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Review Article

SLC7A11 in hepatocellular carcinoma: potential mechanisms, regulation, and clinical significance

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Abstract: Exploring novel early detection biomarkers and developing more efficacious treatments remain pressing tasks in the current research landscape for hepatocellular carcinoma (HCC). Morphologically and molecularly separate from apoptosis, cell death, and autophagy, ferroptosis is a recently discovered, unique, controlled form of cell death. SLC7A11 (also known as xCT) represents a subunit of the cystine-glutamate antiporter (also known as system Xc(-)). A growing body of research suggests that induction of ferroptosis through SLC7A11 can effectively eliminate hepatocellular carcinoma (HCC) cells, particularly those exhibiting resistance to alternative forms of cell death. Thus, targeting ferroptosis via SLC7A11 may become a new direction for the design of therapeutic strategies for HCC. Although many research articles have investigated the possible roles of SLC7A11 in HCC, a study that summarizes the main findings, including the regulators and mechanisms of action of SLC7A11 in HCC is not available. Therefore, we present a comprehensive overview of the functions of ferroptosis, particularly SLC7A11, in the identification, development, and management of HCC in this review. In addition, we discuss how this knowledge can be translated into treatment by providing a systemic therapy in advanced HCC using sorafenib, the first-line drug targeting multiple kinases and SLC7A11. We further dissect the possible barriers as well as the corresponding solutions and provide insights on how to navigate effective treatment using this knowledge.

Keywords: SLC7A11, HCC, ferroptosis

Introduction

Hepatic cancers are categorized as primary or secondary (metastatic) [1]. Hepatocellular carcinomas (HCC) constitute the majority of primary liver cancers, accounting for approximately 90% of cases [2, 3]. Hepatocellular carcinoma (HCC, also called primary liver cancer) ranks fourth in terms of cancer-related mortality and is the sixth most frequent type of cancer worldwide. According to reports, every year there are at least 780,000 deaths from HCC and roughly 840,000 new instances of the disease [4]. The development and progression of HCC are highly intricate processes involving diverse genetic and molecular changes, along with multiple risk factors, including hepatitis B virus (HBV) infection, non-alcoholic steatohepatitis (NASH) associated with metabolic dysregulation, cirrhosis, exposure to environmental toxins such as aflatoxin B1 and aristolochic acid, as well as alcohol consumption [5-7].

Surgical resection (liver resection or transplantation) remains the primary treatment for early-stage HCC. For the majority of advanced-stage patients, therapeutic options typically include transarterial chemoembolization (TACE), radiotherapy, systemic treatments encompassing targeted therapies such as sorafenib, immunotherapy, and conventional cytotoxic chemotherapy (e.g., the FOLFOX4 regimen: fluorouracil, folinic acid, and oxaliplatin) [8-11]. In recent years, tyrosine kinase inhibitors like sorafenib and regorafenib have been approved as first- or second-line treatment options for advanced-stage HCC patients. However, these drugs only marginally extend the median survival by approximately three months for patients with advanced HCC. In addition to the above-dis-

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cussed first-line therapies, which have been shown to significantly improve mean overall survival, there are prospective medications undergoing preclinical or clinical development [12, 13].

In the last decade, extensive basic and clinical researches have enhanced early identification, therapy, and understanding of HCC. Among the most intriguing discoveries are the roles of ferroptosis in tumorigenesis and the newly uncovered functions of SLC7A11 in ferroptosis control.

Numerous transmembrane transporters play vital roles in the physiological processes of liver, which is the body's largest metabolic and immunological organ. During hepatocyte carcinogenesis, proliferating cells, due to their tremendous metabolic rates, necessitate substantial substrates and products for cellular entry and exit [14]. This phenomenon is accompanied by alterations in the expression of transmembrane transporters, especially solute carrier (SLC) transporters [15, 16]. The cystine-glutamate antiporter, also known as system Xc(-) is one of them, and SLC7A11 (also known as xCT) serves as its catalytic subunit [17]. This subunit imports cystine to synthesize glutathione (GSH), a crucial antioxidant peptide for detoxifying phospholipid hydroperoxides. GSH serves as a substrate for phospholipid-hydroperoxide-glutathione-peroxidase (GPX4) [18]. Besides being a crucial mediator in metabolic reprogramming, system Xc(-) is a core regulatory component of ferroptosis - an emerging type of cell death induced by metal iron and reactive oxygen species (ROS), driven by lipid peroxidation. Unlike apoptosis, uncontrolled necrosis, autophagy, and necroptosis, ferroptosis distinguishes itself as an iron-dependent, regulated mode of cell death [19, 20]. Research has shown that ferroptosis plays a significant role in various physiological and pathological conditions, such as cardiac disease, ischemia-reperfusion injury, and neurodegenerative diseases [21, 22]. Physiological states and pathological stressors induce ferroptosis in both humans and animals. Ferroptosis is essential for eliminating cells that are harmed by infection, environmental stress, or nutrient deficiency [23]. Thus, a growing body of research indicates that ferroptosis - like apoptosis - is a crucial tumor suppressor mechanism. Significantly, recent research also showed that conventional cancer treatments such as radiation and immunotherapy might partially trigger ferroptosis by modifying SLC7A11 expression [24]. Small pharmacological inhibitors are frequently employed to induce ferroptosis and have tumor suppression benefits. Examples of these inhibitors are Sulfasalazine, Erastin, and Sorafenib, which act as direct inhibitors of SLC7A11 import function [25-28]. Therefore, ferroptosis and SLC7A11 are tightly associated, and ferroptosis can be effectively promoted by suppressing SLC7A11.

Recent studies increasingly associate SLC7A11 with HCC development and related drug resistance. Regulating SLC7A11 expression emerges as a promising strategy for HCC treatment and a potential biomarker for diagnosis and prognosis. Despite its expression in various malignant tumors and extensive research on its roles in other cancers, the role and implications of SLC7A11 in HCC remain elusive. This review focuses on exploring the potential role of SLC7A11 in HCC development and its connection to ferroptosis. Additionally, it delves into SLC7A11's roles in early detection and prognosis monitoring. Furthermore, the review discusses the prospects of targeting SLC7A11 in HCC therapy, presenting potential issues and solutions to enhance treatment outcomes, particularly for advanced HCC (**Figure 1**).

The relationship between SLC7A11 and HCC

The structure of SLC7A11

Encoded by the SLC7A11 gene, which is found on human chromosome 4 and is widely expressed in tissues like the liver and brain, the SLC7A11 protein, also known as xCT, is a sodium-independent 12-pass transmembrane transporter protein. Furthermore, SLC7A11 is a component of System Xc(-), and it is mostly connected with System Xc(-) for its physiological functions.

System Xc(-) is a chloride-dependent membrane cystine/glutamate antiporter that generally imports cystine and exports glutamate in a 1:1 proportion. It is a heterodimeric protein containing a light chain SLC7A11 and a heavy chain SLC3A2 (4F2 heavy chain, a transmembrane regulatory subunit) [21]. Through its role in both cystine uptake and glutamate release, this system facilitates the synthesis of GSH, an

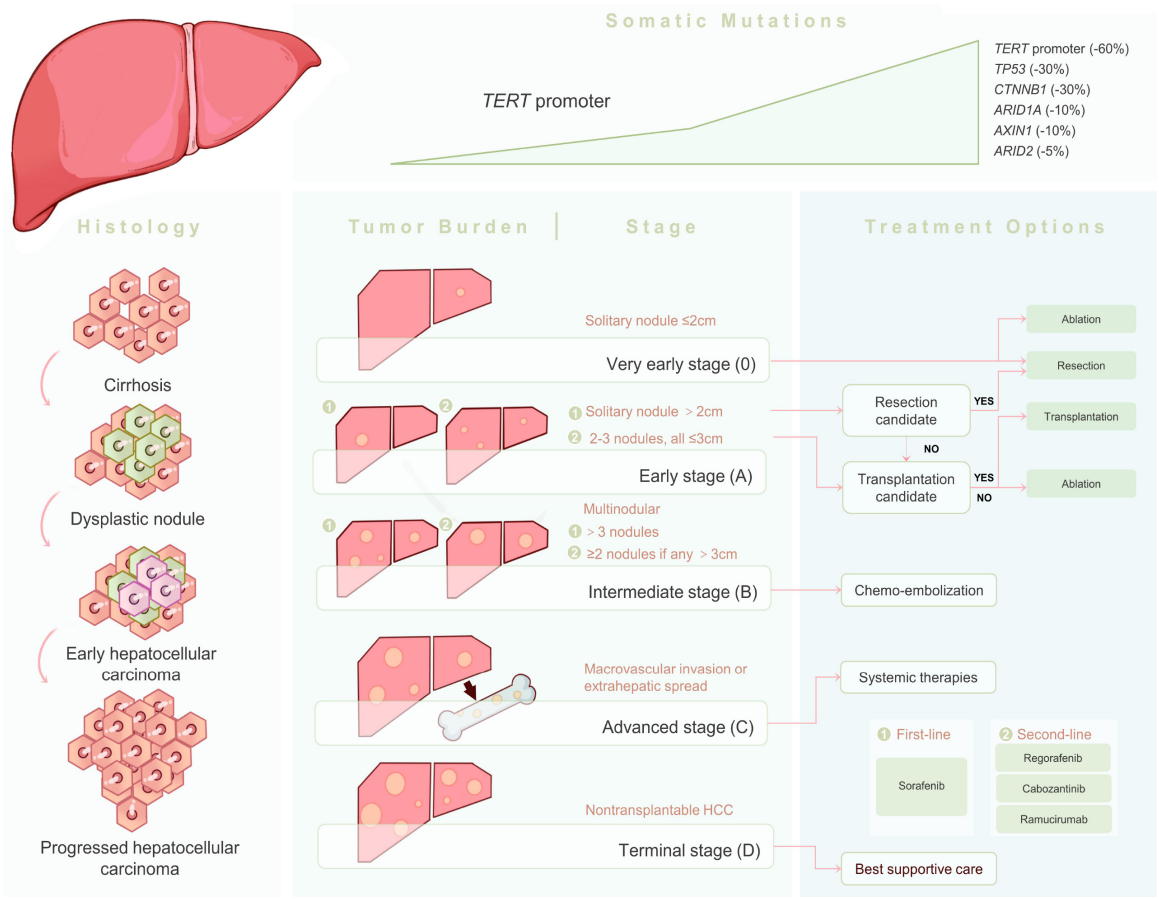

Figure 1. Primary genetic alterations in hepatocellular carcinoma and the clinical algorithm for the management of hepatocellular carcinoma. A summary is provided of the main histologic and molecular changes that occur throughout human hepatocarcinogenesis. The management strategy is based on the Barcelona Clinic liver Cancer algorithm, which classifies patients into five stages according to their tumor burdens.

inhibitor of ferroptosis. To exert this function, both two subunits of the system are required to work synergistically. As the light chain, SLC7A11 is responsible for the basic transporter activity of system Xc(-) since it is highly specific for cystine and glutamate. However, the heavy chain SLC3A2 serves as a chaperone protein with no specificity to the amino acids, regulating the transport of SLC7A11 to the plasma membrane. Thus, SLC7A11 has been the main focus of recent studies, and SLC7A11 will be covered in great detail in this review (**Figure 2**).

Physiological functions of SLC7A11 in HCC

SLC7A11's role is intimately linked to ferroptosis, a unique kind of cell death. Ferroptosis differs from the four recognized forms of cellular death in terms of shape, pathophysiology, and mechanism. It is primarily defined by an imbalance in the antioxidant system of amino acids, a disruption in iron metabolism, and an accumulation of lipid peroxides.

Normal iron uptake is mediated by transferrin (TF), which is recognized by the cell and absorbed as the high-affinity TF-Fe^{3+} complex in serum. The STEAP3 metalloreductase in the endosome then reduces bound Fe^{3+} to free Fe^{2+}, which is then released into the cytosol to form the labile iron pools (LIP) [29-31]. However, when the intracellular free iron increases because of the aberrant iron metabolism, ROS such as hydroxyl radicals (OH•) are generated through a process termed the Fenton reaction, during which Fe^{2+} will also react with hydrogen peroxide (H_2O_2). ROS further promotes lipid peroxidation, causing lipid peroxides to accumulate and inducing ferroptosis. Under normal conditions, those toxic lipid hydroperoxides (e.g., R-OOH) can be reduced to their corresponding nontoxic lipid alcohols (e.g., R-OH) by

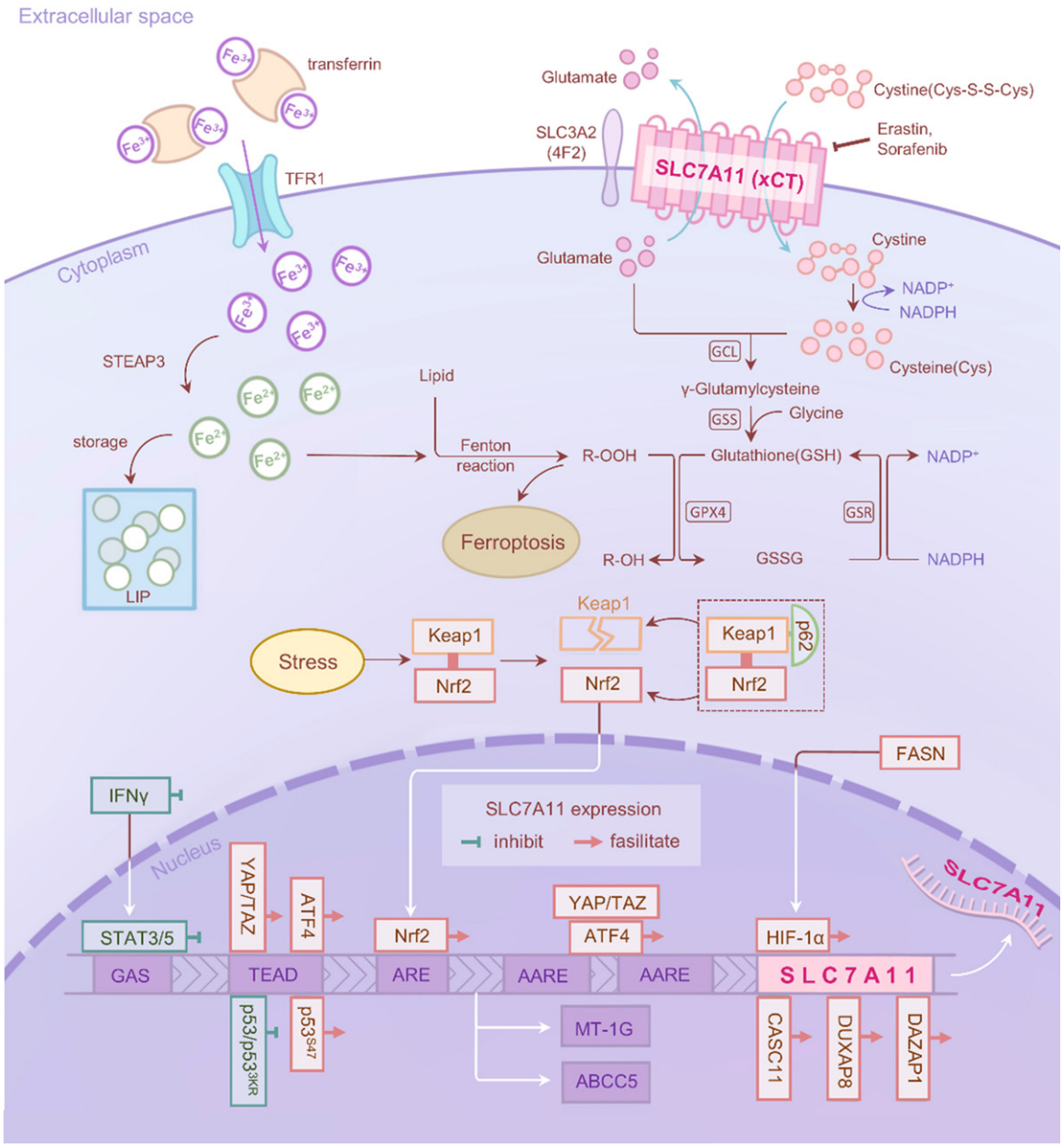

Figure 2. The mechanisms of SLC7A11 in HCC and its regulatory pathways. SLC7A11 protein (also known as xCT) is a Na^+-dependent 12-pass transmembrane transporter protein which is responsible for importing cystine and exporting glutamate in a 1:1 proportion. Through its role in both cystine uptake and glutamate release, this system facilitates the synthesis of glutathione (GSH), an inhibitor of ferroptosis acting by reducing the toxic lipid hydroperoxides (e.g., R-OOH) into nontoxic lipid alcohols (e.g., R-OH), thus eliminating ROS generated through the Fenton reaction. The expression and activity of SLC7A11 are tightly regulated through a variety of mechanisms. Regulators can bind to different promoter motifs, exerting positive or negative effects. Abbreviations: TFR1, Transferrin receptor 1; LIP, labile iron pools; GCL, Glutamate cysteine ligase; GSS, glutathione synthetase; GSH, reduced glutathione; GSSG, oxidized glutathione; GSR, glutathione-disulfide reductase; Keap1, Kelch-like ECH-associated protein 1; AREs, antioxidant response elements; ABCG2, ATP binding box G2; MT-1G, Metallothionein-1G; AARE motifs, amino acid responsive element motifs; GAS, gamma-activated site; FASN, fatty acid synthase.

GPX4 (a unique subtype of GPXs acting as a phospholipid hydroperoxidase). However, reduced GSH needs to be converted to oxidized glutathione (GSSG) in order for this process to take place. GSSG is later reduced back to GSH by glutathione-disulfide reductase (GSR) with

the consumption of NADPH. Thus, to protect against lipid peroxidation, the endogenous redox balance upheld by GSH and GPX4 is crucial. If this balance is disrupted, either by GSH depletion or by GPX4's inadequate capacity to eliminate peroxide, this will cause an excessive lipid peroxidation reaction, which will ultimately result in ferroptosis [32-35] (**Figure 2**). In the liver, the disordered ferroptosis will cause damage to the hepatic structure, thus resulting in precancerous lesions.

As mentioned above, SLC7A11 is closely related to the synthesis of GSH. GSH is synthesized from glutamate, cysteine, and glycine, with cysteine serving as the important rate-limiting precursor. After being transported into the cytoplasm, cystine is rapidly reduced to cysteine, which is an important rate-limiting precursor for GSH biosynthesis. Glutamate cysteine ligase (GCL) then facilitates the combination of intracellular cysteine and glutamate to generate γ-glutamylcysteine, which subsequently works with glycine to synthesize GSH under the catalysis of glutathione synthetase (GSS) [32]. Effectively produced GSH is recognized to be crucial in protecting cells against oxidative stress by removing ROS and preventing ferroptosis by acting as a cofactor of GPX4. Overall, in hepatocellular carcinoma, SLC7A11 serves as a key protein in the system Xc(-) responsible for transporting cystine and glutamate. By controlling the transport of cystine inside and outside the cell, it affects cysteine synthesis, subsequently impacting the synthesis of GSH and ultimately influencing the function of GPX4 and regulating ferroptosis (**Figure 2**).

Additionally, ferroptosis has SLC7A11 as a common regulatory target. Broadly speaking, numerous studies have also demonstrated that different tumor suppressors, such as TP53, NRF2, and ATF4, can control how sensitive cancer cells are to ferroptosis via SLC7A11. While certain tumor suppressor genes have the capacity to inhibit the expression of the SLC7A11 gene, others can modify the way in which the SLC7A11 subunit functions. For example, by blocking the SLC7A11 component and regulating the redox status of cells, TP53 can increase the vulnerability of cells to ferroptosis [20]. Once it is mutated in HCC, ferroptosis can be inhibited through the increased expression of SLC7A11.

Regulators of SLC7A11 in HCC

Regarding modifying ferroptosis, SLC7A11 is a genetic target of many endogenous proteins [23]. The expression and activity of SLC7A11 are tightly regulated through a variety of mechanisms, including transcriptional regulation by transcription factors, epigenetic regulators, and post-transcriptional regulatory mechanisms to control its mRNA levels, protein stability, subcellular localization, and transporter activity, in order to ensure the appropriate functioning of SLC7A11 in maintaining redox homeostasis [24]. In this review, to further elucidate the role of SLC7A11 in HCC, we mainly introduce several typical molecules and narrate the mechanisms of how they are involved in the regulation of ferroptosis in HCC (**Table 1**), including resistance to sorafenib [32].

TP53: The TP53 gene is a well-known tumor suppressor that controls necrosis, autophagy, and apoptosis. An increasing body of research has shown that one of its anticancer strategies also involves promoting ferroptosis. Research indicates that the p53 protein encoded by the TP53 gene is involved in the transcription of SLC7A11. Chromatin immunoprecipitation experiments have demonstrated that the p53 protein was recruited to the promoter region of the SLC7A11 gene [32]. Upon activation of p53, there is a significant reduction in the mRNA and expression of SLC7A11, leading to the inactivation of System Xc(-). The anticancer pathway associated with this process is non-canonical, unaffected by changes in the cell cycle, and primarily linked to the decrease in SLC7A11 and the subsequent reduction in cystine uptake. Consequently, the synthesis of GSH and GPX4 is affected, rendering cells sensitive to ferroptosis [21]. However, mutations at different sites of p53 can exert totally opposite effects on the expression of SLC7A11. For example, the mutation of an additional acetylation site at the backdrop of the p53 3KR mutant markedly attenuated p53's capability to suppress tumor formation and induce ferroptosis in cancer cells [24, 36].

The majority of HCC patients had a nonsynonymous single-nucleotide polymorphism in the TP53 gene at codon 47, sometimes referred to as S47, which affects the gene's ability to induce ferroptosis [37]. As a result, aberrant

Table 1. Main regulators of SLC7A11 in HCC and their effects on ferroptosis

Regulator	Target	Effect	Mechanism
TP53	SLC7A11	Inhibit SLC7A11 expression, thus facilitating ferroptosis.	p53 can be recruited to the promoter region of the SLC7A11 gene. Activation of p53 can significantly reduce the mRNA level and the expression of SLC7A11, leading to the inactivation of system Xc(-).
Nrf2	SLC7A11	Induce SLC7A11 expression, accompanied by decreased ferroptosis, increased tumor growth, and drug resistance.	Under normal conditions, Nrf2 is degraded by ubiquitin ligase. However, under oxidative stress conditions, the released Nrf2 translocates to the nucleus and subsequently binds to antioxidant response elements (AREs), increasing the expression of SLC7A11.
IFNγ	SLC7A11	Inhibit SLC7A11 expression, thus facilitating ferroptosis.	IFNγ downregulates the expression of SLC7A11 by activating the JAK/STAT pathway. STAT1 and STAT3 bind to the promoter sites of SLC7A11, and the expression of SLC7A11 is transcriptionally reduced. Also, increased levels of p-STAT1, p-STAT3, and IRF1 may also exert some effort.
ATF4 and YAP/TAZ	SLC7A11	Induce SLC7A11 expression, accompanied by decreased ferroptosis, increased tumor growth, and drug resistance.	YAP/TAZ binds to a TEAD binding motif located roughly 400 bps upstream of the transcriptional start point in the promoter sequence of SLC7A11, hence upregulating SLC7A11 production. The activation of YAP/TAZ causes ATF4 to translocate to the nucleus, increasing ATF4 expression and its binding to TEAD motifs, ARE motifs, and potentially canonical amino acid-responsive element (AARE) motifs.
Non-coding RNA	SLC7A11		
Long non-coding RNA (lncRNA)	SLC7A11		
lncRNA HEPFAL	SLC7A11	Inhibit SLC7A11 expression, thus facilitating ferroptosis.	Inhibits the stability of SLC7A11.
CASC11 (cancer susceptibility candidate 11)	SLC7A11	Induce SLC7A11 expression, accompanied by decreased ferroptosis, increased tumor growth, and drug resistance.	Increases the stability of SLC7A11.
Double homeobox A pseudogene 8 (DUXAP8)	SLC7A11	Induce SLC7A11 expression, accompanied by decreased ferroptosis, increased tumor growth, and drug resistance.	Facilitates SLC7A11 palmitoylation and impedes its lysosomal degradation.
LINC00654	SLC7A11	Induce SLC7A11 expression, accompanied by decreased ferroptosis, increased tumor growth, and drug resistance.	Increases the recruitment of the transcription factor STAT3 onto the SLC7A11 promoter.
Circular RNAs (circRNAs)	SLC7A11		
Circ0097009	SLC7A11	Induce SLC7A11 expression, accompanied by decreased ferroptosis, increased tumor growth, and drug resistance.	circ0097009/miR-1261/SLC7A11 axis.
Radiotherapy	SLC7A11		
Carbon ions (CI)	SLC7A11	Inhibit SLC7A11 expression, facilitating ferroptosis in HCC cells.	Elevates p53 expression through PERK, inhibits SLC7A11 expression, and facilitates ferroptosis in HCC cells.
Ionizing radiation (IR)	SLC7A11	Inhibit SLC7A11 expression, thus facilitating ferroptosis.	Activates the ATM gene and induces ferroptosis in cancer cells by suppressing the expression of SLC7A11.
	SLC7A11	Induce SLC7A11 expression, accompanied by decreased ferroptosis.	Induced reduction of COMMD10 hinders the ubiquitin HIF1α, disrupting its interaction with HIF1α and facilitating HIF1α nuclear translocation and the transcriptional regulation of CP and SLC7A11, collectively inhibiting ferroptosis in HCC cells. Induces adaptive expression of SLC7A11.
Compound	SLC7A11		
Class I ferroptosis stimulants: erastin, sorafenib	SLC7A11	Inhibit SLC7A11 expression, thus facilitating ferroptosis.	Unclear.
Fatty acid synthase (FASN)	SLC7A11	Induce SLC7A11 expression, accompanied by decreased ferroptosis, increased tumor growth, and drug resistance.	Binds to hypoxia-inducible factor 1-alpha (HIF1α), promoting its nuclear translocation, and subsequently enhancing transcription of SLC7A11.
DAZAP1	SLC7A11	Induce SLC7A11 expression, accompanied by decreased ferroptosis, increased tumor growth, and drug resistance.	DAZAP1 interacts with the 3'UTR (untranslated region) of SLC7A11 mRNA and positively regulates its stability.
Suppressor of cytokine signaling 2 (SOCS2)	SLC7A11	Inhibit SLC7A11 expression, thus facilitating ferroptosis.	SOCS2 recruits ubiquitin molecules, facilitating the ubiquitination and degradation of SLC7A11.

cells exhibit suppressed ferroptosis, as evidenced by elevated SLC7A11 and decreased PTGS2, an in vivo ferroptosis biomarker. Research has demonstrated that in a mouse model, this TP53 gene mutation causes a malfunction in the induction of ferroptosis and increases the risk of cancer [37]. This mutation just exists in Africans and African Americans, so genetic typing has significance in assessing the risk of cancer in these people [38].

In conclusion, the disfunction of p53 is correlated with ferroptosis in human HCC, probably through transcriptionally regulating the expression of SLC7A11 [32]. p53's bidirectional regulation of ferroptosis is intricate and mostly affects cancers that are particular to certain cell types. These data present intriguing opportunities to methodically investigate the distinct function of ferroptosis-based, p53-dependent tumor suppression [21].

Nrf2: Mutations in the Nrf2 gene were found in approximately 15% of HCC cases [39, 40]. The nuclear factor erythroid 2-related factor 2 (Nrf2) is an important transcription factor that can protect cells against various oxidative and toxic insults, such as ferroptosis. Nrf2 functions as an upstream regulator of System Xc(-) and is involved in a variety of biological processes, such as iron metabolism and antioxidant responses [32]. Furthermore, SLC7A11 transcription is induced by NRF2, and this transcription is frequently raised in human malignancies along with drug resistance, increased tumor growth, and decreased ferroptosis [41-43].

The expression of Nrf2 is associated with its negative regulator, Kelch-like ECH-associated protein 1 (Keap1). Under normal circumstances, the Cul3/Rbx1 E3 ubiquitin ligase catalyzes the proteasomal degradation of Nrf2 through Keap1's role as an adapter of the ubiquitin ligase complex. However, under oxidative stress conditions, Keap1 becomes inactivated, and stabilized Nrf2 is released. Then, Nrf2 heterodimerizes with small v-maf (avian musculoaponeurotic fibrosarcoma oncogene homolog) proteins, translocates to the nucleus, and subsequently binds to antioxidant response elements (AREs), regulating genes responsible for protecting against lipid peroxidation, such as SLC7A11 [21, 32]. Therefore, Nrf2 is considered a negative regulator of ferroptosis and a promoter of ferroptosis resistance. When it is upregulated, SLC7A11 expression is enhanced.

Ferroptosis suppression brought on by Nrf2 activation aids in maintaining tissue homeostasis and providing protection against oxidative stress in some stress-induced illnesses. On the other hand, processes involving Nrf2 activation make tumor cells less susceptible to ferroptosis, which makes them more resistant to the effects of sorafenib and other anticancer medications. An increasing body of research indicates that Nrf2 overexpression stimulates the expression of ATP binding box G2 (ABCG2) and Metallothionein-1G (MT-1G), both of which are involved in the development of acquired sorafenib resistance. Consequently, cancer cells may become resistant to sorafenib and use Nrf2 overexpression to ward off ferroptosis [44]. For instance, recent studies have concentrated on the p62-Keap1-NRF2 pathway in HCC. It has been found that both mouse liver cancer models and HCC patients exhibit an imbalance in the p62-Keap1-NRF2 pathway [39, 45, 46]. The indirect activation of the p62-Keap1-Nrf2 pathway prevents Nrf2 degradation, and the subsequent accumulation of Nrf2 protects HCC cells against ferroptosis induced by drugs like sorafenib. At that point, drug resistance started to develop. Consequently, targeting Nrf2-regulated ferroptosis inhibition is a therapeutic strategy for treating HCC [21].

YAP/TAZ and ATF4: Yes-Associated Protein (YAP) and TAZ are widely recognized transducers, exhibiting redundant functional read-outs within the Hippo signaling pathway [47]. They play a pivotal role in transcriptionally regulating the onset, advancement, and metastasis of cancer [25]. Recent research illuminated that YAP/TAZ induced ferroptosis resistance in HCC cells via modulating the amount of SLC7A11 as an inhibitor of ferroptosis in HCC cells [26, 40]. Also, further researches were carried out, indicating that YAP and TAZ knockdown decreased SLC7A11 expression and mRNA levels in HCC cells, with sorafenib-induced ferroptosis increasing. The underlying process may involve YAP/TAZ binding to a TEAD binding motif located roughly 400 bps upstream of the transcriptional start point in the promoter sequence of SLC7A11, hence upregulating SLC7A11 production [25, 32].

It is widely recognized that stress-induced expression of SLC7A11 is regulated by the ROS sensor Nrf2 and the stress regulator ATF4 [48, 49]. In response to sorafenib-induced endoplasmic reticulum (ER) stress, ATF4, a crucial modulator of oxidative homeostasis, upregulates its expression, consequently increasing SLC7A11 levels to counteract ferroptosis. Evidence of ATF4's involvement in HCC resistance to ferroptosis is demonstrated by the promotion of sorafenib-induced ferroptosis in HCC, characterized by elevated lipid peroxidation, reduced GSH, decreased cell viability, and induced expression of SLC7A11 [25, 48, 49]. Further investigation revealed that activation of YAP/TAZ leads to the nuclear translocation of ATF4, inhibiting its polyubiquitination and stabilizing ATF4, thereby playing a role in maintaining ATF4 protein stability, nuclear translocation, and transcriptional activity, resulting in increased ATF4 expression. In essence, YAP/TAZ and ATF4 collaborate to induce the expression of SLC7A11 [25]. Additionally, studies have shown that in the absence of Nrf2, ATF4 is unable to induce SLC7A11 mRNA. Nrf2 not only activates the antioxidant response by binding to antioxidant response elements (AREs) in its target promoters but also collaborates with ATF4 to regulate SLC7A11 expression.

In conclusion, YAP/TAZ and ATF4 are functionally related, with YAP/TAZ serving as a promotor of ATF4 expression. YAP/TAZ interact with ATF4 and, together with TEADs, promote its nuclear import to prevent its ubiquitylation and proteasomal degradation in the cytoplasm. Both inhibit ferroptosis by increasing the expression of SLC7A11, giving HCC cells resistance to drugs like sorafenib, which triggers ferroptosis. Therefore, studies highlight YAP/TAZ as novel repressors of ferroptosis and, thus, as attractive therapeutic targets to overcome therapy resistance.

Interferon gamma (IFNγ): IFNγ, a type II interferon, is mostly released by T cells and natural killer (NK) cells. It can trigger a polarized immune response that includes CD8+ cytotoxic T cells and T helper (Th) CD4+ T cells, hence promoting infection resistance and tumor rejection. It has been demonstrated to perform vital roles in HCC by functioning as an important immune modulator and a tumor killer by binding to receptors expressed on the surface of the tumor and causing autophagy or apoptosis [50-52]. According to multiple studies, patients with high-grade carcinoma in situ (HCC) who have lower-than-normal blood IFNγ levels or negative IFNγ receptor expression in malignant tissues tend to have larger tumors and greater rates of metastasis and recurrence [53]. As previously stated, numerous investigations have discovered that IFNγ has a role in controlling the growth and death of tumor cells. Nevertheless, the function of IFNγ in controlling ferroptosis in HCC has not been thoroughly investigated in many studies.

It was recently discovered that IFNγ, through its negative regulation of SLC7A11 in HCC cells, was intimately linked to ferroptosis. According to experiments, IFNγ treatment led to increased lipid peroxidation, higher glutathione depletion, and heightened sensitivity of cells to ferroptosis activators. It also promoted cell cycle arrest in the G0/G1 phase [19]. IFNγ activated the JAK/STAT pathway in HCC cell lines, which in turn down-regulated the mRNA and protein levels of SLC7A11, hence influencing ferroptosis. It has been confirmed that STAT1 and STAT3 bind to the SLC7A11 promoter regions (gamma-activated site, GAS), resulting in transcriptionally decreased SLC7A11 expression [54]. Correspondingly, increased levels of p-STAT1, p-STAT3, and IRF1 were also observed in HCC cells following the synergic treatment of IFNγ and ferroptosis inducers [19].

In short, IFNγ can negatively regulate the expression of SLC7A11 through the JAK/STAT pathway in HCC cells and increase mitochondrial oxidation, thus sensitizing HCC cells to ferroptosis [32]. It provides new insights for applying IFNγ as a cancer treatment.

Ferroptosis-related non-coding RNA: Long non-coding RNAs (lncRNAs) are a class of non-coding RNAs that consist of more than 200 nucleotides. They exhibit dynamic expression and function in various capacities throughout physiological and pathological processes through a variety of pathways. LncRNAs interact with transcriptional factors, or chromatin-modifying complexes, to participate in almost every stage of gene expression. Additionally, by binding to target mRNAs or participating in the posttranslational modification of proteins, they can control the stability of those mRNAs [55, 56]. It has recently been discovered that some lncRNAs

control ferroptosis in cancer cells. For example, by impeding SLC7A11's stability, the decreased lncRNA HEPFAL in HCC tissues encourages ferroptosis and causes lipid ROS and iron to accumulate [57]. Also, it has been demonstrated that the recently identified molecule known as cancer susceptibility candidate 11 (CASC11) is upregulated in HCC, with both elevated and stabilized levels of SLC7A11 expression and mRNA. Furthermore, lncRNAs' activities will help HCC cells resist sorafenib-induced ferroptosis [58]. Besides HEPFAL and CASC11, Double homeobox A pseudogene 8 (DUXAP8) can also reduce the sensitivity of HCC to sorafenib-induced ferroptosis by facilitating SLC7A11 palmitoylation and impeding its lysosomal degradation [59]. It was recently shown that LINC00654 upregulated the expression of SLC7A11, enhanced treatment resistance in HCC, and functioned as a useful predictive biomarker for HCC. By boosting the recruitment of the transcription factor STAT3 onto the SLC7A11 promoter, it improved the expression of SLC7A11.

Mammals are known to express circular RNAs (circRNAs), a family of non-coding RNAs, extensively. Although a large number of circRNAs have been found, nothing is known about their possible activities. CircRNAs have been shown to compete with shared miRNAs to act as competitive endogenous RNAs (ceRNAs) and co-regulate other RNAs [60]. Circ0097009 acts exactly as a ceRNA, regulating the expression of SLC7A11 by competing with SLC7A11 for binding to miR-1261 in HCC. Circ0097009 is upregulated in HCC cell lines; therefore, less SLC7A11 will bind to miR-1261, meaning more SLC7A11 expression. The circ0097009/miR-1261/SLC7A11 axis mediates HCC progression by regulating ferroptosis. Therefore, circ-0097009 may be a diagnostic biomarker for HCC and a potential target for HCC therapy.

Radiotherapy: An increasing amount of data suggests that radiation therapy may be a useful treatment for HCC, exerting its influence on the progression of HCC through the modulation of SLC7A11 expression [9]. Carbon ions (CI) with high linear energy transfer (LET) are commonly employed in malignancy treatment; they have been demonstrated to elevate p53 expression through PERK (the transmembrane sensor that PKR likes ER kinase) [61, 62]. Elevated p53, in turn, downregulates SLC7A11 expression, facilitating ferroptosis in HCC cells. However, reduced SLC7A11 expression was observed with the combined treatment of CI irradiation and sorafenib, as opposed to CI irradiation alone. Additionally, aside from increased letCI, other studies have demonstrated that ionizing radiation (IR) can activate the ataxia-telangiectasia mutated (ATM) gene. This gene induces iron-dependent cell death in cancer cells by suppressing the expression of SLC7A11 [63].

Conversely, IR-induced reduction of copper metabolism MURR1 domain 10 (COMMD10), a member of copper metabolism-related proteins, hinders the ubiquitin degradation of hypoxia-inducible factor 1 alpha (HIF1α) (via induced copper accumulation), disrupting its interaction with HIF1α. Consequently, this facilitates HIF1α nuclear translocation and the transcriptional regulation of ceruloplasmin (CP) and SLC7A11, collectively inhibiting iron-dependent cell death in HCC cells [64]. An alternative study has demonstrated that IR induces adaptive expression of SLC7A11 and GPX4, thereby mitigating ionizing radiation-induced lipid peroxidation and suppressing PTGS2 expression, contributing to radioresistance [65].

Other compounds: There are other compounds that can precisely modulate the expression of SLC7A11, serving as inducers or inhibitors of ferroptosis. Take ferroptosis inducers as an example, Class I ferroptosis stimulants like erastin as well as sorafenib are compounds targeting SLC7A11 [21].

Also, the up-regulation of fatty acid synthase (FASN) can enhance sorafenib-induced ferroptosis resistance by binding to hypoxia-inducible factor 1-alpha (HIF1α), promoting its nuclear translocation, inhibiting its ubiquitination and proteasomal degradation, and subsequently enhancing transcription of SLC7A11.

DAZAP1, an RNA-binding protein (RBP), was found to be an effective binding partner of SLC7A11 mRNA and a strong inhibitor of ferroptosis. Subsequent investigation demonstrated that DAZAP1 favorably regulated the stability of SLC7A11 mRNA by interacting with its 3'UTR (untranslated region) [66].

The suppressor of cytokine signaling 2 (SOCS2), a protein-coding gene, is a cytokine-inducible negative regulator. SOCS2 recruits ubiquitin molecules and acts as a bridge to transfer attached ubiquitin to the N-terminal domain of SLC7A11, facilitating the ubiquitination and degradation of SLC7A11, ultimately leading to ferroptosis and radiosensitization in HCC [67].

The significance of studying SLC7A11 in HCC

Research conducted domestically and internationally has demonstrated that SLC7A11 is extensively expressed in a variety of malignant tumors, including breast and hepatocellular carcinomas, impacting the tumor's formation, metabolism, prognosis, and course of treatment. A new perspective on HCC treatment and prognosis has been provided by the identification of SLC7A11 and its underlying mechanism. Future research is necessary to fully understand the significance of SLC7A11 in the identification and management of HCC. Furthermore, SLC7A11 may function as a strong marker for the prognostic classification of HCC, which is linked to the invasion of diverse immune cells.

SLC7A11 contributes to the early diagnosis and prognosis of HCC

SLC7A11 may have oncogene properties, as it has been shown to be elevated in a number of human tumor tissues, including lymphomas, brain cancer, pancreatic cancer, and leukemias [68-71]. The data from 2013 suggested that there was a larger functional requirement for xCT in tumor tissues, despite the fact that xCT expression is not exclusive to tumor cells and has also been seen in normal cell types such as fibroblasts, monocytes, and macrophages [72-75]. The main source of cysteine for most cancer cells is SLC7A11, maybe due to the fact that de novo biosynthesis or protein catabolism are often unable to meet the enormous need for antioxidant defense in cancer cells [24]. Additionally, ferroptosis, one of the antitumor strategies, is rendered ineffective against tumor cells due to the elevated expression of SLC7A11. Subsequent research has revealed that SLC7A11 expression is frequently higher in HCC tumor tissues than in normal tissues and that this is linked to a bad prognosis for HCC patients [76]. Increased intracellular GSH content and decreased ROS accumulation may be the underlying causes of the bad prognosis; as a result, malignant cells are difficult to undergo ferroptosis, and some may even develop medication resistance [76]. SLC7A11 overexpression can also inhibit ferroptosis and neutralize the effects of other oncogenes' tumor-suppressive mechanisms [73, 76]. Notably, SLC7A11 mRNA was significantly elevated in primary HCC tumors compared with nearby liver parenchyma, according to immunohistochemical examination and multi-tissue arrays [25]. Based on this genetic signature, SLC7A11 can be combined with other genes to construct prognosis models for HCC, predicting the outcomes of HCC patients in the long run.

SLC7A11 serves as a drug target in HCC therapy

Over recent years, inducing nonapoptotic cell death has opened new avenues for cancer treatment and reduced the likelihood of drug-resistant clones. Since the first demonstration in 2012, a series of strategies have been developed to induce ferroptosis in cancer cells, including the use of nanomaterials, clinical drugs (such as sorafenib), sulfasalazine, experimental compounds, and deprivation of cystine [26, 38, 77-79]. As an important constituent of ferroptosis, SLC7A11 becomes a hot spot for HCC treatment because it can induce ferroptosis in cancer cells. As a result, there has been a lot of interest in learning about the function and regulatory mechanisms of SLC-7A11 in ferroptosis and tumor biology, as well as in using SLC7A11 as a therapeutic target in cancer treatment [24].

Approved in 2007, the tyrosine kinase inhibitor (TKI), sorafenib, was the first systemic treatment for HCC and had been used globally [10]. Also, meta-analysis established that it was more effective in HCV-associated HCC and liver-only disease than in HCC from non-HCV causes or in extrahepatic disease [80, 81].

According to previous knowledge, sorafenib exerts its anticancer potential with its kinase inhibitory effects. Thus, the medication can directly suppress cellular proliferation and induce apoptosis by targeting the Ras/Raf/MAPK pathway, the VEGF pathway, and FMS-like tyrosine kinase 3 (FLT3) [82, 83]. Put another way, it has the ability to "kill two birds with one stone" by acting as both an inhibitor of angiogenesis and a suppressor of tumor cell prolif-

eration simultaneously [84]. In 2013, sorafenib was found to induce a new type of regulated cell death (RCD) - ferroptosis [78]. Additionally, Lachaier et al. found that sorafenib was the only medication to exhibit ferroptotic efficacy when compared to other kinase inhibitors, indicating that sorafenib's ability to induce ferroptosis was a unique characteristic that had nothing to do with its well-known kinase inhibitory properties [18, 85]. In terms of mechanism, another study showed sorafenib could induce ferroptosis by inhibiting SLC7A11, just like erastin, a ferroptosis inducer. When SLC7A11 is suppressed, GSH synthesis is stopped, which can lead to an increase in reactive oxygen species (ROS) and subsequent ferroptosis [32, 38, 86]. All things considered, sorafenib-induced ferroptosis is a potent method for inducing cell death in HCC that is not dependent on the inhibitory impact of kinases. To clarify the specific mechanisms involved in this process, more researches are still necessary.

Moreover, non-toxic xCT-inhibitory drugs such as sulfasalazine may prove to be effective cancer therapies. Serving as an xCT inhibitor, sulfasalazine has been routinely used in the clinical therapy of inflammatory bowel disease and rheumatoid arthritis [27]. Also, it has been demonstrated to result in cellular growth arrest in various cancers, including lymphoma, prostate, and breast cancer cell lines [28, 87, 88]. This SLC7A11 inhibitor prevents the import of cystine into the cytoplasm, leading to decreased GSH generation. Therefore, the cytotoxic ROS accumulates in cancer cells, inhibiting cell proliferation as well as tumor growth. Recent studies have identified this process in HCC cell lines, proving that SLC7A11 can be a therapeutic target and that such inhibitory drugs may serve as a promising treatment option for HCC patients [76]. However, more clinical trials are required to confirm the availability of the drugs for HCC patients.

Haloperidol, an antagonist of the sigma 1 receptor (S1R), an oxidative stress metabolism modulator, was found by Bai et al. to have positive effects on sorafenib-induced ferroptosis, in contrast to the previously mentioned negative regulators of the condition. These effects were observed even at relatively lower doses of sorafenib [89]. The sigma-1 receptor is a non-opioid receptor that exhibits molecular chaperone activity, serving as a negative regulator of ferroptosis in human HCC cells through involvement in ROS and iron metabolism. Reduced expression of SLC7A11 and impaired system Xc(-) function have been linked to S1R knockdown, along with elevated endogenous ROS levels [90-92]. It leads to the conclusion that haloperidol may benefit HCC patients treated with sorafenib by reducing the dosage or potentiating the effectiveness of this drug [38, 89].

With the increasing use of nanotechnology in recent years, there has been discussion on the potential use of nanoparticle pharmaceuticals to cause ferroptosis and other synergistic effects (such as apoptosis), which together can enhance the anticancer impact. The novel drugs can exert multiple functions by combining different drugs together, including sorafenib and other particles. For instance, Tian et al. (2022) reported the development of a unique cascade copper-based metal-organic framework (MOF) therapeutic nanocatalyst using HKUST-1, a type of metal-organic framework, in combination with sorafenib (Sol) and meloxicam (Mel), an inhibitor of cyclooxygenase-2 (COX-2). In this architecture, sorafenib stimulates ferroptosis by blocking SLC7A11 expression, whereas COX-2 inhibitors induce mitochondrial autophagy [93]. With an increasing number of anticancer nanopowder medications approved by the FDA, the path to developing medications with improved safety and efficacy will become an emerging road for future cancer treatment [94].

Conclusions and future perspectives

Taken together, we can conclude that SLC7A11-mediated ferroptosis plays a pivotal role in the development and treatment of liver cancer. We discussed ferroptosis as a novel pathogenesis mechanism and provided a brief introduction to the pathogenesis of HCC in this review. Subsequently, SLC7A11's structure and function were revealed, and the intimate connection between SLC7A11 and ferroptosis was thoroughly explained. These developments demonstrated the critical role SLC7A11 plays in the diagnosis, prognosis, and treatment of HCC. Additionally, this research documented sorafenib resistance in advanced HCC, with various strategies aiming at SLC7A11 to overcome the drug resistance. One potential tactic

that could be used to boost sorafenib efficacy in clinical combination therapy is the stimulation of ferroptosis via SLC7A11. We are at the start of a new era, despite the fact that medication resistance has made systemic therapy in HCC disappointing in the past. To enhance the prognosis of HCC patients and progress the field, more research utilizing genomic profiling, immunotherapy, biomarker-matched molecularly targeted therapy, and combinations of the above is required [2].

However, the knowledge of ferroptosis and SLC7A11 in relation to HCC remains understudied, and a number of questions regarding the application of SLC7A11 in HCC have not been addressed:

(I) The main cause is the paucity of studies being done on ferroptosis at the moment, considering that the condition was only discovered in 2012. Furthermore, the connection between ferroptosis and other forms of RCD is not well understood. In addition, the connection between ferroptosis and HCC is further complicated by the metabolic reprogramming linked to SLC7A11. Although ferroptosis induction has been used to increase sorafenib efficacy, the evidence currently available is insufficiently strong to make definite judgments about whether interfering with ferroptosis is generally advantageous at the cellular level.

(II) There have been few clinical trials using ferroptosis modulation of SLC7A11, and the great majority of research that is now accessible was carried out in vitro or in animal models. Furthermore, some ferroptosis inducers' in vivo pharmacokinetics still make them unsuitable for in vivo use. Certain ferroptosis inducers, like Erastin, are highly efficient in vitro in killing cancer cells, but their pharmacokinetic characteristics - such as solubility and metabolic stability - make them unsuitable for use in living organisms [95].

(III) Ferroptosis has been shown to have distinct effects on chronic liver disease and HCC, two conditions that are intimately linked to one another. Ferroptosis is the main cause of liver damage in chronic liver diseases (such as ALD and NAFLD), and blocking ferroptosis would counteract the harmful effect. On the other hand, ferroptosis in HCC may make cells more susceptible to sorafenib; blocking this cell death leads to medication resistance. We are interested in knowing if there is a window of opportunity when ferroptosis intervention can stop chronic liver disease from developing into HCC.

(IV) In terms of SLC7A11 regulators, such findings were not convergent across all known cancers. It can be challenging to extrapolate the findings to other malignancies since some can have opposing effects on various cancers. For instance, Nrf2 has dual functions as an oncogene and a tumor suppressor, and the Nrf2-mediated antioxidant response pathway is thought to have a "double-edged sword" effect on the onset and progression of cancer [39, 96]. Also, Xie et al. observed that p53 limited erastin-induced ferroptosis by further increasing the expression of SLC7A11 in human colorectal cancer [97]. However, p53 was found to inhibit the expression of SLC7A11 in HCC.

As was previously mentioned, ferroptosis presents a novel therapeutic opportunity in the age of apoptosis resistance. The discovery of SLC7A11 suggests that ferroptosis biomarkers need to be further investigated, as this is one of the most crucial requirements for advancing ferroptosis assessment and clinical applications. Considering all of these different factors combined, there is currently a dearth of data that clearly explains how ferroptosis and SLC7A11 contribute to liver illnesses like HCC, making this sector full of unknowns. The answers to these queries will shed more light on the ferroptosis pathway and create opportunities for methodical investigation into the potential therapeutic benefits of ferroptosis in the treatment of HCC.

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Disclosure of conflict of interest

None.

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