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Ferroptosis: insight into the treatment of hepatocellular carcinoma

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Abstract
Hepatocellular carcinoma (HCC) is one of the most common malignances in the world, with high morbidity and mortality. Due to the hidden onset of symptoms, there are huge obstacles in early diagnosis, recurrence, metastasis and drug resistance. Although great strides have been made in the treatment of HCC, effective treatment options are still limited and achieving longer survival for patients remains urgent. Ferroptosis is a novel type of programmed cell death that is mainly caused by iron-dependent oxidative damage. With further investigations, ferroptosis has been proved to be associated with the occurrence and development of various tumors. This article reviews the regulatory mechanism and signal transduction pathways of ferroptosis, investigates the complex relationship between autophagy, sorafenib resistance and immunotherapy with ferroptosis involved in HCC, providing new ideas and directions for the treatment of HCC.

Keywords Ferroptosis, Hepatocellular carcinoma, Autophagy, Sorafenib, Tumor immune microenvironment

Introduction

With the development of aging population, urbanization and industrialization, the incidence of cancer is increasing year by year. GLOBOCAN revealed that primary liver cancer was the sixth most common cancer and the third leading cause of cancer death worldwide in 2020, with about 906,000 new cases and 830,000 deaths [1]. Among primary liver cancers, hepatocellular carcinoma (HCC) is the most common type, accounting for 75–85% of cases [2]. The selection of treatment methods for HCC is related to clinical and pathological stage, liver resection (LR), transarterial chemoembolization (TACE), transarterial radioembolization (TARE), chemotherapy and radiotherapy are commonly used as treatment methods, in addition to liver transplantation (LT) [3]. HCC is a stealthy adversary, often beginning with a subtle onset but advancing swiftly,, which brings great challenges to people in terms of early diagnosis, recurrence, metastasis and drug resistance.

In recent years, with the emergence of the concept of "ferroptosis" [4], and the intensification of its research, ferroptosis has been expected to provide innovative approaches for cancer treatment. Ferroptosis is a novel type of programmed cell death, which can be induced by Erastin and RSL3, and is mainly caused by iron-dependent oxidative damage, distinguished from other cell death mechanisms including apoptosis, pyroptosis, autophagy and programmed necrosis [5]. When ferroptosis occurs, cellular integrity is compromised as the cell membrane disintegrates. It can be observed under an electron microscope that the mitochondria undergoing a reduction in size and an increase in the density of their double membranes, the mitochondrial cristae may diminish or vanish entirely, and the outer membrane may

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exhibit signs of shrinkage and fracturing [6]. Studies have confirmed the pivotal regulatory influence of ferroptosis in the genesis and progression of various malignancies, such as HCC, pancreatic cancer, breast cancer, prostate cancer [7–10], and it also associated with tumor recurrence and chemotherapy resistance [11, 12].

This article reviews the regulatory mechanism and research advancements of ferroptosis in HCC, aiming at enhancing our comprehension of the underlying mechanisms of tumorigenesis and progression, thereby offering novel perspectives for the clinical management of HCC in the future (Fig. 1).

Key regulatory pathways and factors

Studies have shown that in the regulatory pathway of ferroptosis in HCC, including a spectrum of tumor-associated genes, non-coding RNAs and other factors can exert rich and diverse effects on the progression of HCC.

System Xc^- pathway

System Xc^- is a cystine/glutamate antiporter situated on the cell membrane, responsible for the exchange of glutamate out of the extracellular and cystine into the intracellular in a ratio of 1:1. Cystine is formed by an enzymatic reaction to cysteine, which is then further reacted to synthesize glutathione (GSH) [13]. GSH serves as a vital antioxidant and free radical scavenger in the body, and peroxidase can reduce lipid peroxidation and reactive oxygen species (ROS) within cells [14]. System Xc^- mainly consists of the light chain of SLC7A11 and the heavy chain of SLC3A2 in the solute carrier family, of which SLC7A11 has been found to be overexpressed in a variety of human cancers [15], and several regulatory factors in the system Xc^- pathway that cause ferroptosis in HCC are also found to be related to SLC7A11. Furthermore, activating transcription factor 4 (ATF4) and nuclear factor erythroid 2-related factor 2 (NRF2) are two major transcription factors that mediate stress-induced

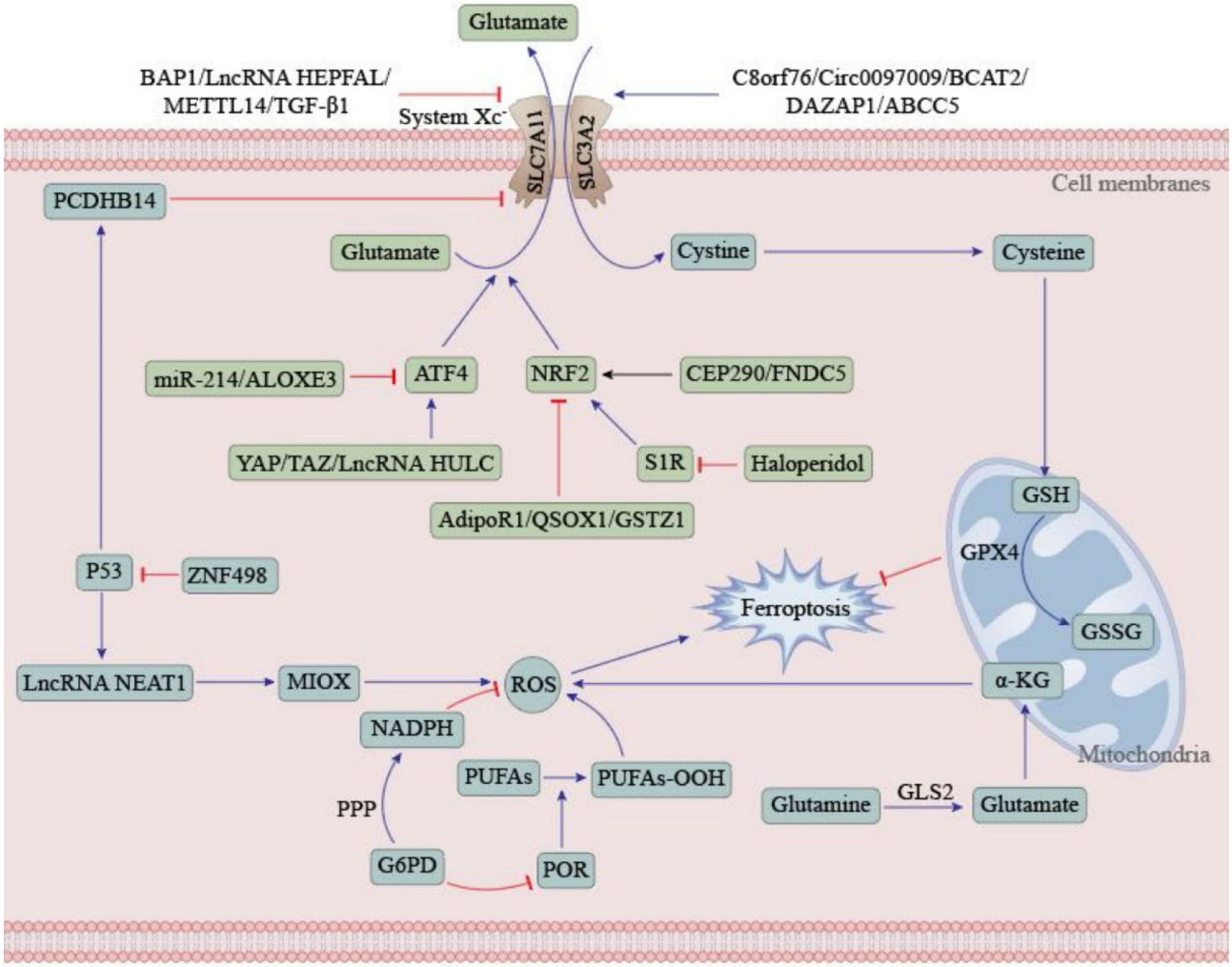

Fig. 1 Factors associated with ferroptosis in HCC

transcription of SLC7A11 [16]. Cells with elevated NRF2 exhibited a remarkable increase of tumor proliferation, along with enhanced capabilities of migration and invasion [17].

Researches have also revealed that the tumor suppressor protein p53 repressed the uptake of cystine, thereby sensitizing cells to ferroptosis by inhibiting SLC7A11 expression [18]. It has been reported that the up-regulation of myo-inositol oxygenase (MIOX) promoted the production of ROS while the production of NADPH and GSH reduced [19], thereby decreased the antioxidant capacity of tumor cells. p53 increased the expression of lncRNA NEAT1 by binding to its promoter, competitively binding more miR-362-3p and releasing miR-362-3p-mediated MIOX inhibition, resulted in the enhanced ferroptosis sensitivity of hepatoma cells ultimately [20]. In addition, p53 activated the expression of PCDHB14 to decrease the expression of SLC7A11 by enhancing the degradation of p65 mediated by E3 ubiquitin ligase RNF182 to block p65 binding to the promoter of SLC7A11, which resulted in the increased sensitivity of ferroptosis and suppressed the progression of HCC [21]. The Ser46 phosphorylation of p53, which was inhibited by ZNF498, a zinc finger protein with high expression in HCC, was reported to restain the apoptosis and ferroptosis of HCC [22].

BRCA1-associated protein 1 (BAP1) is the product of histone 2A mono-ubiquitination (H2Aub) at lysine-119 on SLC7A11 [23], which could repress the expression of SLC7A11 by diminishing H2A ubiquitination on the SLC7A11 promoter, which was independent of the influence of p53, NRF2 and ATF4 [24]. Additionally, overexpression of suppressor of cytokine signaling 2 (SOCS2) has been shown to augment the radiosensitivity of HCC by promoting the ubiquitination and degradation of SLC7A11 [25]. The ubiquitin specific peptidase 8 (USP8), which was found to favor HCC progression, inhibited the O-GlcNAcylation of SLC7A11 to stabilize its expression, thus facilitating the ferroptosis of HCC [26, 27].

C8orf76 has been confirmed to be associated with the occurrence and metastasis of gastric cancer [28], and its elevated expression also predicted poor prognosis of breast cancer [29]. Li et al. found that the upregulation of C8orf76 in HCC binded to the promoter region and transcriptionally up-regulated the expression of SLC7A11, thus inhibiting lipid peroxidation and accelerating tumor growth [30].

TEA domain (TEAD) proteins comprise a family of transcription factors that regulate the expression of various genes involved in cell proliferation, differentiation, and apoptosis [31]. Evidence has indicated that YAP/TAZ, a co-activated transcription factor, upregulated the expression of SLC7A11 in a TEAD-dependent manner and maintaining the protein stability, nuclear localization and transcriptional activity of ATF4 cooperately, resulting in the prevention of ferroptosis in HCC [32]. Concurrently, the overexpression of lipoxygenase ALOXE3, a target gene of YAP-TEAD, effectively increased the susceptibility of hepatoma cells to ferroptosis [33].

Transforming growth factor β1 (TGF-β1) has been found to promote ferroptosis of hepatoma cells by inhibiting SLC7A11 [34], while branched-chain amino acid aminotransferase 2 (BCAT2), as a key enzyme mediating the metabolism of sulfur-containing amino acids, could specifically antagonize the inhibitory effect of system Xc^- and protect HCC from ferroptosis by modulating the intracellular glutamate level [35]. Moreover, Shan et al. have validated the involvement of centrosomal protein 290 (CEP290) in the ferroptosis of HCC via modulating NRF2 signaling pathway [36], while adiponectin receptor 1 (AdipoR1) has been shown to govern the induction of radiotherapy-induced ferroptosis in hepatoma cells through the NRF2-Xc^- pathway [37]. Quiescin sulfhydryl oxidase 1 (QSOX1) was a cellular pro-oxidant that inhibited the activity of NRF2 by promoting ubiquitination-mediated EGFR degradation and accelerating its endosomal transport within cells [38]. Sigma-1 receptor (S1R) serves as a protein regulator that modulates ROS accumulation through NRF2 to confer protection to HCC from ferroptosis [39].

GPX4 in HCC with ferroptosis

Glutathione peroxidative 4 (GPX4) is a central cytoprotective factor downstream of system Xc^- [40]. The overexpression of GPX4 predicted a poor prognosis of HCC patients by shielding cells from oxidative stress and reducing intracellular ROS levels, thereby promoting the proliferation, migration, angiogenesis and immune cell penetration of tumor cells [41, 42].

It has been found that circIL4R was up-regulated in HCC tissues and cell lines, which targeted GPX4 through miR-541-3p, thus inhibiting ferroptosis and promoting the progression of HCC [43]. The absence of phosphoseryl-tRNA kinase (PSTK) could lead to the inactivation of GPX4, then blocked GSH metabolism and increased the sensitivity of hepatoma cells to chemotherapy [44]. Glutathione S-transferase zeta 1 (GSTZ1) was an enzyme in phenylalanine catabolism, and known to suppress the expression of NRF2 [45]. GSTZ1-1 deficiency led to succinylacetone accumulation, alkylation modification of Kelch-like ECH-associated protein 1 (Keap1), thus resulting in NRF2 activation and GPX4 upregulation to promote the progression of HCC [46, 47]. Feng et al. have demonstrated that the silencing of SEH1 like nucleoporin (SEH1L) could trigger ferroptosis and impede the progression of HCC through the ATF3/HMOX1/GPX4 axis [48].

Furthermore, CHAC1 recognized as a critical gene for GSH degradation, has been correlated with an adverse poor tumor prognosis [49], while dihydroartemisinin could promote the up-regulation of CHAC1 expression induced by the reaction with unfolded protein, reducing GSH synthesis and down-regulating GPX4 expression in hepatoma cells, then promoting ferroptosis in HCC [50].

Lipid peroxidation

Glucose-6-phosphate dehydrogenase (G6PD) functions as a rate-limiting enzyme in the pentose phosphate pathway (PPP), in which ribose-5-phosphate and NADPH are produced to foster tumor growth. A study has illuminated that G6PD could enhance the invasive and migratory capabilities of hepatoma cells by inducing epithelial-mesenchymal transition (EMT) via signal transducer and activator of transcription 3 (STAT3) pathway [51]. Zou et al. have uncovered that P450 oxidoreductase (POR) promoted ferroptosis by peroxidation of membrane polyunsaturated phospholipids [52], while G6PD deficiency could inhibit cell growth, metastasis and tumor occurrence by up-regulating POR [53]. Li et al. have confirmed that polyunsaturated fatty acids (PUFAs) were particularly susceptible to be oxidized when ferroptosis occurred, resulting in the destruction of lipid bilayer and affecting the function of cell membrane. Biosynthesis of PUFAs in cell membranes and maintenance of normal physiological functions required a series of enzymes, such as ACSL4 and LPCAT3, to ensure cell membranes remain intact [54]. High-density lipoprotein-binding protein (HDLBP) was an important transporter to protect cells from excessive cholesterol accumulation, and its expression was increased in HCC tissues. HDLBP has the capacity to modulate the ubiquitination of ferroptosis suppressor protein 1 (FSP1) through stabilizing lncFAL, thereby inhibiting ferroptosis in HCC [55]. As a component of the complement system, Ficolin 3 has been found to exhibit significantly diminished expression in HCC, and this reduction leaded to the accumulation of monounsaturated fatty acid (MUFA), and promoted ferroptosis resistance [56].

In addition, studies have indicated that glutamine synthase 2 (GLS2) promoted the production of α-ketoglutaric acid via glutamate, thereby increasing lipid ROS and propelling ferroptosis in HCC [57]. Erastin, known as an ferroptosis inducer, up-regulated lncRNA Gabpb1-AS1, but down-regulated GABPB1 protein levels by blocking GABPB1 translation, resulting in decreased expression of PRDX5 peroxidase gene. Subsequently, this chain of events culminated in a swift accumulation of ROS within HepG2 cells, ultimately impairing the cells' antioxidant defenses [58].

Non-coding RNAs

There are a vast array of non-coding RNAs in the body, and a growing number of studies have demonstrated that they can affect numerous molecular targets and act as oncogenes or tumor suppressors [59]. In recent years, the spotlight in oncology research has focused on micro RNA (miRNA), long non-coding RNA (lncRNA) and circular RNA (circRNA) [60].

It has revealed that circ0097009 was markedly overexpressed in HCC and sponged with miR-1261 competively to enhance the expression of SLC7A11, while inhibition of circ0097009 exhibited an opposite effect [61]. LncRNA HULC has been identified to modulate the activity of ATF4 by interacting with miR-3200-5P [62], thereby participating in the regulation process of ferroptosis in hepatoma cells. The expression of lncRNA HEPFAL was confirmed to be lower in HCC tissues than in normal liver tissues. Moreover, in vitro and in vivo experiments have corroborated that lncRNA HEPFAL could reduce the migration and invasion of hepatoma cells, as well as ferroptosis promotion by regulating SLC7A11 ubiquitination [63]. Zhai et al. have discovered that the expression of RBMS1 was down-regulated in HCC, which was associated with poor survival of HCC patients. The inhibition of the circIDE/miR-19b-3p/RBMS1 axis could up-regulate GPX4 and favor tumor growth [64]. Additionally, circPIAS1 inhibited ferroptosis and promoted HCC progression through the miR-455-3p/NUPR1/FTH1 axis [65].

N6-methyladenosine (m6A) refers to the methylation modification of the sixth nitrogen atom on adenine on RNA, which is the most common epigenetic modification in all RNAs including mRNA and non-coding RNA [66, 67]. The m6A modification showed a close involvment in the occurrence and development of human malignancies [68]. Methyltransferase-like 14 (METTL14) induced m6A modification in the 5' non-coding region of SLC7A11 through YTHDF2-dependent pathway, resulting in the degradation of SLC7A11 and ferroptosis promotion in HCC [69]. Another m6A methylase, METTL9, was also found to faciliate HCC progression through SLC7A11 [70]. In addition, the methylase WTAP confered the m6A modification on circCMTM3 was reported to inhibite ferroptosis in HCC by recruiting IGF2BP1 to increase the stability of PARK7 [71].

Autophagy-related pathways and factors in ferroptosis

Autophagy is a ubiquitous self-protection mechanism in eukaryotic cells, which can facilitate cellular metabolism and maintain cell homeostasis by degrading damaged organelles, proteins and lipids in a lysosomal dependent manner to renew cells' energy. Autophagy plays a crucial role in the process of cell survival and death [72]. It

has been shown that autophagy played a dynamic role in inhibiting or promoting tumor through oxidative stress in different backgrounds and stages of tumor development [73, 74]. Recent studies have found that the activation of autophagy can induce ferroptosis through a variety of molecular mechanisms, and it is more believed that ferroptosis is actually an autophagic cell death regulated by a series of crosstalk proteins between autophagy and ferroptosis.

p62 is a multifunctional protein related to autophagy, Wu et al. have confirmed that p62 directly inhibited Keap1 under physiological conditions to activate NRF2 and then protect hepatoma cells from ferroptosis [75, 76]. Zhang et al. have found that RNA binding protein ZFP36/TTP prevented ferroptosis by regulating the autophagy signaling pathway of hepatic stellate cells. Its overexpression could lead to the decline of ATG16L1 mRNA by combining with AU-rich elements (AREs) in the 3'-untranslated region (3'-UTR), triggered autophagy inactivation and prevented the degradation of autophagy ferritin, ultimately leading to ferroptosis resistance [77]. BECN1 was another key regulator of autophagy [78], which have been shown to bind with SLC7A11 to promote ferroptosis in HCC [79].

The great success of all-trans-retinoic acid (ATRA) in the differentiated treatment of acute promyelocytic leukemia (APL) not only improved the prognosis of APL, but also facilitated the study of ATRA in the treatment of other tumors [80]. Fang et al. have discovered that ATRA induced autophagy through the Bcl-2/BECN1 pathway, meanwhile, ATRA induced autophagy participated in the inhibition of malignant behavior of hepatoma cells by reversing the EMT process [81]. In addition, Sun et al. have demonstrated that ATRA inhibited the transport of glutamate and cystine, and the reduction of raw material inhibited GSH synthesis, thus promoting ferroptosis in hepatoma cells [82].

Rapamycin is an inducer of autophagy, and mammalian target of rapamycin (mTOR) has been found to be associated with ferroptosis of tumor cells in several studies [83–85]. Huang et al. have found that MCF2L was highly expressed in HCC tissues, and the down-regulation of MCF2L promoted ferroptosis in hepatoma cells through the PI3K/mTOR pathway [86]. MiR-21-5p and maternal embryonic leucine zipper kinase (MELK) were highly expressed in HCC, and their overexpression could promote EMT of HCC cells. It was also confirmed that miR-21-5p targeted MELK and inhibited ferroptosis by regulating AKT/mTOR signaling pathway, thereby promoting the development of HCC [87]. Tribble, a member of the CAMK Ser/Thr protein kinase family, performed its biological functions through direct interaction with AKT proteins to regulate cell proliferation, apoptosis, and differentiation [88]. Ubiquitin (Ub) was required for ubiquitination and subsequent degradation of GPX4, tribbles homolog 2 (TRIB2) mitigated the effects of oxidative damage by reducing the availability of Ub, enabling exclusive manipulation of RSL3 and Erastin induced ferroptosis independent of GPX4 and GSH [89].

As a selective autophagy method, ferritinophagy mediated ferritin degradation and released of free iron to participate in the regulation of intracellular iron content. Moderate ferritinophagy kept iron content stable, but excessive ferritinophagy released a lot of free iron. Nuclear receptor co-activator 4 (NCOA4) was considered to be a key regulatory factor of ferritinophagy, which was targeted to ferritin and delivered to lysosomes for degradation and release of free iron, and its mediated ferritinophagy constituted an important part of iron metabolism [90]. Recent studies have shown that NCOA4 was regulated by iron content, autophagy, lysosome, hypoxia and other factors, indicating that NCOA4-mediated ferritin degradation was related to ferroptosis [91] (Table 1).

Table 1 Autophagy-related pathways and factors of ferroptosis in HCC

Factors	Mechanism	Effect on ferroptosis	Reference
P62	Inhibiting Keap1 under physiological conditions, promoting the activation and preventing the degradation of NRF2	Inhibition	[76]
ZFP36/TTP	Leading to the decline of ATG16L1 mRNA by combining with AU-rich elements (AREs) in the 3'-untranslated region (3'-UTR), thus triggering autophagy inactivation, preventing the degradation of autophagy ferritin	Inhibition	[77]
BECN1	Binding to SLC7A11	Promotion	[79]
ATRA	Inducing autophagy through the Bcl-2/BECN1 pathway, reversing the EMT process, inhibiting the transport of glutamate and cystine	Promotion	[80]
MCF2L	The down-regulation of MCF2L promoting ferroptosis in hepatoma cells through the PI3K/mTOR pathway	Inhibition	[86]
MELK	MiR-21-5p targeted MELK and inhibited ferroptosis by regulating AKT/mTOR signaling pathway	Inhibition	[87]
TRIB2	Reducing the availability of Ub, mitigating the effects of oxidative damage	Inhibition	[89]
CISD2	The inhibition of CISD2 promoting excessive accumulation of iron ions through autophagy	Inhibition	[109]

The mechanism of ferroptosis and sorafenib resistance

Sorafenib is a multi-targeted tyrosine kinase inhibitor approved by the FDA for the systemic treatment of advanced HCC, which exhibits anti-tumor effects by suppressing tumor proliferation and angiogenesis to prolong the median overall survival of patients with advanced HCC [92]. However, the resistance of sorafenib makes it difficult for HCC patients to benefit in the long term. Studies have found that sorafenib could induce ferroptosis in cells, indicating that ferroptosis was closely related to sorafenib resistance. The epigenetic biological modification, transport process and tumor microenvironment might be responsible for sorafenib resistance [93–95]. Moreover, an amount of studies have shown that additional induction of ferroptosis can significantly improve the efficacy of sorafenib, especially in sorafenib-resistant HCC cells [96].

The molecular mechanism of ferroptosis involved in sorafenib resistance were colorful and complex. DAZ-associated protein 1 (DAZAP1) is a highly conserved RNA binding protein (RBPs) [97] and has been found to be significantly up-regulated in HCC. The aberrant expression of DAZAP1 was positively correlated with larger tumor volume, high incidence of vascular invasion and poor prognosis of HCC patients. DAZAP1 has also been revealed to inhibit sorafenib induced ferroptosis by regulating SLC7A11 transcriptionally [98].

ATP-binding cassette (ABC) transporters constitute one of the largest families of membrane proteins in most organisms. Huang et al. have showed that the expression of ABCC5 was significantly induced in sorafenib-resistant hepatoma cells, and ABCC5 inhibited ferroptosis of hepatoma cells by stabilizing SLC7A11 protein to increase intracellular GSH content and reduce lipid peroxidation accumulation via PI3K/AKT/NRF2 axis [99]. Some studies have found that NRF2 signals promote the differentiation and migration of cancer stem cells and ABC transporter gene display ferroptosis suppression effect to acquire sorafenib resistance in hepatoma cells [100]. Metallothionein-1G (MT-1G) was identified as a novel transcriptional target of NRF2 with an up-regulation in HCC. Ferroptosis inhibition via lipid peroxidation regulation by MT-1G was unveiled to attribute to sorafenib-injury in HCC cells [101].

The transcription level of miR-23a-3p in sorafenib resistant cells was found to enhance in an ETS proto-oncogene 1 (ETS1) -dependent manner through ferroptosis inhibition by modulating cellular iron accumulation and lipid peroxidation via the ETS1/miR-23a-3p/ACSL4 axis [102]. In addition, IGF2BP3 has been shown to promote the stability of NRF2 mRNA by m6A modification and negatively regulate sorafenib-induced ferroptosis in hepatoma cells [103]. LncRNA HCG18 was confirmed to be highly expressed in HCC [104], and silencing lncRNA HCG18 regulated GPX4-mediated ferroptosis by sponging miR-450B-5P to reduce sorafenib resistance [105]. Highly expression of lncRNA DUXAP8 in HCC was indicated with sorafenib resistance and poor prognosis. And the palmitoylation of SLC7A11 was promoted by lncRNA DUXAP8 to prevent the lysosomal degradation of SLC7A11 to inhibit HCC ferroptosis [106].

In addition, fibronectin type III domain containing 5 (FNDC5) has been found to promote the nuclear translocation pathway of NRF2 by activating PI3K/AKT, enhancing intracellular antioxidant capacity and ultimately reducing sorafenib-induced ferroptosis [107]. PI3K/AKT is also a common pathway in autophagy [108], implying another crosstalk between autophagy and ferroptosis in the mechanism related to sorafenib resistance. For instance, Li et al. have found that CISD2 was highly expressed in hepatoma cells, and the inhibition of CISD2 promoted excessive accumulation of iron ions through autophagy to promote sorafenib-induced ferroptosis [109].

On the other hand, some researches have indicated that ferroptosis may promote sorafenib resistance. Sestrin2 (Sesn2), an antioxidant protein, has been upregulated by sorafenib-induced ferroptosis in a dose and time dependent manner [110]. Additionally, sorafenib effectively activated endoplasmic reticulum phagocytosis mediated by receptor protein FAM134B to reduce lipid peroxidation and thus maintain cell homeostasis [111]. Autophagy and the change of the tumor microenvironment may play a dual role under the background of ferroptosis and sorafenib, so the interplay between sorafenib and ferroptosis is intricate and profound investigation would be necessitated to demystify the phenomenon of sorafenib resistance and enhance the therapeutic implications (Table 2).

Relationship between ferroptosis and tumor immune microenvironment

The immune component of tumor is referred to as tumor immune microenvironment (TIME), which exerts a multifaceted and crucial influence in tumor occurrence, development and chemotherapy resistance. Concurrently, immunotherapy for tumors is also a beneficial treatment modality for patients.

Macrophages are an important part of the TIME, which can be polarized in different directions under the action of different microenvironments and stimulating factors. Existing studies have shown that M1 macrophages can promote inflammation, kill pathogens and anti-tumor, while M2 macrophages can promote angiogenesis and tissue repair, and even promote tumor growth through immunosuppression [112]. Hao et al. have demonstrated that knockdown of APOC1 enhanced

Table 2 Mechanisms of ferroptosis in HCC associated with sorafenib resistance

Factors	Mechanism	Reference
EZH2	Epigenetic regulation of TFR2	[93]
FASN	Binding to HIF1α and subsequently enhancing transcription of SLC7A11	[94]
DUSP4	Modulating the intricate iron metabolism	[95]
DAZAP1	Regulating SLC7A11 transcription	[98]
ABCC5	Stabilizing SLC7A11 protein, increasing intracellular GSH content, reducing lipid peroxidation accumulation, and activating PI3K/AKT/NRF2 axis	[99]
MT-1G	A novel transcriptional target of NRF2, inhibiting lipid peroxidation	[101]
MiR-23a-3p	Inhibiting cellular iron accumulation and lipid peroxidation	[102]
IGF-2BP3	Reading NRF2 mRNA's m6A modification	[103]
LncRNA HCG18	Silencing lncRNA HCG18 regulated GPX4-mediated ferroptosis by sponging miR-450B-5P to reduce the degree of sorafenib resistance	[105]
LncRNA DUXAP8	Promoting the palmitoylation of SLC7A11 and preventing its lysosomal degradation, thereby enhancing the action of SLC7A11	[106]
FNDC5	Promoting the nuclear translocation pathway of NRF2 by activating PI3K/AKT, enhancing intracellular antioxidant capacity	[107]

ferroptosis and induced the polarization of tumor-associated macrophages into M1 type through the pathways of lipid metabolism and iron metabolism, thereby inhibiting HCC [113]. Studies have shown that knockdown of SLC7A11 reduced the expression of phosphorylated STAT6 and PPAR-γ in macrophages, while enhancing the expression of SOCS3 and inhibiting the polarization of M2 macrophages. Moreover, SLC7A11-mediated ferroptosis of macrophages could increase the expression of PD-L1 in macrophages and improve the efficacy of anti-PD-L1 therapy [114]. And Huang et al. have found that transmembrane protein 147 (TMEM147) could inhibit ferroptosis and promote the polarization of M2 macrophages, thus promoting HCC progression [115]. Other studies have shown that mitochondrial translocator protein (TSPO) could inhibit ferroptosis of HCC cells through NRF2-mediated antioxidant defense system, and promote immune escape of HCC by up-regulating the expression of PD-L1 through NRF2-mediated transcription [116].

In addition, studies have found that FSP1 was significantly overexpressed in HCC and regulated by Keap1/NRF2, while iFSP1 (FSP1 inhibitor) can effectively reduce the burden of HCC and significantly increase the immune penetration including dendritic cells (DC), macrophages and T cells [117]. Li et al. have showed that MAT1A was low expressed in HCC, and its overexpression could promote ferroptosis of HCC cells by increasing the level of S-adenosylmethionine, increasing the cytotoxic effect of CD8+T cells and interferon-γ production [118]. It has also been shown that in GPX4-deficient tumors, CD8+T cells have increased IFN γ secretion, further manifested by T-cell-dependent upregulation of PD-L1 expression, suggesting that ferroptosis increases CD8+T cell functional activation [119]. Zheng et al. have found that high expression of phosphoglycerate mutase 1 (PGAM1) in HCC was associated with poor prognosis and poor response to immunotherapy, while inhibition of PGAM1 played an anti-tumor role by promoting ferroptosis and CD8+T cell infiltration to work synergistically with anti-PD-1 immunotherapy [120]. Additionally, MER proto-oncogene tyrosine kinase (MerTK) upregulated SLC7A11 through ERK/SP1 pathway to cause immunosuppressive TME by recruiting myeloid-derived suppressor cells (MDSCs), leading to anti-PD-1 /PD-L1 treatment resistance [121].

Summary and perspectives

It is difficult to diagnose HCC in the early stage, with high recurrence and metastasis rates and easy to be resistant to drugs. The existing diagnosis and treatment methods are still difficult to meet good expectations, and the lives of patients are still facing great threats. Therefore, seeking more efficient and accurate diagnosis and treatment are still the focus of research. With the introduction of the concept of "ferroptosis" and the deepening of the research on its relationship with diseases, more and more evidence showed that ferroptosis was involved in the occurrence and development of HCC. The treatment targeting ferroptosis related pathways is expected to provide a new and more potential treatment plan for traditional treatment. Combined with relevant studies in recent years, this article reviews the mechanism and progress of ferroptosis in HCC from four aspects: ferroptosis related pathways, the crosstalk between ferroptosis and autophagy, sorafenib resistance, and tumor immune microenvironment, in order to provide a theoretical basis for targeted ferroptosis therapy of HCC.

For example, high expression of SLC7A11 in cancer cells also implied glucose and glutamine dependence, which provided a potential metabolic vulnerability for targeted therapy of tumors with high SLC7A11 expression [122]. Ceruloplasmin (Cp) was a multicopper enzyme endowed with ferroxidase activity, and its

knockout could promote the accumulation of intracellular iron and lipid ROS induced by Erastin and RSL3 [123], whereas copper metabolism MURR1 domain 10 (COMMD10) could bind to HIF1α in HCC to inhibit SlC7A11-mediated ferroptosis [124]. In addition, ENO1 recruited CNOT6 to accelerate the mRNA decay of iron regulatory protein 1 (IRP1) in cancer cells, resulting in inhibition of the expression of mitoferrin-1 (Mfrn1), then inhibited mitochondrial- induced ferroptosis [125]. Visible, there are still many factors regulate the process of ferroptosis through various channels.

Targeted ferroptosis is expected to overcome drug resistance in HCC. How to exploit the vulnerability of ferroptosis to make tumor cells more susceptible to death and how to combine drugs to improve the efficacy will be the focus of future research. Prior to 2017, sorafenib was the only FDA-approved treatment option for advanced HCC, and as research continues, more and more patients are benefiting from new targeted therapies.

Taking sorafenib as an example, as a multi-kinase inhibitor with a multitude of molecular targets, it has been confirmed to induce ferroptosis in various types of cancer. However, we cannot ignore that sorafenib can cause changes in numerous genes and signaling pathways, which subsequently affect the tumor microenvironment and lead to the observation of resistance to ferroptosis. In addition, alterations in the tumor microenvironment can also impact the effectiveness of immunotherapy. Therefore, in the future, when targeting ferroptosis for disease treatment, it is essential to thoroughly consider the interactions between mechanisms, monitor the changes in the tumor microenvironment during the treatment process, and actively foster the synergistic benefits that combination therapies can offer.

In conclusion, due to the involvement of ferroptosis in the resistance mechanism of HCC, further research and elaboration on it will help to develop targeted drugs, provide new application prospects for cancer targeted therapy and improve the prognosis of patients.

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Author contributions
CL designed this study, GD directed the study, YH and XL sorted out documents and made tables. CL drafted the manuscript and drew figures. All authors reviewed the manuscript.

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Data availability
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Declarations

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Competing interests
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