 in cancer cells could potentially improve the efficacy of chemotherapy and radiation therapy by overcoming chemoresistance and radioresistance. Of note, the dual role of this molecule also suggests the possibility of more complex interconnections with iron transport-related molecules, including TfR1. The

magnitude and extent of the impact remains worth exploring. Recent research advances have shown that Nrf2 can be modulated or completely silenced by the action of certain molecules, including curcumin. This process is associated with a variety of molecules, including TfR1 (79).

Epigenetic modifications and metabolic molecules. RNA-binding proteins (RBPs) alter RNA fate by influencing splicing, transport, translation and degradation. For instance, DAZ-associated protein 1 is an RBP that stabilizes solute carrier family 7 member 11 (SLC7A11) mRNA, reducing ferroptosis in cancer cells. Alpha-enolase 1, traditionally a glycolytic enzyme, also acts as an RBP, promoting the degradation of IRP1 mRNA, maintaining iron homeostasis and protecting cells from ferroptosis (80). Circular RNAs (circRNAs) are single-stranded noncoding RNAs that form covalently closed loops. Circ0097009, for example, stabilizes SLC7A11 by sponging microRNA-1261, thereby protecting cells from ferroptosis (81).

Lactate, an important metabolic intermediate, enters cancer cells mainly through monocarboxylate transporter 1, regulated by hydroxycarboxylic acid receptor 1. Lactate increases the synthesis of monounsaturated fatty acids and decreases the synthesis of PUFAs, inhibiting lipid peroxidation and ferroptosis (82). This process involves the upregulation of sterol regulatory element-binding protein 1 and stearoyl-CoA desaturase-1, facilitated by enhanced ATP production and disrupted AMPK signaling. In addition, inactivation of the AMPK pathway upregulates branched-chain amino acid aminotransferase 2, another ferroptosis inhibitor that increases intracellular glutamate levels, enhancing system xc^- activity and cystine uptake.

Overall, it is clear that these metabolic processes highlight the importance of various metabolites in protecting against ferroptosis, thus revealing potential therapeutic targets in cancer treatment.

4. Regulation of immune cells in the tumor microenvironment by iron

In the tumor microenvironment, iron and its metabolism not only affect tumor cells, but also have a series of effects on immune cells. This section will comprehensively describe the effects of iron on immune cells and attempt to provide new possible perspectives for immune cell activation in the tumor microenvironment.

Regulation of the tumor immune microenvironment by iron metabolism

Iron regulation of macrophage polarization. Macrophages play a crucial role in the tumor immune microenvironment, significantly influencing tumor progression and development through their polarization states. Macrophages can polarize into three primary types: Unactivated M0 macrophages, classically activated M1 macrophages and alternatively activated M2 macrophages. M1 macrophages exhibit pro-inflammatory functions, secreting cytokines such as $\text{TNF-}\alpha$ and $\text{IL-1}\beta$, primarily functioning in antimicrobial and antitumor activities. By contrast, M2 macrophages have anti-inflammatory roles, secreting $\text{TGF-}\beta$ and platelet-derived growth factor, contributing to tissue repair and tumor promotion.

Regarding iron metabolism, M1 and M2 macrophages exhibit distinct characteristics (83). M1 macrophages tend to store iron, which helps them combat bacteria and tumor cells. They exhibit increased expression of iron-sequestering proteins such as ferritin and decreased expression of iron-exporting proteins such as FPN. Conversely, M2 macrophages are inclined to release iron due to their high expression of CD163 and CD94, as well as iron-exporting protein FPN, and lower ferritin expression. The released iron promotes cell proliferation, matrix remodeling and immune regulation, aligning with the functions of M2 macrophages. Iron overload induces M1 macrophage activation, leading to the expression of TNF- α , IL-12p40 and CD163 (84). This suggests that iron can promote M1 polarization under certain conditions. However, iron may also promote M2 polarization under different circumstances, demonstrating the heterogeneity and dynamic nature of macrophages in various environments. Mechanistically, M1 polarization is usually accompanied by downregulation of FPN and upregulation of TfR1. Low FPN expression and high ferritin expression facilitate M1 polarization. Conversely, M2 polarization is typically associated with upregulation of TF receptors and lipid carriers.

Tumor-associated macrophages (TAMs), which often exhibit an M2-like phenotype, can release iron, further supporting tumor growth and immune evasion. Targeting iron metabolism in cancer therapy has emerged as a novel strategy. Modulating iron levels in the tumor microenvironment can alter the polarization of TAMs, potentially shifting them from a tumor-promoting M2 phenotype to a tumor-suppressing M1 phenotype.

In summary, iron metabolism significantly influences macrophage polarization. Macrophages are more prone to M1 polarization in iron-rich environments, while iron-deficient conditions favor M2 polarization. Iron chelators inducing iron-deficient environments often lead to M2 polarization, though specific studies on M2 subtypes are limited. The promoting effect of M2 polarization on tumors makes it a possible target for cancer treatment. These findings suggest a need for further investigation into the underlying mechanisms of iron metabolism's effect on macrophage polarization.

Iron regulation of neutrophil recruitment and inflammation. Neutrophils are critical cells in the innate immune system, playing essential roles in defending against microbial invasion. Iron metabolism also plays a key role in neutrophil function. Neutrophils express iron metabolism-related proteins such as TfR1, ferritin heavy chain and FPN (85), enabling them to absorb or release iron when stimulated. Iron is crucial for neutrophil function; for example, the iron-dependent metalloprotein myeloperoxidase in neutrophils exerts antibacterial effects through its Fe³⁺/Fe²⁺ redox state (86).

Hepcidin, a peptide that increases intracellular iron by inducing FPN degradation, also increases neutrophil recruitment by inducing the production of C-X-C motif chemokine ligand 1 (87). This process is critical in acute inflammation and the body's initial response to infection. Conversely, iron chelators such as deferasirox can significantly reduce neutrophil-mediated inflammation, highlighting the potential therapeutic role of modulating iron levels to control excessive inflammatory responses (88). Under chronic inflammatory conditions, iron metabolism dysregulation in neutrophils can

exacerbate tissue damage and disease progression. Elevated iron levels can enhance the production of ROS by neutrophils, leading to increased oxidative stress and damage to surrounding tissues. This underscores the importance of balanced iron homeostasis in maintaining appropriate neutrophil function and preventing chronic inflammation.

These findings highlight the significant regulatory role of iron metabolism in neutrophil recruitment and inflammation; however, direct evidence remains limited. Further research is needed to elucidate the precise mechanisms by which iron influences neutrophil behavior and to develop targeted therapies for conditions involving neutrophil-mediated inflammation.

Iron and natural killer (NK) cells. Iron plays a crucial role in the function and metabolism of NK cells. NK cells increase iron absorption during viral infection to meet their metabolic needs and antiviral activity (89). Iron deficiency can impair the cytotoxicity and cytokine production of NK cells, leading to increased susceptibility to viral infections and cancer. In obesity, iron deficiency can lead to metabolic defects in NK cells, mitochondrial adaptation and cytokine responses.

It is clear that iron deficiency leads to the loss of NK-cell function, indicating that iron is essential not only for NK-cell development and proliferation but also for their activation and function in antiviral responses. The impaired function of NK cells under iron-deficient conditions can result in decreased cytotoxic activity and reduced production of critical cytokines such as IFN- γ , weakening the body's ability to combat viral infections and tumor cells (89). Conversely, iron overload can also negatively impact NK-cell function by promoting oxidative stress and cellular damage. Excess iron can lead to the generation of ROS, which can impair NK cell viability and function (90). Maintaining optimal iron levels is crucial for effective NK cell-mediated immune responses against pathogens and cancer cells (89,90).

Iron and adaptive immunity. Iron metabolism is also vital in the adaptive immune system. The function and differentiation of T cells and B cells depend on iron availability. T-cell activation and proliferation are regulated by iron absorption mediated by TfR1 (CD71), with iron deficiency resulting in T-cell dysfunction and delayed immune responses. Iron is also required for the proliferation of activated T cells, as it is necessary for DNA synthesis and cellular respiration. Iron deficiency can lead to impaired T-cell proliferation, reduced cytokine production and compromised immune responses (91). In addition, iron chelation can be used therapeutically to inhibit T-cell proliferation in autoimmune diseases, where excessive T-cell activity contributes to disease pathology. Iron deficiency leads to weakened antibody responses, compromising the body's ability to mount effective humoral immunity (89). The regulation of iron levels is therefore critical for maintaining balanced and effective adaptive immune responses.

Summary. Iron metabolism plays a critical regulatory role in the tumor immune microenvironment by influencing the functions of macrophages, neutrophils, NK cells, T cells and B cells. Future research should further explore the specific impacts of iron metabolism on these immune cells and their mechanisms in diseases to provide new insight for treating conditions such as cancer and autoimmune diseases. Understanding the intricate relationship between iron

metabolism and immune function will pave the way for novel therapeutic approaches targeting iron homeostasis to modulate immune responses and improve disease outcomes.

Ferroptosis and immunotherapy: Interplay to enhance anti-tumor efficacy. Ferroptosis has been identified as a crucial player in the modulation of immune responses within the tumor microenvironment. Its role in immunotherapy, a treatment modality that leverages the immune system to combat cancer, is becoming increasingly evident. This section will delve into the intricate relationship between ferroptosis and immune responses in detail, emphasizing strategies that exploit iron metabolism to enhance the efficacy of tumor immunotherapy.

Immunogenic cell death and ferroptosis. Ferroptosis shares several characteristics with other forms of immunogenic cell death, such as apoptosis and necroptosis, which can stimulate antitumor immunity. Ferroptotic cells release lipid mediators that serve as ‘find me’ signals, attracting antigen-presenting cells (APCs) and other immune cells to the tumor microenvironment. These lipid mediators, including oxidized phospholipids and eicosanoids, play pivotal roles in modulating immune responses.

For instance, inducible GPX4 depletion in cancer cells triggers the release of eicosanoids, which are involved in the regulation of inflammation and immune responses (92). Conversely, enhancing GPX4 activity through TNF or IL-1 β stimulation can suppress the activation of pro-inflammatory lipid mediators like leukotriene B4 (LTB4), mediated by NF- κ B signaling. Given LTB4's significant role in carcinogenesis, understanding its modulation through ferroptosis is crucial for designing therapeutic strategies.

In addition, lipid peroxidation products released during ferroptosis, such as oxidized phosphatidylethanolamines, have immunomodulatory effects (92). These oxidized lipids can promote the activity of APCs, leading to enhanced phagocytosis and clearance of apoptotic cells. For instance, macrophages preferentially engulf apoptotic cells with peroxidized phosphatidylserine on their outer membranes. Furthermore, ferroptotic cells secrete 1-stearoyl-2-15-HpET E-sn-glycero-3-phosphatidylethanolamine, an ‘eat-me’ signal that activates macrophages for phagocytosis. These findings suggest that the oxidized lipids from ferroptotic cells can modulate immune cell activity, although this hypothesis requires further experimental validation.

Immune cell resistance to ferroptosis. Certain immunosuppressive cells, such as M2-type macrophages, regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), exhibit resistance to ferroptosis by expressing high levels of GPX4 or other protective components. Inducing ferroptosis in these cells can lead to their death and reverse their tumor-promoting functions. Of note, M1 macrophages are more resistant to ferroptosis than M2 macrophages, even in the absence of GPX4. This resistance is attributed to the high expression of inducible nitric oxide synthase and the production of nitric oxide radicals (NO $\cdot$), which can inhibit lipid peroxidation reactions. Thus, ferroptosis inducers can trigger ferroptosis in M2 macrophages or repolarize them to the M1 phenotype, thereby enhancing antitumor effects.

Similarly, Tregs activated by T-cell receptor/CD28 co-stimulation upregulate GPX4 expression, reducing ferroptosis

occurrence. Deletion of the GPX4 gene in Tregs leads to excessive lipid peroxide accumulation and ferroptosis, promoting an antitumor immune response through IL-1 β production and T helper 17 cell activation. MDSCs, on the other hand, rely on lipid transport and metabolism for their function. Polymorphonuclear MDSCs undergo lipid peroxidation via myeloperoxidase and transfer lipids to dendritic cells, inhibiting cross-presentation and promoting tumor growth. MDSCs also accumulate specific lipid species, such as arachidonic acid esterified triglycerides and prostaglandin E2, which confer resistance to ferroptosis (93). Furthermore, MDSCs deplete cystine and cysteine from the extracellular environment, depriving T cells of these essential amino acids needed for activation (94). Unlike antigen-presenting cells, MDSCs do not export cysteine, further limiting its availability to T cells (94). In addition, MDSCs downregulate L-selectin on T cells, disrupting their trafficking patterns and inhibiting activation (95). The p53 pathway also regulates ferroptosis in MDSCs, where increased p53 stability inhibits ROS production and ferroptosis. Due to the special role of immune suppressive cells, represented by MDSCs, in negatively regulating immune responses in cancer and other diseases, it is important to focus on promoting ferroptosis as a starting point to reduce immune escape of tumor cells.

Enhancing tumor immunotherapy through ferroptosis. Recent studies have revealed a novel mechanism by which immune cells exert antitumor effects through promoting ferroptosis in cancer cells. Interferon-gamma (IFN γ) released by CD8 $^{+}$ T cells has a crucial role in this process by downregulating the expression of SLC3A2 and SLC7A11, two subunits of the glutamate-cystine antiporter system xc- (96). This impairs cystine uptake by tumor cells, leading to increased lipid peroxidation and ferroptosis (97). In addition, transforming growth factor (TGF)- β 1 has been shown to sensitize cancer cells to IFN γ -induced ferroptosis by further decreasing system xc-expression (97). The induction of ferroptosis in cancer cells enhances tumor immunogenicity and promotes the activation of immune cells, creating a positive feedback loop (98). These findings suggest that targeting the ferroptosis pathway in combination with immunotherapy could be a promising approach for cancer treatment.

These interactions suggest potential therapeutic strategies to enhance immunotherapy efficacy by modulating ferroptosis. For instance, targeting GPX4 in immunosuppressive cells like Tregs and MDSCs can induce ferroptosis, reversing their tumor-promoting functions and enhancing the immune response. In addition, it is worth noting that leveraging cytokines such as IFN γ and TGF- β 1 to induce ferroptosis in tumor cells can synergize with existing immunotherapies, leading to improved antitumor outcomes. By combining drugs that promote ferroptosis with traditional immune checkpoint inhibitors, the killing efficiency of immune cells against tumor cells can be improved. In addition, given the importance of ferroptosis in the tumor microenvironment, further research on how these signaling pathways specifically function and their differences in different types of cancer will help develop more precise treatment methods. Overall, ferroptosis not only serves as a mechanism of cell death, but also as a strategy for regulating immune responses, demonstrating its broad potential in cancer treatment (Fig. 2).

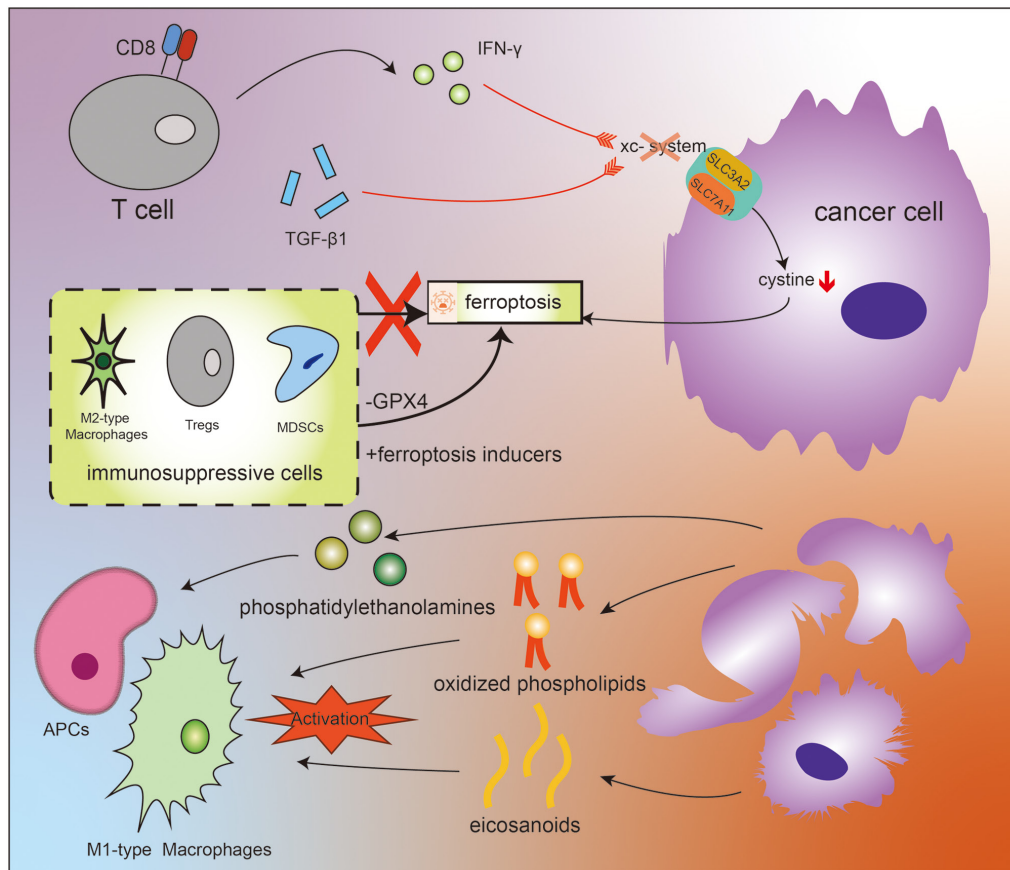


Figure 2. Diagram illustrating the integrated effects of ferroptosis and the tumor microenvironment. CD8⁺ T cells indirectly induce ferroptosis in tumor cells by targeting the xc-system with small molecules. This process is primarily related to the actions of the aforementioned molecules on the two core components, SLC3A2 and SLC7A11, which together directly determine the ability of the xc-system to uptake cystine. Cystine is involved in the crucial lipid peroxidation process associated with ferroptosis. Some immunosuppressive cells' (including M2-type macrophages, Tregs and MDSCs) resistance to ferroptosis can be overcome by certain methods such as reducing GPX4 levels or using ferroptosis inducers. Oxidative lipids resulting from ferroptosis activate APCs, triggering a series of physiological processes, including the activation of macrophage phagocytosis. Among them, various lipid molecules, including oxidized phospholipids and eicosanoids, play a key role in the activation of M1-type macrophages. The fundamental pathways through which they exert their effects are illustrated in this diagram. APCs, antigen-presenting cells; CD8⁺ T cells, CD8 positive T cells; MDSCs, myeloid-derived suppressor cells; GPX4, glutathione peroxidase 4; Tregs, regulatory T cells; xc⁻ system, cystine/glutamate antiporter system; SLC3A2, solute carrier family 3 member 2; SLC7A11, solute carrier family 7 member 11; IFN, interferon; TGF, transforming growth factor.

5. Targeting iron metabolism for cancer treatment

Targeting ferroptosis in cancer therapy. Recent advances in cancer research have highlighted the therapeutic potential of ferroptosis-inducing agents (FINs) (8). These agents, along with various nanomaterials designed to locally induce ferroptosis or enhance the activity of FINs, have shown promise in treating cancer. Ferroptosis has also been recognized to be implicated in the tumor-suppressive effects of conventional cancer therapies such as radiotherapy, chemotherapy, targeted therapy and immunotherapy. By inducing ferroptosis, FINs could enhance the efficacy of these treatments, particularly in cancers with specific characteristics. Ferroptosis represents a significant vulnerability in certain cancer types, making it an attractive target for therapy (8,99). For instance, lung and breast cancer cells are more sensitive to ferroptosis compared to their normal epithelial counterparts, suggesting a therapeutic window for selective ferroptosis induction in tumors while sparing normal tissues. As mentioned earlier, overcoming ferroptosis resistance, which is mediated by various genetic and molecular mechanisms, is another potential strategy.

Disrupting these resistance mechanisms may re-sensitize cancer cells to ferroptosis and enhance the effectiveness of FINs (8).

Combining FINs with conventional therapies is another promising approach. Conventional treatments can trigger ferroptosis, and enhancing this effect with FINs can potentiate their therapeutic efficacy. For instance, radiotherapy induces ferroptosis through multiple mechanisms and combining it with FINs targeting SLC7A11 or GPX4 can radiosensitize cancer cells. Similarly, chemotherapeutic agents like gemcitabine and cisplatin induce GPX4 expression, and inhibiting GPX4 can increase the sensitivity of cancer cells to these drugs. Immunotherapy, when combined with FINs, can also boost ferroptosis induction and overcome resistance to immune checkpoint inhibitors (100).

The integration of ferroptosis induction with conventional therapies offers a comprehensive strategy to combat cancer, particularly in resistant or aggressive tumors. As research progresses, refining these approaches to enhance specificity, efficacy and safety will be crucial in transforming the cancer treatment landscape.

Table II. Tumor immunotherapies targeting iron metabolism that have been initiated or are currently being researched.

Potential therapeutic strategy	Mechanism	Examples	Challenges
Iron chelation	Sequestering iron to deprive cancer cells	DFO, DFP, DFX, Dp44mT, Super-polyphenols	Adaptive resistance, side effects in non-cancerous tissues
Targeting TfR1	Reducing iron uptake by cancer cells	Monoclonal antibodies, siRNA	Variability in TfR1 expression in normal tissues
Inhibition of HIFs	Disrupting hypoxia response and iron retention	YC-1	Optimizing therapeutic potential, understanding systemic impacts
Modulation of hepcidin-ferroportin	Regulating iron export to reduce intracellular iron in cancer cells	<i>Angelica sinensis</i> polysaccharide, anti-hemojuvelin antibodies	Long-term efficacy, systemic effects
Inducing ferroptosis	Promoting iron-dependent cell death via lipid peroxidation	System xc ⁻ inhibitors, GPX4 inhibitors	Identifying specific vulnerabilities, combination with other treatments

TfR1, transferrin receptor 1; HIFs, hypoxia-inducible factors; DFO, deferoxamine; DFP, deferiprone; DFX, deferasirox; System xc⁻, cystine/glutamate antiporter system; Dp44mT, a synthetic iron chelator; YC-1, Lifiquat; GPX4, glutathione peroxidase 4.

Potential future therapeutic strategies. In the realm of cancer therapy, targeting iron metabolism holds considerable promise due to the essential role of iron in tumor growth and survival. Several strategies are being explored, focusing on disrupting iron homeostasis in cancer cells, as well as immunosuppressive cells.

It is the significant role of iron in cancer biology that has prompted the exploration of new therapeutic strategies targeting iron metabolism. This approach aims to exploit the dependency of cancer cells on iron for proliferation and survival, thereby offering promising new avenues for cancer treatment. While challenges exist, such as adaptive resistance and potential side effects, ongoing research and combination approaches may enhance the efficacy and specificity of these treatments, paving the way for more effective cancer therapies. The tumor immunotherapies targeting iron metabolism that have been initiated or are currently under research were elaborated on in this chapter. Although these therapies only provide certain possible ideas and there are still unresolved issues, they fully demonstrate the great application value and broad prospects of iron metabolism-centered treatment (Table II).

Limitations of therapies targeting iron metabolism mechanisms. Despite its significant potential for application, research related to iron metabolism and ferroptosis currently shows limitations that impact the translation of iron metabolism theories into therapies. The mechanisms underlying ferroptosis remain to be fully elucidated and various triggering factors still need further identification, which affects the safety of selectively controlling ferroptosis. For instance, systemic targeting of GPX4 may lead to toxicity, including kidney damage, neurodegeneration and injury to other organs (101). In addition, the diverse and complex effects of iron metabolism on immune cells make clinical outcomes difficult to control. In the future, these issues may be further addressed with the development of more precisely targeted drugs.

6. Conclusion and future perspectives

The complex relationship between iron metabolism and tumor biology is a complex network that significantly impacts tumor progression and the tumor microenvironment. Tumor cells and their associated stromal cells orchestrate the finely tuned regulation of iron uptake, accumulation and homeostasis, which is crucial for their survival and proliferation. Ferroptosis, a form of regulated cell death driven by iron-dependent lipid peroxidation, is a potent tumor-suppressive mechanism. However, cancer cells have developed sophisticated strategies to evade ferroptosis, which poses a challenge to their therapeutic exploitation. The role of iron metabolism in modulating the tumor immune microenvironment adds another layer of intricacy. Iron availability and regulation influence the function of tumor-associated immune cells, affecting immune surveillance and evasion. The relationship between ferroptosis and immune responses creates new avenues for enhancing cancer immunotherapy. By targeting iron metabolism, it is possible to disrupt the protective barriers of tumors and sensitize them to immune-mediated destruction.

Current therapeutic approaches leveraging ferroptosis show promise, yet the full potential of iron metabolism-based strategies remains underexplored. Future research should prioritize several areas, including targeting cancer cells to iron-dependent proteins to ensure their iron supply and conducting further practical research on the iron-mediated death of immunosuppressive proteins. The future of cancer therapy lies in a comprehensive approach that integrates our understanding of iron metabolism and ferroptosis with advanced therapeutic strategies. By unravelling the complexities of iron regulation in tumors and developing innovative treatments, the way may be paved for more effective and personalized cancer therapies. Ongoing research and future discoveries hold the promise of transforming the landscape of cancer treatment, offering hope for improved patient outcomes and long-term survival.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

LFW designed the study, XRB collected the related papers and drafted the manuscript, and LFW and XRB generated the figures and critically reviewed the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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