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Original Article

Targeting ferroptosis for cancer therapy: iron metabolism and anticancer immunity

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Abstract: Ferroptosis is a new form of programmed cell death characterized by iron-dependent accumulation of lipid peroxidation, which plays an important role in cancer biology. Ferroptosis is involved in many biological processes, such as amino acid metabolism, glutathione metabolism, iron metabolism, and lipid metabolism. Iron is an essential trace element in a variety of normal cell processes, such as DNA synthesis and repair, cell respiration, metabolism and signal transduction, etc., and iron metabolism disorder has been considered as one of the metabolic markers of malignant cancer cells. In addition, iron is involved in the regulation of innate and adaptive immune responses, suggesting that targeted regulation of iron metabolism may contribute to anti-tumor immunity and cancer therapy. In this review, the regulatory mechanism of ferroptosis, the interaction between ferroptosis on tumor cell metabolism, and anti-tumor immunity were systematically reviewed. Immunotherapy combined with targeted regulation of iron and iron-dependent regulation of ferroptosis should be the focus of future ferroptosis research.

Keywords: Ferroptosis, cancer, metabolism, lipid peroxidation, anti-tumor immunity

Introduction

The concept of ferroptosis was formally introduced in 2012 [1]. Ferroptosis has been described as an overwhelming mode of cell death triggered by iron-mediated lipid peroxidation. From a biochemical point of view, ferroptosis is characterized by the accumulation of iron-dependent peroxidation that produces lethal levels. Like other cell death patterns, ferroptosis is genetically regulated. Ferroptosis is also accompanied by a range of morphological, biochemical features and is highly associated with multiple intracellular metabolic pathways. Iron metabolism, amino acid metabolism, lipid metabolism, and different metabolic pathways directly affect the occurrence and development of ferroptosis and cells' sensitivity to this cell death.

During the development and progression of cancer, the metabolism within cancer cells undergoes subtle changes. Cancer cells undergo stronger oxidative metabolism, along with increased dependence and demand for iron in cancer tissue. This undoubtedly makes ferroptosis an ideal target for the treatment of cancer [2]. But does not rule out the exclusion of some cancer cells are indeed sensitive to ferroptosis. However, some cell lines have activity against ferroptosis, because the regulation of ferroptosis is highly relevant and sensitive to cellular metabolism. Simultaneously, classical tumor suppressor genes such as P53 [3] have also been found to be involved in the regulation of ferroptosis, which also suggests the complex correlation between ferroptosis and metabolic pathways. At the same time, ferroptosis is also involved in and regulates other processes related to cancer cells, such as mesenchymalization and metastasis of cancer cells and anti-tumor immunity [4]. Those undoubtedly demonstrate the important role of ferroptosis in cancer. In this review, we list various metabolic activities associated with ferroptosis in the hope of providing ideas and inspiration for further understanding and treatment of cancer.

Characteristics of ferroptosis

Ferroptosis is an iron-dependent mode of regulatory cell death caused by the accumulation of reactive oxygen species in lipids. Unlike other cell death modes, such as necrosis, apoptosis, and autophagy, ferroptosis is mainly manifested by pyknosis of mitochondrial membrane, increased membrane density, blurred, reduced, or disappeared mitochondrial crest, and intact nuclear membrane [5]. In the biochemical aspect, increased iron ion level produces a large number of reactive oxygen species (ROS), decreased glutathione peroxidase 4 (GPX4) activity, and accumulation of lipid metabolites [6]. In terms of molecular mechanism, studies have found that nuclear factor-erythroid 2-related factor 2 (NRF2) plays a renal protective role by inhibiting ferroptosis in folate-induced acute kidney injury mice [7, 8].

The mechanism of ferroptosis

Lipid oxidation induces ferroptosis: When the distribution of iron in the body is abnormal, various injuries and diseases will occur. The central role of lipid peroxidation in ferroptosis in driver cells suggests that ferroptosis can be caused by the breakdown of the glutathione (GSH) -glutathione peroxidase 4 (GPX4) antioxidant system [9]. Polyunsaturated fatty acids (PUFAs) are one of the main components of the phospholipid bilayer of cell membranes. They play an important role in maintaining cell membranes' fluidity, but excessive PUFAs can induce ferroptosis. The main mechanism is that Fe2+ oxidizes excess PUFAs to hydroxyl radicals through the Fenton reaction, and these groups also oxidize PUFAs in a chain reaction way, producing a large number of lipid peroxides and inducing ferroptosis of cells [10]. Lipid peroxidation products of the cell membrane are sources of ROS production, and a large accumulation of lipid ROS will directly trigger ferroptosis, a process that can be prevented by lipophilic antioxidants and iron chelators (**Table 1**).

Antioxidant defense resists ferroptosis: ROS produced by oxidative stress can directly or indirectly damage intracellular macromolecules' physiological functions such as proteins, lipids, and nucleic acids, which is the pathophysiological basis of many diseases. Nrf2 is a key factor in the oxidative stress response of cells and controls the cellular antioxidant system in cancer cells [11]. By regulating Keap1 (Kelch Like ECH Associated Protein 1)-Nrf2 through reaction with antioxidant components (antioxidant response element) interaction, regulating antioxidants' expression and phase alexipharmic alcohol [12-14]. Clinically, cancer and other chronic diseases involved in oxidative and inflammatory stress can be prevented by enhancing the activity of NRF2 [15]. Recent studies have identified the antioxidant enzyme Dehydrogenase (DHODH) localized in mitochondria, which acts independently of FSP1 and GPX4 to resist ferroptosis [16]. It resists ferroptosis by promoting the production of CoQ10.

Unbalanced iron induces ferroptosis

Iron is essential in the accumulation of lipid peroxide and the execution of ferroptosis. Therefore, the amount of intracellular iron affects the sensitivity to ferroptosis. It is well known that intracellular iron metabolism and iron homeostasis are in a state of dynamic equilibrium. The body maintains iron intake, storage, and outflow processes through a complex regulatory network [17]. Transferrin receptor (TFR) and divalent metal-ion transporter-1 (DMT1) regulate extracellular iron intake, while ferroportin (FPN), on the other hand, transfers excess iron from intracellular to extracellular in order to maintain iron homeostasis in the cell [18, 19]. In the periphery, transferrin (Trf) has a high affinity with ferric iron (Fe3+), and one Trf molecule can transport 2 Fe3+. Trf transfers Fe3+ to the TFR1 of the cell membrane and then forms Trf- [Fe3+] 2-TFR complex on the on the surface of cell membrane [20]. Basuli et al. [21] showed that this process could be significantly up-regulated in ovarian cancer, breast cancer, and other cancers. Studies have shown that iron transporter proteins (FER-) are found in a variety of cancer cells down-regulation of FPN and up-regulation of TFR1 make cancer cells have a higher demand for iron than non-cancer cells, and such "iron addiction" makes cancer cells more susceptible to the impact of iron overload and ROS accumulation [22-24].

Lipid metabolism associate with ferroptosis

Lipid metabolism is closely related to the sensitivity of cells to ferroptosis. Polyunsaturated fatty acids are a double-edged sword, and their peroxidation may also cause damage to cells. It can be integrated into the membrane by Acyl-CoA Synthetase Long Chain Family Member 4

Table 1. The inducers and inhibitors of ferroptosis

	Reagents	Target/Funtion	Mechamism	Reference
Inducers	Erastin	System xc-	prevents cystine import, causes GSH depletion	[1]
	IKE	System xc-	prevents cystine import, causes GSH depletion	[97]
	Glutamate	System xc-	high extracellular glutamate leads to prevent cystine import, causes GSH depletion	[98]
	IFNG/IFNγ	System xc-	Down-regulates the expression of SLC3A2 and SLC7A11, two subunits of system xc-	[76]
	Sorafenib	System xc-	Inhibits system xc- in a non-enzymatic target-dependent manner	[99]
	Sulfasalazine	System xc-	Inhibition of nuclear factor κB signaling pathway; inhibition of xc-transporter	[99]
	FIN56	GPX4	Cause GPX4 depletion	[100]
	FINO2	GPX4	Inactive GPX4 and oxidizes iron	[101]
	Altretamine	GPX4	Inhibits GPX4 activity, causes ROS accumulation	[102]
	JKE-1674/1716	GPX4	Inhibits GPX4 activity, causes ROS accumulation	[103]
	ML162	GPX4	Inhibits GPX4 activity, causes ROS accumulation	[28]
	ML210	GPX4	Inhibits GPX4 activity, causes ROS accumulation	[104]
	RSL3	GPX4	Inhibits GPX4 activity, causes ROS accumulation	[28]
	Artemisinin	Organic peroxides	ROS manufacturing, disruption of antioxidant defenses by downregulates of GPX4 and GSH causes an imbalance in intracellular oxidative responses	[105]
	Artesunate	Organic peroxides	Causes rapid ROS accumulation	[106]
	Salinomycin	Ferritinophagy	Increases intracellular iron, causes peroxidation by activating ferritinophagy	[107]
	Ironomycin	Ferritinophagy	Increases intracellular iron, causes peroxidation by activating ferritinophagy	[108]
	iFSP1	FSP1	Inhibit FSP1 activity, cause the accumulation of lipid peroxidation	[109]
	BSO	GCLC	Induces GSH depletion	[110]
	Doxorubicin	HO-1	Induces iron overload	[111]
Inhibitors	CoQ10	Antioxidant/RTA	Prevents lipid peroxidation by the FSP1-catalyzed ubiquinol form	[100]
	Fer-1	Antioxidant/RTA	Prevents the accumulation of ROS by reducing activity	[1]
	Lip-1	Antioxidant/RTA	Inhibits lipid peroxidation directly	[112]
	Vitamin E	Antioxidant/RTA	Inhibits lipid peroxidation directly	[113]
	NAC	Antioxidant/RTA	Suppresses ferroptosis through supplementing GSH	[28]
	Ciclopirox	Iron chelator	Reduces intracellular free iron	[1]
	Deferiprone	Iron chelator	Reduces intracellular free iron	[114]
	Deferoxamine	Iron chelator	Reduces intracellular free iron	[1]
	Dexrazoxane	Iron chelator	Reduces intracellular free iron	[115]
	Baicalein	ALOXs	Reduces ROS by inhibits ALOXs, and stabilizes GPX4 to protect cells from excessive lipid peroxidation	[116]
	AA-861	ALOXs	Inhibits lipid ALOXs-mediated peroxidation	[117]
	CDC	ALOXs	Inhibits lipid ALOXs-mediated peroxidation	[117]
	Triacsin C	ACSL4	Prevents the transfer process of PUFA to the cell membrane, inhibits lipid ACSL4-mediated peroxidation	[118]
	Troglitazone	ACSL4	Prevents the transfer process of PUFA to the cell membrane, inhibits lipid ACSL4-mediated peroxidation	[119]
	Rosiglitazone	ACSL4	Prevents the transfer process of PUFA to the cell membrane, inhibits lipid ACSL4-mediated peroxidation	[118]
	DPI	NOXs	Inhibit lipid NOXs-mediated peroxidation	[120]
	TMZ	System xc-	Induces system xc-expression	[121]
	KI-696	Keap1	Binds to Keap1 and prevents it from mediating NRF2 degradation	[122]
	Lactate	HCAR1/MCT1	Promotes PUFAs production	[123]
	MUFAs	Lipid	Block PUFA peroxidation	[124]

(ACSK4) and lysophosphatidyl-choline acyltransferase 3 (LPCAT3) [25]. The oxidation of PUFA can be done either by a non-enzymatic free radical chain reaction or enzymatic catalysis. Taking AA as an example [26], ACSL4 catalyzed the linking of CoA to AA to form the intermediate of CoA-AA, which LPCAT3 esterified to form phosphatidylethanolamine (PE-AA) to form arachidonic acid-phosphatidylethanolamine (PE-AA). The resulting PE-AA can be oxidized by LOX in the presence of enzymes or by autooxidation in non-enzymes to form PE-AA-OOH, both of which eventually lead to cell death.

During ferroptosis, the accumulation of lipid peroxides, especially phospholipid peroxides, is considered a symbolic event of ferroptosis [27]. At present, it is generally believed that the ultimate actor of ferroptosis is lipid peroxides, and when excessive accumulation of lipid peroxides causes plasma membrane damage, eventually leading to the occurrence of ferroptosis in cells [10]. Inhibition of GPX4 from a genetic or pharmacological perspective leads to ferroptosis even when cysteine/cysteine supplies are sufficient in cells [5, 28]. Studies have shown that lipid peroxides cause cell damage in various ways [29, 30]. One is the further decomposition of lipid peroxides into ROS, which further amplifies the lipid peroxidation process. The other is by changing the physical structure of the membrane, such as the thickness and bending degree of the membrane, or by forming holes in the membrane to release harmful substances and disrupt the metabolism in the cell; Third, the byproducts (aldehydes) produced in the process of lipid peroxidation can cause cell damages, such as MDA and 4-HNE.

Amino acid metabolism associate with ferroptosis

Amino acid metabolism is closely related to the regulation of ferroptosis [31]. The entry and exit of amino acids into and out of the cell require specific transporters, cystine/glutamate antiporter System Xc-. The XC - system is a Na - independent reverse transporter that outputs intracellular glutamate and extracellular cystine in a 1:1 ratio [32, 33]. Consisting of two subunits connected by a disulfide bond, including member 2 of the heavy chain subunit solute carrier family 3 member 2 (SLC3A2; CD98 or 4F2HC) and light chain subunit solute carrier family 7 member 11 (SLC7A11; Also commonly referred to as XCT). SLC7A11 is a multichannel transmembrane protein that mediates cystine/glutamate antiporter activity in the XC - system [34, 35]. SLC3A2 is the chaperone protein that maintains SLC7A11 protein stability and proper membrane localization [36]. Inhibition of the imbalance in amino acid metabolism caused by SystemXC - causes ferroptosis, and glutamate itself can affect the function of SystemXC -. As a substrate of GPX4, GSH participates in the intracellular antioxidant system and is a key factor affecting the occurrence of ferroptosis [37] (**Table 2**).

Moreover, GSH synthesis is closely related to the metabolism of amino acids. Besides, indole-3-acetone hydrochloride (I3P) inhibits ferroptosis by directly scavenging free radicals and activating antioxidant gene expression programs. Therefore, interleukin-4-inducible 1 (IL4I1) is likely mediated by a local iron-promoting pathway in the metabolism of aromatic amino acids, suggesting that IL4I inhibitors may regulate the death pathway tumor cells [38].

Glutamate and glutamine are important regulators of ferroptosis [23]. Extracellular high concentrations of glutamate can inhibit cystine uptake by inhibiting the activity of SystemXC -, resulting in ferroptosis [18, 39]. Notably, outside the cell, reduced glutamate levels protected SystemXC - knockout mice from neurotoxic damage [40]. Therefore, the accumulation of extracellular glutamate may serve as a natural trigger for inducing ferroptosis in the physiological environment. Because ferroptosis is considered an associated cell death [41, 42] mechanism in tissue damage, glutaminolysis targeted therapy may effectively treat organ damage mediated by ferroptosis. In fact, in experimental models, inhibition of glutamine breakdown has been shown to reduce heart and kidney injury and cerebral hemorrhage due to ischemia/reperfusion [23, 42, 43].

Other metabolic pathways associate with ferroptosis

In addition to iron metabolism, lipid metabolism, and amino acid metabolism, factors including Ferropsor suppressor protein 1 (FSP1), NRF2, heat shock proteins (HSPs) also regulate ferroptosis.

In 2019, Conrad and Olzmann et al. respective found a new ferroptosis inhibitory protein 1 (FSP1, previously known as mitochondrial apoptosis-inducing factor 2, AIFM2) almost at the same time [44, 45]. FSP1 can be used as a biomarker of ferroptosis resistance in a variety of cancer cells. It has NADPH-dependent coenzyme Q oxidoreductase function and can catalyze the regeneration of CoQ10 by NAD(P)H, while CoQ10 can inhibit peroxidation and prevent ferroptosis [46]. The FSP1-CoQ10-NAD(P)H pathway is an independent system that acts synergistically with GPX4 and glutathione to inhibit phospholipid peroxidation and ferroptosis KEAP1-Nrf2-ARE signaling pathway forms a complex oxidative stress response system, and Nrf2 plays a regulatory role in intracellular Fe2+ [6]. Under normal conditions, Nrf2 is inactive,

Table 2. Genes involved in ferroptosis

	Gene	Name	Funtion	Ref.
Antioxidant defense	GPX4	glutathione peroxidase 4	Reduces lipid ROS with the aid of GSH	[1]
	FSP1	ferroptosis suppressor protein 1	Reduces lipid peroxidation mediated by ubiquinone (CoQ10)	[109, 125]
	GCH1	GTP Cyclohydrolase 1	Prevents lipid peroxidation by its metabolic derivatives BH4/BH2	[126]
	FANCD2	Fanconi anemia complementation group D2	Regulats ferroptosis by affacting GPX4 expression	[127]
Peroxidation	ALOXs	lipoxygenases	Directly mediates lipid oxidation	[128]
	DPP4	dipeptidyl peptidase 4	Assists NOXs-mediated oxidation reaction	[129]
	NOXs	NADPH oxidases	Transfers electrons through the biofilm and reduces oxygen to superoxide, thus enabling the accumulation of ROS	[1]
	POR	NADPH-cytochrome P450 reductase	Promotes lipid peroxidation by Catalyzing the Production of H2O2	[130]
	CyB5R1	NADH-cytochrome b5 reductase	Promotes lipid peroxidation by Catalyzing the Production of H2O2	[130]
Iron metabolism	ELAVL1	embryonic lethal, abnormal vision, Drosophila-like 1	Selectively active ferrotinophagy as an RNA binding protein	[131]
	ZFP36	zinc-finger protein 36	Selectively inactive ferrotinophagy as an RNA binding protein	[132]
	FTMT	mitochondrial ferritin	Stores free iron in mitochondria	[133]
	Prominin2	Prominin2	Mediates iron ion export by the exocytic form	[134]
	HO-1	heme oxygenase-1	Elevates intracellular free iron levels by promoting heme degradation	[135]
	SLC39A14	solute carrier family 39 member 14	Sensitizes cells to ferroptosis by mediating the transport of NTBI	[136]
	SLC11A2	solute carrier family 11 member 2	Sensitizes cells to ferroptosis by mediating the transport of NTBI	[136]
	SLC39A8	solute carrier family 39 member 8	Sensitizes cells to ferroptosis by mediating the transport of NTBI	[136]
	SLC40A1	solute carrier family 40 member 1	Sensitizes cells to ferroptosis by mediating the transport of NTBI	[136]
	Trf	transferrin	Extracellularly binds iron	[137]
	TfR	transferrin receptor	Mediates Transferrin bound iron import	[138]
	CISD1	CDGSH iron sulfur domain 1	Increases iron-mediated intramitochondrial lipid peroxidation	[139]
	HSPB1	heat shock protein beta-1	Inhibits of ferroptosis by affecting iron metabolism	[140]
	NFS1	l-cysteine desulfurase	Inhibits ferroptosis by maintaining iron-sulfur cofactor stability	[141]
Lipid metabolism	LPCAT3	lysophosphatidyl-choline acyltransferase 3	Involves in key steps of PUFA synthesis	[25, 128]
	ACSL4	Long-chain acyl-CoA synthetase-4	Mediates PUFA insertion into cell membranes	[118]
	AMPK	AMP-activated protein kinase	Energy stress-mediated regulation of PUFA synthesis	[142]
	ELOVL5	elongation of very longchain fatty acid protein 5	Affects the synthesis of PUFAs necessary for ferroptosis	[143]
	FADS1	fatty acid desaturase 1	Affects the synthesis of PUFAs necessary for ferroptosis	[143]
	PPARα	peroxisome proliferator-activated receptor α	Regulates intracellular lipid homeostasis	[144]
	ACSL3	Long-chain acyl-CoA synthetase-3	Mediates MUFA insertion into cell membranes	[124]
	SCD1	Stearyl-coenzyme A desaturase 1	Prevents ferroptosis by modulating ACSL4 activity	[123]
	RAB7A	member RAS oncogene family 7	Regulates lipophagy	[145]
Amino acid metabolism	SLC7A11	solute carrier family 7 member 11	Transports cysteine by composing the system xc-	[34]
	SLC3A2	solute carrier family 3 member 2	Transports cysteine by composing the system xc-	[34]
	mTORC1	mechanistic tar-get of rapamycin complex 1	Promotes degradation of SLC7A11 in lysosomes	[146]
	mTORC2	mechanistic target of rapamycin complex2	Inhibits the activity of the SLC7A11 transporter by phosphorylating serine 26 of SLC7A11	[147]
	CD44v	CD44 variant	Stabilizes system xc- activity	[148, 149]

	GCLC	glutamylcysteine ligase	Involves in the synthesis of GSH, but also has unconventional anti-ferroptosis activity	[150, 151]
	CBS	Corticobasal Syndrome	Participates in the rate-limiting step of the transsulfuration pathway	[152]
	CGL	coagulation	prevents cellular ferroptosis when cysteine acquisition is limited	[152]
	SLC38A1	solute carrier family 38 member 1	Mediates glutamate import and sensitizes ferroptosis	[153-155]
	SLC1A5	solute carrier family 1 member 5	Mediates glutamate import and sensitizes ferroptosis	[153-155]
	BECN1	Beclin 1	Directly binds to system xc - and blocks its activity	[156]
	GLS2	glutaminase 2	Prevents ferroptosis by mediating the degradation of glutamate	[153]
Other metabolic pathways	ACSF2	acyl-CoA synthetase family member 2	Regulates mitochondria-associated lipid metabolism	[1]
	VDAC2	voltage-dependent Anion Channel2	Iron transporter on mitochondria, affects iron availability	[157]
	FXN	Frataxin	Affects the availability of iron as well as some antioxidant enzyme activities by controlling the synthesis of iron-sulfur clusters	[158]
	NFE2L2	nuclear factor erythroid synthase 2	Affects ferroptosis by affecting the expression of a variety of ferroptosis-associated proteins	[159]
	TP53	tumor protein 53	Affects ferroptosis by affecting the expression of a variety of ferroptosis-associated proteins	[160]
	YAP	Yes-associated protein	Regulates lipid metabolism in the presence of high cell density	[68, 161, 162]

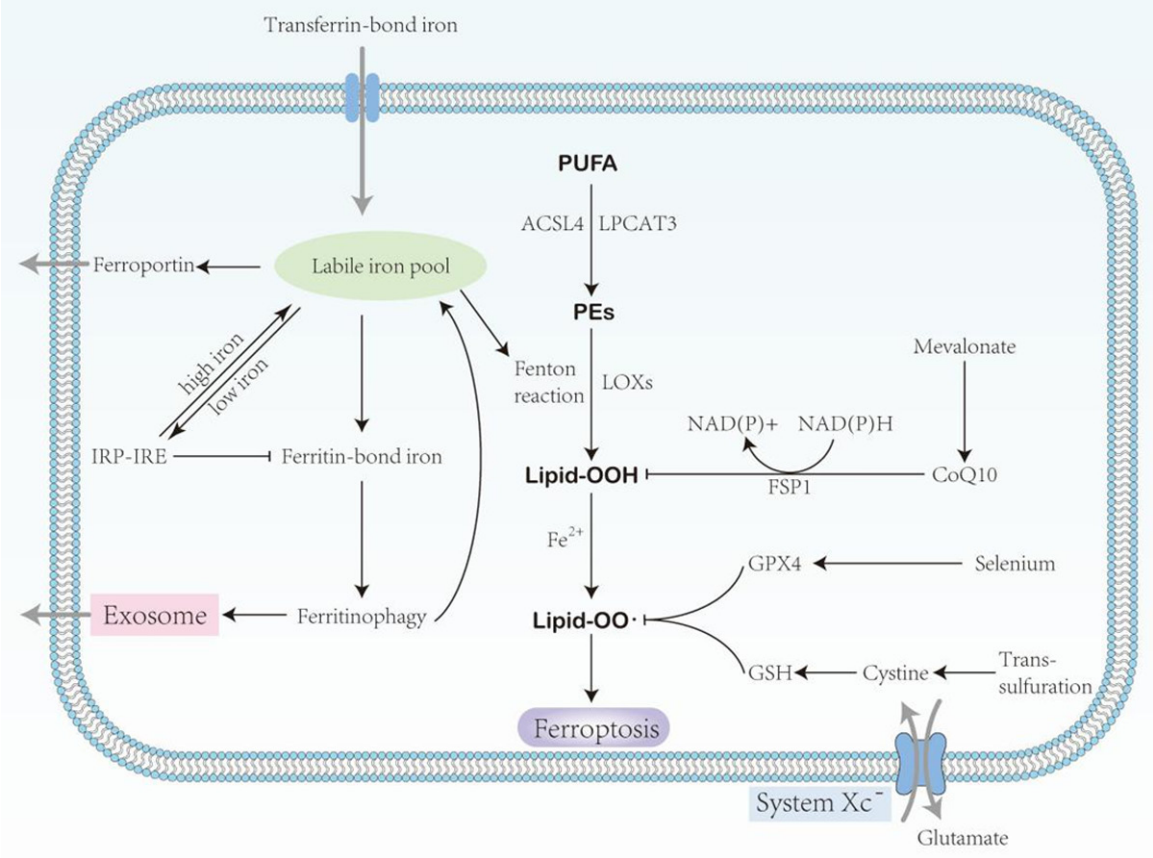

Figure 1. Schematic description of the signaling pathway of ferroptosis. polyunsaturated fatty acids (PUFA); Acyl-CoA synthetase long-chain family member 4 (ACSL4); lysophosphatidylcholine acyltransferase 3 (LPCAT3); phosphatidylethano- lamines (PEs); ferroptosis suppressor protein 1 (FSP1); lipoxygenases (LOXs); glutathione peroxidase 4 (GPX4); Glutathione (GSH).

and when exposed to electrophile reagents or reactive oxygen species, it can induce a series of protective proteins to inhibit ferroptosis [47].

Heat shock protein B1 (HSPB1) is also a regulator closely related to ferroptosis [48]. Overexpression of HSP is induced under stress conditions such as heat shock, pH shift, and hypoxia [49]. Phosphorylated HSPB1 inhibits ferroptosis by reducing cellular iron uptake and lipid ROS production. Therefore, inhibition of HSPB1 expression or phosphorylation can increase ferroptosis mediated by Erastin, providing a new research direction for cancer cells to avoid ferroptosis [48].

The interaction between ferroptosis and tumor metabolism

The metabolic specificity of tumor cells confers their particular relationship to ferroptosis. Nowadays, it has been proved that ferroptosis plays an important role in oncogenes and tumor suppressor genes, as well as tumor migration and invasion, tumor microenvironment and immunity. Elucidating the relationship between ferroptosis and these neoplastic events could help to develop better targeted ferroptosis treatment strategies.

Tumor suppressor genes

P53 has been a recognized tumor suppressor since its discovery [47], and it plays an important role in tumor metabolism [50, 51]. In 2015, Jiang et al. linked p53 with ferroptosis for the first time [52], indicating that p53 can inhibit SLC7A11 transcription and thus inhibit SystemXC - to absorb cystine (**Figure 1**), thereby regulating ferroptosis and playing a key role in tumor inhibition. In addition to SLC7A11, some p53 target genes, such as Spermidine/Spermine N1-acetyltransferase 1 (SAT1), prostaglandin peroxidase synthase 2 (PTGS2) and

Glutaminase 2 (GLS2) can promote ferroptosis in cells [23, 28, 53]. Coding mutant p53 protein accumulation within the tumor cells promotes oncogenes' function or promotes different cell proliferation. The wild-type p53 can suppress abnormal cell proliferation by regulating cell cycle arrest, thus promoting tumor occurrence and development [54, 55]. P53 known effects on cell metabolism are complex, involving multiple control nodes [56], through the transcription or transcriptional regulation, activity in various metabolic pathways, such as glycolysis, mitochondrial oxidative phosphorylation, etc. P53 also controls the cancer cells to the fitness of nutrients and oxygen condition. This is the key to survival under metabolically impaired conditions formed in the tumor microenvironment [57].

EMT

EMT refers to the transformation of epithelial cells into mesenchymal cells under certain physiological and pathological conditions. Ferroptosis is known to be sensitive to epithelial-mesenchymal transition (EMT) cells [58]. Studies have confirmed that transcription factors (such as Snail [59-62], Twist [63-65], ZEB [66], etc.) and microRNAs [67] play an important role in EMT. Activation of transcription factors such as YAP1 and WWTR1 (also known as TAZ), which are involved in the Hippo pathway, promotes ferroptosis during growth by regulating ferroptosis-related expression factors as ACSL4, TFRC, EMP1, and AngPTL4 [68]. Viswanathan et al. [69] found that anti-therapy cancer cells undergoing epithelial-mesenchymal transformation (EMT) are more likely to be killed by ferroptosis inducers than non-drug-resistant cancer cells [70-72], which may serve as a starting point for the application of ferroptosis in tumor metabolism. Importantly, through the study of EMT related experimental results, the exaggerated expression in breast cancer cells significantly lower iron deprivation of Fpn get the transfer capacity of EMT marker expression and damaged [73], but Mangmang CSO and others [58] found - SS - Cy7 - Hex/SPION SRFN compound self-assembly mediated ferritin acid, can resist EMT during breast cancer drug resistance, more aggressive and metastasis. Cell adhesion promoters, such as integrin subunits α6 and β4, also protect breast cancer-derived cells from ferroptosis *in vitro* [74]. Meanwhile, Peng Chen et al. [75] found that β-element combined with cetuximab can inhibit the migration of KRAS mutant CRC cells by inhibiting EMT and inhibiting the growth of KRAS mutant tumor, which provides a new treatment strategy for CRC patients with RAS mutation. In conclusion, EMT plays a key role in the mechanism of ferroptosis in tumor metabolism (**Figure 2**), but its potential value is unclear.

Ferroptosis and tumor immunity

Current studies have confirmed that ferroptosis plays an important role in cancer immunity. Ferroptosis, as a mode of cell death, is triggered by immune cells as a target. IFNγ released by CD8+ T cells [76] and TGFβ1 released by macrophages [77] can induce ferroptosis in cancer cells by reducing the expression of ferroptosis-related inhibitory proteins. The method of constructing nanoplatforms, such as oxygen-enhanced photodynamic therapy with a nanoplatform of Ferro hemoglobin, successfully induced IFNγ release from T cells, which sensitized cancer cells ferroptosis [78]. The "eat me" signal is an important way for cells to be recognized and remove [79]. Recent studies have found that peroxides produced by ferroptosis on cell membranes can act as "eat me" signals recognized by the immune system and thus removed [80]. This also demonstrates that ferroptosis regulates tumor immunity through peroxidation products. Therefore, it is argued that oxidases like ALOX act as triggers of ferroptosis and modulate immune signaling. Notably, the reduction of GPX4 inhibited the release of proinflammatory mediators such as HETE, LTB4, and thus the oncogenic process [81]. Also, oxidized phospholipids catalyzed by ALOXs can modulate immunity by promoting DC maturation and differentiation of helper T cells [82]. Besides, oxidolipids and lipid droplets are also involved in the regulation of antitumor immune responses. In the tumor microenvironment, dendritic cells accumulate a large amount of peroxidation, leading to antitumor immunodeficiency [83]. Lipid species of the external environment can also affect cancer migration through ferroptosis, and the lymphatic system protects melanoma cells from iron ptosis by increasing ACSL3-dependent MUFAs production, thereby promoting tumor metastasis [84].

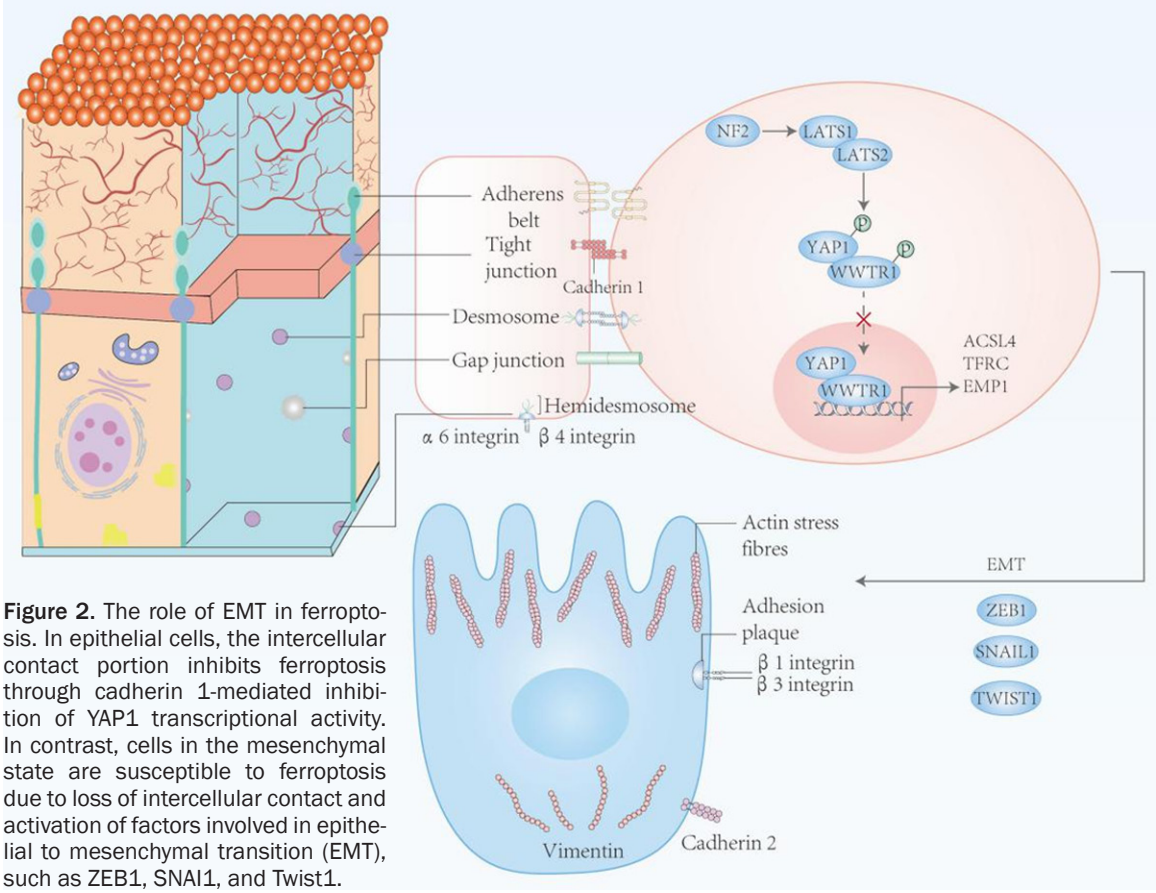

Figure 2. The role of EMT in ferroptosis. In epithelial cells, the intercellular contact portion inhibits ferroptosis through cadherin 1-mediated inhibition of YAP1 transcriptional activity. In contrast, cells in the mesenchymal state are susceptible to ferroptosis due to loss of intercellular contact and activation of factors involved in epithelial to mesenchymal transition (EMT), such as ZEB1, SNAI1, and Twist1.

In addition to peroxidation, damage-associated molecular patterns (DAMPs) of ferroptosis release can modulate immune progression. There has been controversy as to whether ferroptosis is immunogenic. Luliia et al. found that ferroptosis released ATP and HMGB1 in a time-dependent manner and demonstrated that ferroptosis is immunogenic both in vitro and in vivo [85]. The release of DAMPs mediates immunogenic cells' death and inflammatory responses that promote tumor growth [86, 87]. HMGB1, as a member of DAMPs, is released by iron-dead cancer cells and promotes their inflammatory reaction by binding to AGER of macrophages. There is evidence that induction of ferroptosis in cancer cells increases the release of PGE2, an important immunomodulator. And this process may be negatively correlated with GPX4 activity. PGE2, on the one hand, blunts the function of CDC1-type cells and prevents the infiltration of CDC1 cells [88] into the immune microenvironment by NK [89] cells. Besides, PGE2 is active in T cells. Although further studies are needed regarding the downstream signaling of PGE2, it has been demonstrated that PGE2 impairs tumor immune function by acting on the innate immune system. Since the formation of PGE2 is negatively correlated with GPX4 activity, it can be speculated that iron-death-sensitive cell lines can more easily release PGE2 and ensure tumor development by means. It has been shown that PGE2 is released from tumors and neighboring cells during chemotherapy cycles, which is essential for tumor repropagation of cancer stem cells [90].

In recent years, immune checkpoint inhibitors (ICIs) have made effective progress in cancer treatment. Among them, the anti-PD-L1 antibody can promote ferroptosis in cancer cells. The phenomena of ferroptosis induced by ICIs is very similar to cancer cell killed by cytotoxic T cells and macrophages mentioned above. For example, interferon γ released by T cells activates the JAK-STAT1 pathway and downregulates the expression of SLC7A11 and SLC3A2, which leads to the development of ferroptosis in cancer cells. Reduced SLC3A2 names in melanoma patients are consistently associat-

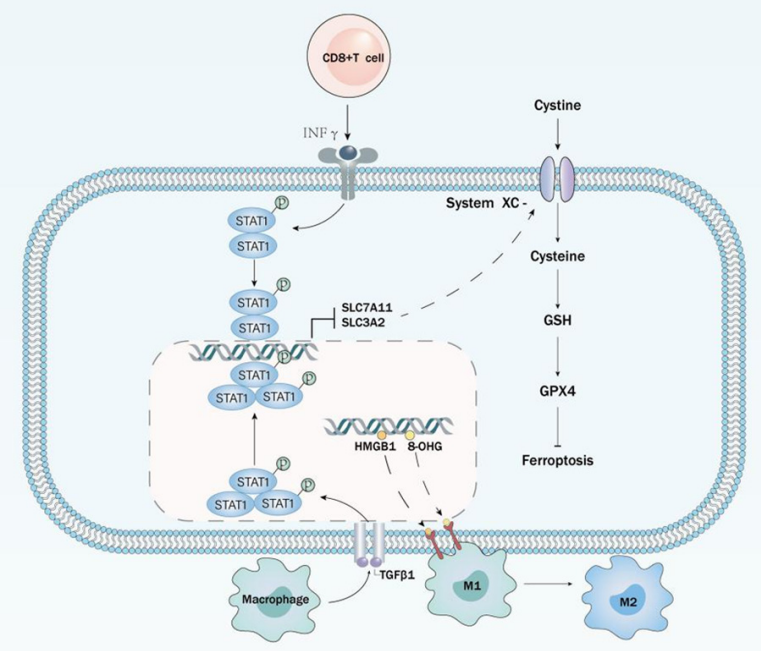

Figure 3. The link between cancer and immunity. Immune cells regulate the ferroptosis sensitivity of cancer cells on the one hand. CD8+T cells and macrophages affect the expression of ferroptosis-related genes in cancer cells by secreting INFγ and TGFβ1, respectively, sensitizing ferroptosis. On the other hand, DAMPs released from iron-dead cells result in M2 polarization of macrophages, leading to immune remodeling.

ed with enhanced response to ICIs [7]. It can be speculated that the immune checkpoint PD-L1 also palys a role in reducing ferroptosis. But whether anti-PD-L1 antibodies enhance the progress of ferroptosis only remains to be determined because multiple ligands activate the JAK-STAT pathway.

Ferroptosis also acts on immune cells and plays a role in regulating tumor immunity [91]. It was found that CD4+ T cells and CD8+ T cells lacking GPX4 underwent ferroptosis with the rapid accumulation of ROS. This undoubtedly prevents the expansion of T cells, rendering them incompetent for immune activity [92]. In contrast, overexpression of FSP1 and GPX4 in immune cells ensured CD8+ T cells' immune activity. Interestingly, knockdown of ACSL4, while sparing CD8+ T cells from ferroptosis, impaired their immune activity [93]. There are few studies on B cells, but it has been demonstrated that B cells have a constant sensitivity to ferroptosis [94]. GPX4 activity is unnecessary in the process by which some types of B cells remain immunocompetent. Similar to B cells, M1 and M2 macrophages also have different sensitivities to ferroptosis (**Figure 3**). In contrast, M1-type cells are more susceptible to induction of ferroptosis, this process regulated by cellular Inos [103]. In addition, ferroptosis pancreatic cancer cells release KRAS-G12D and can be taken up by macrophages, leading to M2 polarization that promotes the tumor phenotype [95]. This strongly demonstrates that ferroptosis can be a promising target to drive immune reprogramming [96]. Existing studies have demonstrated the importance of regulating immune cells in tumor immunity, but the mechanisms regulating ferroptosis in immune cells still need further investigation.

Conclusion and perspective

As a new type of cell death, ferroptosis is highly closely related to cell metabolism. The metabolic reprogramming of cancer cells, as well as the tumor microenvironment, gives cancer cells different responsiveness from normal tissue cells to ferroptosis. Recent studies have shown that ferroptosis can provide a new research direction for inducing targeted removal of tumor cells and overcoming tumor drug resistance [163, 164]. In radiation therapy, induction of ferroptosis can greatly reduce tumor resistance to radiation; while in immunotherapy, the immunogenicity of ferroptosis has been confirmed, and cancer cell ferroptosis is one of the outcomes of cells performing immune killing. However, more clinical studies are needed to prove the value of inducing ferroptosis for existing clinical treatment modalities. At the same time, although the upstream metabolism and signaling pathways of ferroptosis have been explored, it is still inconclusive what the final effector downstream of ferroptosis is, and it is not certain that peroxidation directly leads to ferroptosis. In future studies, it will become the general trend to further elucidate the effector mechanism of ferroptosis, as well as the application of ferroptosis in clinical treatment.

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Disclosure of conflict of interest

None.

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