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SLC7A11 as a bridge between ferroptosis and disulfidptosis: a promising target for tumor treatment

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Abstract

Cell death is a basic physiological process involved in embryonic development, aging, immune responses and other life processes. In particular, ferroptosis and disulfidptosis are two forms of regulatory cell death (RCD) that have been identified in recent years as being caused by imbalances in cellular metabolism. Solute Carrier Family 7 Member 11 (SLC7A11, xCT), a cystine transporter, is often highly expressed in tumor cells, which not only participates in the synthesis of glutathione (GSH), but also plays an indispensable role in the inhibition of oxidative stress-induced ferroptosis. However, glucose starvation of SLC7A11 ^{high} tumor cells consumes a large amount of NADPH, leading to disulfide stress in actin cytoskeletal proteins, which triggers disulfidptosis. These findings suggest that there is an intrinsic relationship between ferroptosis and disulfidptosis and that SLC7A11 connects the regulation of both forms of death. In this article, we first reviewed the regulatory mechanism controlling SLC7A11 expression and its function and then focused on its role and mechanism in mediating ferroptosis and disulfidptosis in tumorigenesis and treatment. Finally, we carefully discussed the intrinsic links between ferroptosis and disulfidptosis as well as the remaining scientific issues related to their mediation of tumorigenesis and treatment, aiming to provide a new perspective for cancer treatment, especially in the development of strategies for targeted treatment against specific metabolic pathways.

Highlights

• SLC7A11, a multipass transmembrane protein, mediates the cystine/glutamate antiporter activity in the system x_c^- and is overexpressed in multiple human cancers.

• SLC7A11 has two distinct functions in ferroptosis and disulfidptosis, suggesting a possible intrinsic link between these two types of cell death.

• SLC7A11 plays a vital role in the occurrence and development of tumors, and is emerging as a promising target in oncotherapy.

Keywords SLC7A11, Ferroptosis, Disulfidptosis, Tumor, Metabolism

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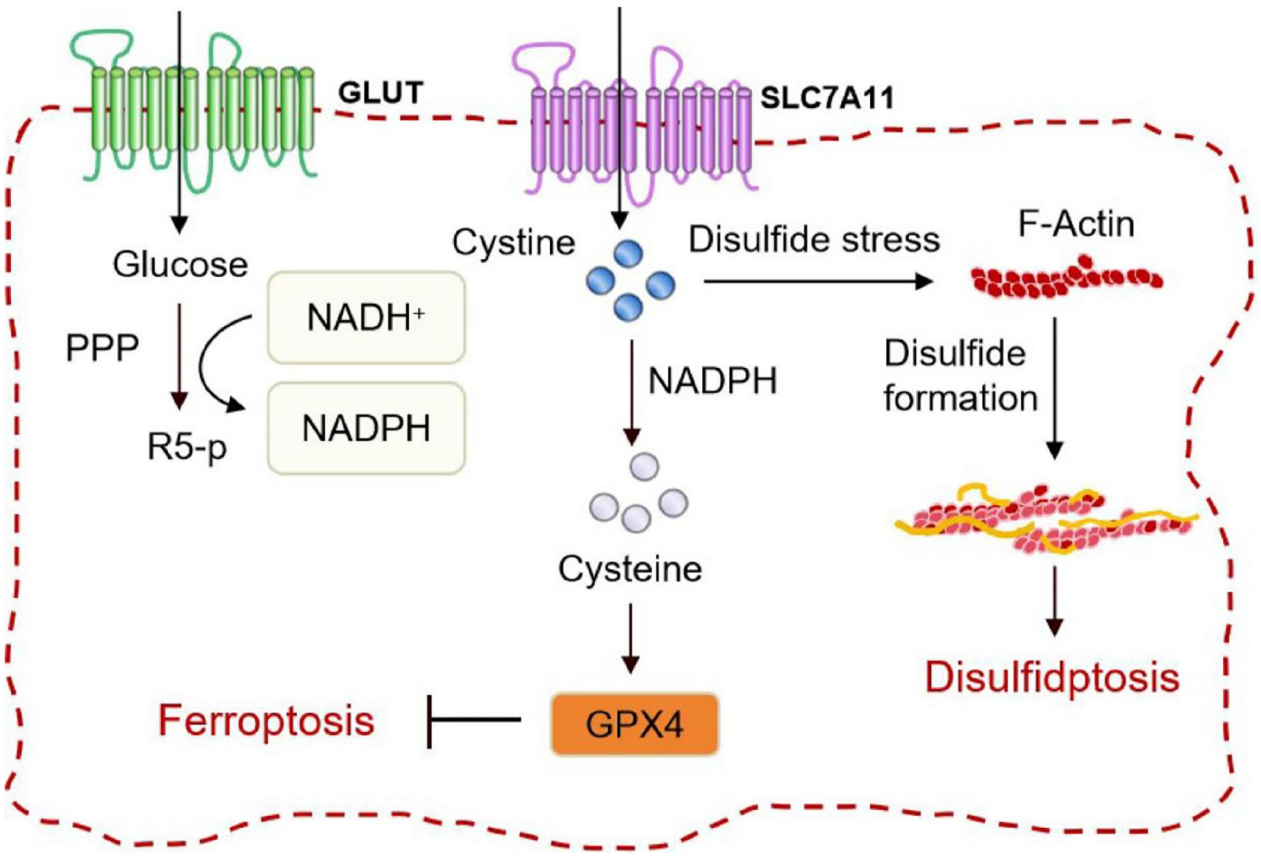
Graphical Abstract



Introduction

Cell death plays an indispensable role in the development and maintenance of homeostasis in organisms, such as by participating in the clearance of damaged cells and inhibiting the spread of pathogens, but this balance may be disrupted in metabolic diseases such as cancer [1]. In 2012, Green DR [2] classified several unique forms of regulatory cell death (RCD), including disulfidptosis, ferroptosis and cuproptosis into metabolic cell death, which is a form of cell death caused by an imbalance in cell metabolism caused by excess/deficiency of specific nutrients (glucose, amino acids, etc.) or metals (iron, copper, etc.).

In 2012, Dr. Brent R. Stockwell first proposed the concept of ferroptosis [3] (Table 1), which is an RCD process characterized by intracellular ROS accumulation and iron overload leading to lipid peroxidation and is highly correlated with the proliferation, invasion, and drug resistance of tumor cells and remodeling the tumor microenvironment (TME) [8, 15–17]. Disulfidptosis [10] is another form of cell death first reported by Professor Ganboyi's team in February 2023, resulting from disulfide stress caused by excess cystine accumulation in cells (Table 1). Recent studies further suggest that the molecular junction of these two forms of metabolic cell death is SLC7A11, which appears to have opposite effects on ferroptosis and disulfidptosis. In ferroptosis, increased SLC7A11 expression promotes the synthesis of GSH and inhibits lipid peroxidation [9, 18], whereas the accumulation of cystine in disulfidptosis depends on the transport activity of SLC7A11. Although both types of RCD involve intense oxidative stress, the results are markedly different: ferroptosis involves lipid peroxidation and the accumulation of ROS, whereas disulfidptosis involves the accumulation of disulfides such as cystine and the consumption of NADPH. Therefore, a comprehensive understanding of the complex mechanisms of these two types of metabolic cell death is highly important for the development of therapeutic targets in the field of oncology.

Overview of SLC7A11

The structure and expression of SLC7A11

The Xc^- system was first discovered in 1980 by Bannai and Kitamura in cultured human fetal lung fibroblasts [4]. It is a cysteine/glutamic acid exchange transporter consisting of a light-chain subunit solute carrier family

Table 1 Overview of the key events for the SLC7A11, Ferroptosis and Disulfidptosis

Year	Events	Ref
1980	SLC7A11 was first discovered in cultured human fetal lung fibroblasts by Bannai and Kitamura.	[4]
2012	SLC7A11 is widely expressed in tissues and cells including brain, liver, macrophages and retinal pigment cells under physiological conditions.	[5]
2012	Ferroptosis is an iron-dependent regulated cell death due to excessive accumulation of PUFAs, which has been discovered by Brent Stockwell.	[3]
2018	SLC7A11 is induced to express under various stress conditions, including oxidative stress and amino acid starvation, which plays an important role in cell redox homeostasis.	[6]
2019	The SLC7A11 is negatively correlated with the frequency of tumor infiltrating $CD8^+$ T cells in melanoma, while the ferroptosis signature is positively correlated with $CD8^+$ T cells.	[7]
2020	The SLC7A11^{high} and accumulation of cystine are more prone to cell death under the absence of glucose. However, this process can be retarded by inhibiting the formation of disulfides.	[8]
2021	The SLC7A11 expression has been found to be closely related to ferroptosis sensitivity and a large number of studies have explored its role in ferroptosis.	[9]
2023	Disulfidptosis is a form of cell death caused by excess cystine accumulation and disulfide stress, which was first reported by professor Ganboyi's team.	[10]
2024	Selenide production is facilitated by SLC7A11 activity, and selenide can reduce CoQ_{10} *via* the SQOR-dependent mechanism, thereby suppressing ferroptosis.	[11]
2024	Ferroptosis and disulfidptosis may interact intrinsically, with SLC7A11 potentially bridging the regulation of both forms of death.	[12, 13]
2024	It is necessary to further explore the association between ferroptosis and disulfidptosis, especially involving metabolic pathways related to SLC7A11.	[12, 14]

7 member 11 (SLC7A11, xCT) connected to a heavy-chain subunit (SLC3A2, CD98hc) *via* extracellular covalent disulfide bonds [19] (Fig. 1.) To date, there are 779 *SLC7A11* genes in the PubMed gene database, which are highly conserved in a variety of vertebrates, but no obvious homologous proteins have been found in most lower organisms. The human *SLC7A11* gene is located at 4q28.3 and has full-length cDNA of 9648 bp. Notably, cDNA library cloning of human SLC7A11 from many different cell lines (human embryonic lung tissue diploid fibroblast cell line WI-26 VA4, human retinal pigment epithelial cell line ARPE-19, human glioma U87 cells, etc.). was performed. Although their transcripts vary in length [20–23], all of these cDNA sequences share a common feature of a 231-bp 5'UTR and an open reading frame (ORF) of 1506-bp [24].

SLC7A11 is widely expressed in tissues and cells, including the brain, liver, macrophages and retinal pigment cells, under physiological conditions [5]. However, under pathological conditions, SLC7A11 is highly expressed in many cancers, including breast cancer [25], pancreatic cancer [26], ovarian cancer [27] and glioma [28]– [29]. Furthermore, Yuan et al. [30] revealed that Epstein-Barr virus infection is associated with activation of the p62-Keap1-Nrf2 signaling pathway, upregulation of SLC7A11 and glutathione peroxidase 4 (GPX4), a reduction in the sensitivity of nasopharyngeal carcinoma cells to ferroptosis and the promotion of chemotherapy resistance and tumor progression in nasopharyngeal carcinoma, suggesting that the expression pattern of SLC7A11 is related to abnormal cell metabolism.

The function of SLC7A11

SLC7A11 can mediate the proportional exchange of Glu and cystine. High SLC7A11 expression maintains the redox balance of tumor cells and tumor-related immune cells by regulating cystine metabolism and GSH synthesis, thus providing favorable conditions for tumor growth and metastasis [31]. Notably, recent studies have reported that increased xCT activity creates a more reducing extracellular environment, which facilitates the reduction of selenite to selenide [11] (Fig. 1.). Indeed, selenium uptake is markedly impaired under SLC7A11 or SLC3A2 knockout conditions, and the impairment can be reversed by supplementing with thiol-containing compounds such as GSH [11, 32, 33].

In addition, SLC7A11 also plays a dominant role in regulating cellular glucose dependence and glutamine (Gln) metabolism [6]. For example, Gln deficiency can inhibit the growth of SLC7A11^{high} cells, whereas glucose starvation leads to the rapid death of SLC7A11^{high} cells [34]. Mechanistically, when tumor cells highly express SLC7A11, high Glu output could cause partial consumption of intracellular Glu and the feedback mechanism of the body drives cells to absorb more Gln and activate glutaminase (GLS) to convert it into Glu, resulting in a lack of Gln sensitivity in SLC7A11^{high} tumor [35]– [36]. A large amount of cystine is cytotoxic to cells in highly SLC7A11-expressing tumor cells, but the protective mechanism of the body can drive cells to rapidly reduce cystine to soluble Cys. This process requires NADPH, which is provided mainly by the glucose-pentose phosphate (PPP) pathway. Therefore, tumor cells with high SLC7A11 expression are glucose-PPP dependent. Notably, lung cancer cells with KEAP1 mutations exhibit Nrf2 activation and sensitivity to GLS inhibition [37], suggesting that the use of GLS inhibitors has a good prospect in the treatment of lung cancer patients with KEAP1 mutations, and may provide a new therapeutic strategy for the treatment of patients with high SLC7A11 expression in their lung tumors.

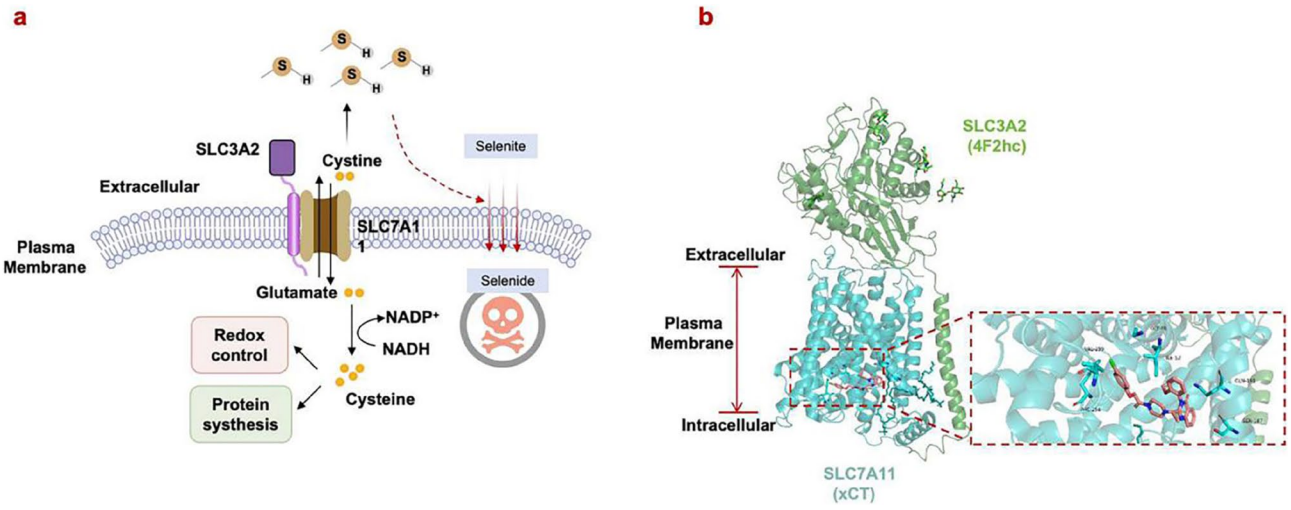


Fig. 1 The structure of erastin-bound SLC7A11-SLC3A2 complex. **a.**System X_C^-consists of a heavy chain component SLC3A2 and a transport module SLC7A11, and functions as a dedicated cystine import system, exchanging extracellular L-cystine for intracellular L-glutamate. The expression of the gene SLC7A11 in selenium-sensitive cancer cells leads to an increase in cystine uptake, resulting in the accumulation of thiol outside the cells, which can reduce selenite to volatile selenides and can induce them to enter the cells, causing cytotoxicity. **b.**Cartoon representation of system X_C^- that consists of the transmembrane transporter protein SLC7A11 (blue, with 12 membrane-spanning segments) and the regulatory subunit SLC3A2 (green). The PDB file is downloaded from RCSB PDB Database (http://www.rcsb.org).

Regulatory mechanism of SLC7A11

Transcriptional, epigenetic modification and post-transcriptional regulation of SLC7A11

Different stress conditions (such as amino acid deficiency including cystine, oxidative stress and electrophilic reagents) can induce the activity of the SLC7A11 transporter [38–40]. Moreover, activating transcription factor 4 (ATF4) can enable cells to adapt to amino acid deficient environments by regulating the transcription of genes involved in the stress response, including SLC7A11 [41]. Notably, under conditions of proteasome inhibitor treatment or glucose starvation, only the combination of ATF4 and Nrf2 can induce the expression of SLC7A11 [42, 43]. Recent work has revealed that ATF3 binds to the promoter of SLC7A11, and represses the expression of SLC7A11 in a p53- independent manner, thus promoting erastin-induced ferroptosis [44, 45].

MDM2 is an important protein that regulates the p53 pathway by ubiquitinating and degrading p53. Moreover, p53 is involved in regulating the ferroptosis process, and inhibiting p53 can increase the transcriptional level of SLC7A11 [44]. Nevertheless, the exact stress conditions that trigger p53-mediated repression of SLC7A11 expression remain to be further clarified (Fig. 2)

Epigenetic changes also regulate the transcription of SLC7A11, such changes include alterations of BRCA1-associated protein-1 (BAP1), polycomb repressive complex 1 (PRC1)-associated histone H2A ubiquitination, ubiquitin-specific processing protease 7 (USP7), p53-associated histone H2A ubiquitination and KDM3B histone H3 lysine 9 demethylase 3B (KDM3B) and so on [46, 47]. In addition, Tsuchihashi K et al. [48] reported that the cell surface localization of SLC7A11 can also be regulated by, e.g., the EGF receptor (EGFR), whose interaction with SLC7A11 can maintain its localization on the plasma membrane. Certainly, the stability, localization and activity of SLC7A11 are regulated not only by phosphorylation, but also by mRNA modification and ubiquitination. For example, one study [49] reported that SLC7A11 mRNA is modified by MeTTL3-mediated m6A, thereby increasing its expression, and that IGF2 mRNA-binding protein (IGF2BP) acts as a reader of m6A, it can also inhibit the deadenylation of SLC7A11 mRNA to increase the stability and expression of SLC7A11mRNA. Furthermore, Zhu's research indicated that TRIM26 physically interacts with SLC7A11 and mediates its ubiquitination [50] (Fig. 2).

Posttranscriptionally, SLC7A11 mRNA is regulated by various factors, including multiple siRNAs and miRNAs (miR-26a, miR-26b, miR-27a, miR-375, etc.). These microRNAs directly target SLC7A11 and suppress SLC7A11 mRNA stability and/or translation [51].

Posttranslational level and protein modification regulation of SLC7A11

Recent studies have further demonstrated that the expression of SLC7A11 is also regulated by a variety of posttranslational modifications. As mentioned above, SLC3A2, as a chaperone of SLC7A11, can regulate its protein stability [36]. The adhesion molecule CD44 variant (CD44v) is a protein recently found to interact with SLC7A11, and it was reported that [52] when there is a deficiency of CD44v, the cell surface localization and stability of SLC7A11 are impaired, leading to intracellular

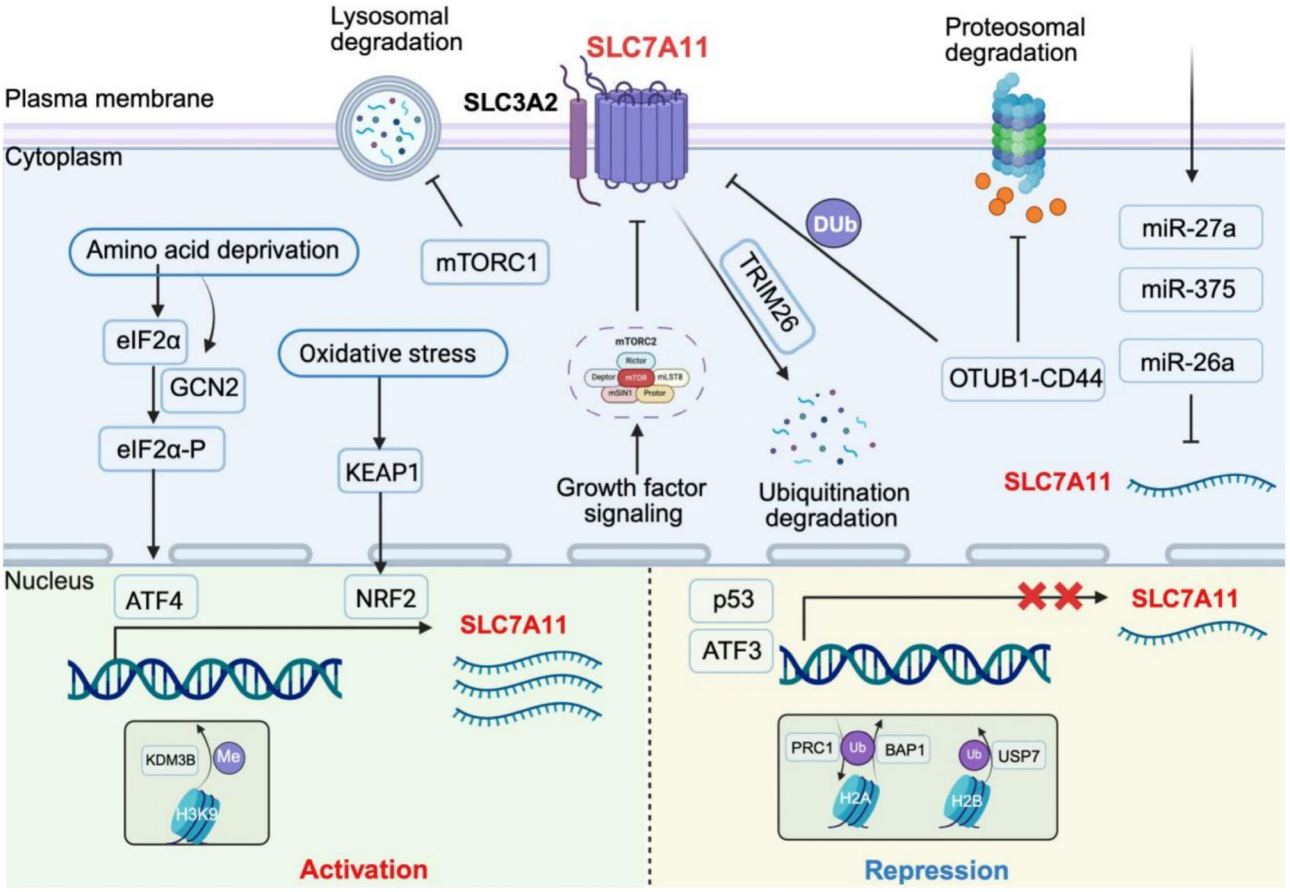


Fig. 2 The regulation of SLC7A11 gene expression at multiple levels. Transcription levels, ATF4 and NRF2 act as transcriptional activators of SLC7A11, and their expression or activity is enhanced in response to amino acid deprivation and oxidative stress. In contrast, p53, ATF3 serve as transcriptional suppressors of SLC7A11, with their level or activity; Epigenetic modification levels, BAP1 and PRC1-associated histone H2A ubiquitination, USP7 and p53-associated histone H2B ubiquitination and KDM3B histone methylation; Post-transcriptionally, SLC7A11 mRNA is regulated by various factors, including multiple miRNAs (miR-26a, miR-26b, miR-27a miR-375 etc); In terms of post-translational regulation, OTUB1 and CD44 form a trimeric complex with SLC7A11, ubiquitinating it to prevent its degradation by the proteasome, thereby stabilizing SLC7A11 protein, the mTORC1 promotes SLC7A11 degradation in lysosomes and the mTORC2 inhibits the activity of the SLC7A11 transporter by phosphorylating serine 26 on SLC7A11. More details are shown in the text. Abbreviations: ATF3, activating transcription factor 3; ATF4, activating transcription factor 4; BAP1, BRCA1-associated protein-1; CD44, CD44 molecule; eIF-2α, eukaryotic initiation factor 2α; GCN2, general control nonderepressible-2; H2A ub, histone H2A ubiquitination; H2B ub, histone H2B ubiquitination; H3K9 me, methylation of histone H3 Lys 9; KDM3B, histone H3 lysine 9 demethylase 3B; KEAP1, Kelch-like ECH-associated protein-1; mTORC1, mechanistic target of rapamycin complex 1; NRF2, nuclear factor erythroid 2-related factor 2; OTUB1, OTU deubiquitinase, ubiquitin aldehyde binding 1; p53, tumour protein p53; PRC1, polycomb repressive complex 1; SLC3A2, solute carrier family 3 member 2; SLC7A11, solute carrier family 7 member 11; TRIM26, tripartite motif-containing protein 26; USP7, ubiquitin-specific processing protease 7.

GSH depletion, ROS induction and suppression of the progression of gastrointestinal tumors. Furthermore, the transmembrane protein SLC7A11 is also thought to be regulated by lysosomal and proteasome degradation due to its localization on the plasma membrane. The mechanistic target of rapamycin (mTOR) is present in two distinct kinase complexes, mTORC1 and mTORC2, which exert regulatory effects on SLC7A11. Studies have shown that the inactivation of mTORC1 can promote the lysosomal degradation of SLC7A11, although the specific mechanism remains unknown [53, 54]. Gu et al. reported that mTORC2 physically interacts with xCT to phosphorylate Ser26 of xCT and therapy inhibiting xCT activity. The posttranslational regulation of xCT by mTORC2 has an important role in allowing tumor cells to respond to the changing external environment [55] (Fig. 2.).

Moreover, ubiquitin-fold modifier 1 (UFM1) can be covalently bound to the target protein through a series of enzymatic reactions, and SLC7A11 is a substrate for UFMylation. Yang et al. [25] reported that metformin can reduce the protein stability of SLC7A11 by inhibiting its UFMylation, suggesting that UFM1/SLC7A11 may be a new potential anticancer target, but the specific mechanism by which UFM1 acts on SLC7A11 remains unclear.

Ferroptosis and disulfidptosis in tumorigenesis

Ferroptosis

Involvement of SLC7A11 in regulating ferroptosis

SLC7A11 is a key regulator of ferroptosis, and its downregulation can inhibit cysteine metabolism, resulting in lower cystine levels and reduced GSH biosynthesis in cells. In addition, it can also indirectly suppress the activity of GPX4, resulting in the accumulation of intracellular lipid peroxides and ultimately inducing ferroptosis [56]. In particular, the inhibition of GPX4-induced ferroptosis is dependent on the acyl-CoA synthetase long chain family member 4 (ACSL4). ACSL4 can help to integrate polyunsaturated fatty acids (PUFAs) into phospholipids, which are the main source of lipid peroxidation. Hence cells lacking ACSL4 are significantly resistant to GPX4-induced ferroptosis [57, 58] (Fig. 3). Interestingly, recent studies have shown that the existence of GSH-GPX4 and ACSL4 independent mechanisms can promote ferroptosis [59]. Specifically, SLC7A11 can interact with arachidonic acid 12-lipoxygenase (ALOX12) to restrain the lipoxygenase activity of ALOX12 and mediate the peroxidation of PUFAs, thereby inhibiting ferroptosis (Fig. 2). In addition to its canonical role in GPX4 synthesis, recent studies have shown that selenide can reduce CoQ10 *via* the SQOR-dependent mechanism, thereby suppressing ferroptosis and lipid peroxidation [11].

p53 is a tumor suppressor gene that plays important roles in cell cycle, apoptosis, senescence and other life phenomena. However, the latest research [60] has revealed that p53 3KR (K117R, K161R, K162R), an acetylation-deficient mutant, fails to carry out these tumor suppressor functions, but it retains its metabolic activity, which can reduce cystine uptake and the sensitivity of cells to ferroptosis by inhibiting the expression of SLC7A11. In addition, the African-specific p53 mutant (S47 mutant) has also been shown to modulate SLC7A11 and ferroptosis, which is closely associated with tumor suppression [61]. In summary, the inhibition of ferroptosis is at least partly due to the tumor suppressor function of p53.

The tumor suppressor BAP1 is a deubiquitinating enzyme containing the ubiquitin C-terminal hydrolase

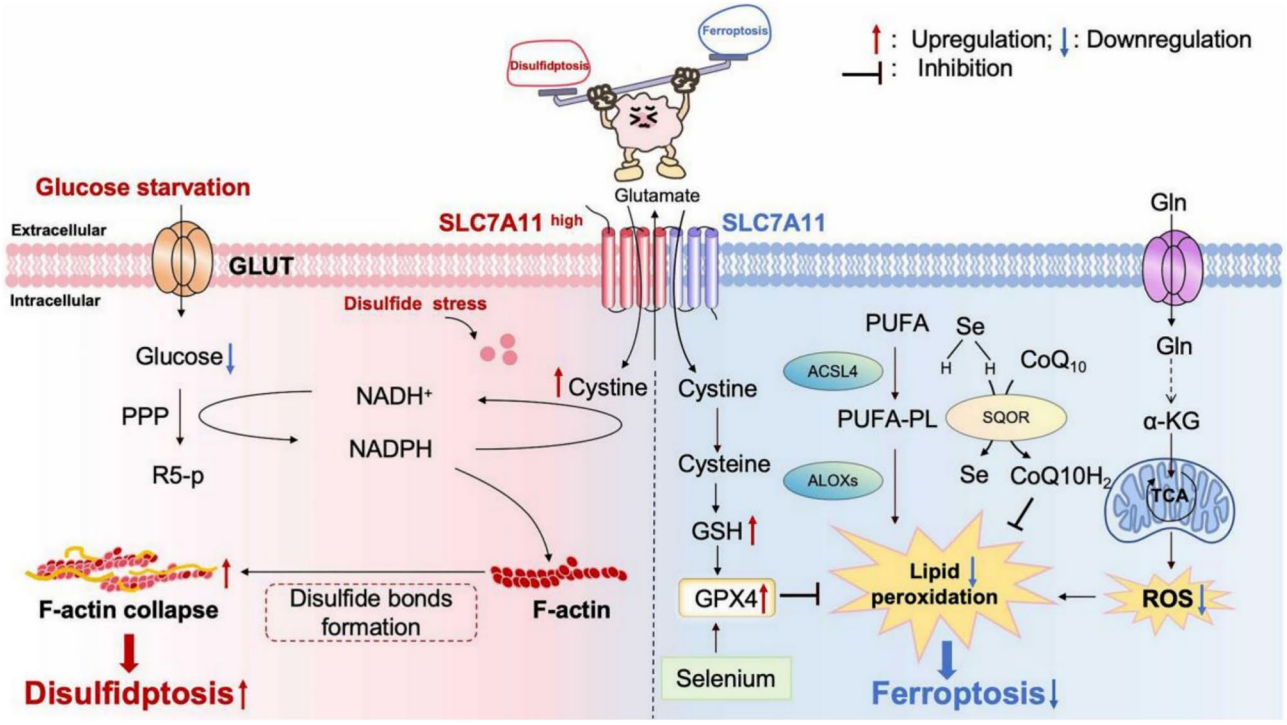


Fig. 3 The model of SLC7A11-mediated cell death: interplay between disulfidptosis and ferroptosis. Extracellular cystine is taken into the cell through SLC7A11 and then transformed into cysteine by a reduction reaction that depletes NADPH. When tumor cells over-express SLC7A11, this indicates high cystine uptake coupled with the depletion of NAPDH under the circumstance of glucose starvation. This will trigger the production of disulfide stress in the cell, leading to the formation of disulfide bonds between actin cytoskeleton proteins and the collapse of the F-actin network, eventually triggering disulfidptosis (Left). Once extracellular cystine is transported into the cell, it is reduced by NADPH to cysteine. GSH prevents ferroptosis by reducing lipid peroxides or by reducing the accumulation of ROS. Furthermore, Selenium can enhance the expression of GPX4, the increased GPX4 uses GSH to reduce lipid peroxides or ROS into their inactive forms, thereby preventing ferroptosis process (Right). More details are shown in the text. Abbreviations: PPP, glucose-pentose phosphate pathway; R5P, Ribose 5-phosphate; F-actin, actin filament; PUFA, polyunsaturated fatty acids; PUFA-PL, PUFA-containing phospholipids; ACSL4, Acyl-CoA synthetase long chain family member 4; ALOXs, Arachidonic acid x-lipoxygenase; GPX4, Glutathione peroxidase 4; TCA, tricarboxylic acid cycle; Gln, glutamine.

domain that acts by reducing histone 2 A ubiquitination (H2Aub) on chromatin. In particular, SLC7A11 is a key target gene of BAP1 in the processes of tumorigenesis and fetal development [62]. BAP1 can reduce the H2Aub occupancy on the promoter of SLC7A11 in a deubiquitinating dependent manner, inhibit the expression of SLC7A11 and decrease the uptake of cystine, thus leading to lipid peroxidation and ferroptosis. In conclusion, BAP1 promotes ferroptosis at least in part by suppressing SLC7A11, thus inhibiting tumor growth. Additionally, Liu et al. [63] reported that the ubiquitin hydrolase OTUB1 could inhibit ferroptosis and promote tumor growth by stabilizing SLC7A11.

Notably, SLC7A11-mediated inhibition of ferroptosis not only plays a role in tumors caused by the absence of tumor suppressor factors such as BAP1 and p53, but also contributes to proto-oncogene-driven tumorigenesis. KRAS is a well-known proto-oncogene in human tumors and is frequently mutated in many types of cancers, including nonsmall lung cell cancer (NSCLC) [64], hepatocellular carcinoma (HCC) [65] and pancreatic ductal adenocarcinoma (PDAC) [66]. Research by Hu et al. [67] revealed that, oncogenic KRAS can promote the transcription of SLC7A11 through Nrf2. However, another study [68] revealed that the transcription factor ETS-1 can mediate KRAS expression by synergizing with ATF4 to facilitate the expression of SLC7A11. Further studies revealed that in pancreatic tumors with carcinomatous KRAS activation, SLC7A11 deletion significantly inhibits the development of PDAC driven by KRAS by inducing ferroptosis [26]. Overall, these studies showed that the suppression of SLC7A11 obviously weakens KRAS-induced tumor growth.

Involvement of SLC7A11 in immunotherapy

Tumor immunotherapy is a highly effective tumor treatment method that has shown encouraging clinical efficacy in recent years. Studies have shown that immune checkpoint inhibitors (ICIs) can activate $CD8^+$ T cells, release IFN-γ, activate the JAK-STAT1 pathway, and then downregulate the expression of SLC7A11and SLC3A2, ultimately promoting lipid peroxidation-dependent ferroptosis of tumor cells [69, 70]. Furthermore, ferroptosis can modify the TME, reducing the number and activity of immunosuppressive cells (i.e., Tregs, TAM_S, CAF_S, $MDSC_S$, etc.), thereby enhancing the ability of the immune system to attack the tumors. Additionally, macrophages can suppress the expression of SLC7A11 by releasing the TGF-β activating tumor cell SMAD-related signal, which likewise promotes ferroptosis of tumor cells [71]. The damage-associated molecular patterns (DAMPs) released by ferroptotic cells promote DC maturation and induce the activation of $CD8^+$ T cells as well as neutrophil granulocytes. Interestingly, Dai et al. [72] reported that ferroptosis can promote the growth of tumor cells by driving the polarization of macrophages in the TME. The $KRAS^{G12D}$ is the most common mutant form of the KRAS protein. Under the induction of oxidative stress, tumor cells undergo autophagy-dependent ferroptosis and release DAMPs, which are taken up by macrophages in the TME. **(**Fig. 4**)**. Immediately after that, macrophages induce macrophage polarization to the M2 phenotype through the STAT3-dependent fatty acid oxidation pathway, accelerating the development of tumors.

Notably, SLC7A11 is also involved in the development of immunotherapy resistance. Relevant studies have shown that noncoding RNA can affect chemotherapy resistance through the SLC7A11-mediated signaling axis. For example, miR-6077 induces cisplatin resistance in lung adenocarcinoma through the SLC7A11-mediated ferroptosis pathway [73] and circSnx12 improves cisplatin resistance in ovarian cancer by blocking ferroptosis through the miR-194-5p/SLC7A11 pathway [74]. Additionally, in patients with triple-negative breast cancer, the expression levels of SLC7A11 and ATF4 are much higher than those in normal breast tissue. The eIF2α/ATF4 axis can upregulate the expression of SLC7A11, promote GSH synthesis and inhibit ROS accumulation, while dephosphorylation of eIF2α can decrease the expression of SLC7A11 and increase the expression of caspase-3. Inducing apoptosis in triple-negative breast cancer cells increases their sensitivity to cisplatin and doxorubicin and reduces resistance [75, 76]. These studies suggest that SLC7A11 may be a therapeutic target for the treatment of multiple drug-resistant tumors.

Disulfidptosis

Involvement of SLC7A11 in the regulation of disulfidptosis

The intracellular transport of cystine by SLC7A11 can promote tumor growth, and SLC7A11 overexpression can result in an abnormal accumulation of intracellular disulfide, due to the uptake of excessive cystine (along with other disulfide molecules), thereby inducing disulfide stress since it is highly toxic to cells. Therefore, cells can reduce insoluble cystine into more soluble cysteine to alleviate the toxicity, and this process is highly dependent on NADPH [36]. Under conditions of glucose deficiency, a large amount of NADPH is consumed. Homocysteine uptake coupled with an inadequate NADPH supply leads to NADPH depletion. Moreover, abnormal disulfide bond binding in actin cytoskeletal proteins causes disulfide stress reactions, resulting in the collapse of the actin network and subsequent cell death, namely disulfidptosis **(**Fig. 3**)**. Thus, SLC7A11 is an important target for regulating the mechanism of disulfidptosis.

Researchers reported that ferroptosis inhibitors (Ferr-1 and DFO), an apoptosis inhibitor (Z-VAD-fmk), necrotizing apoptosis inhibitors (Nec-1 and Nec-2) and an

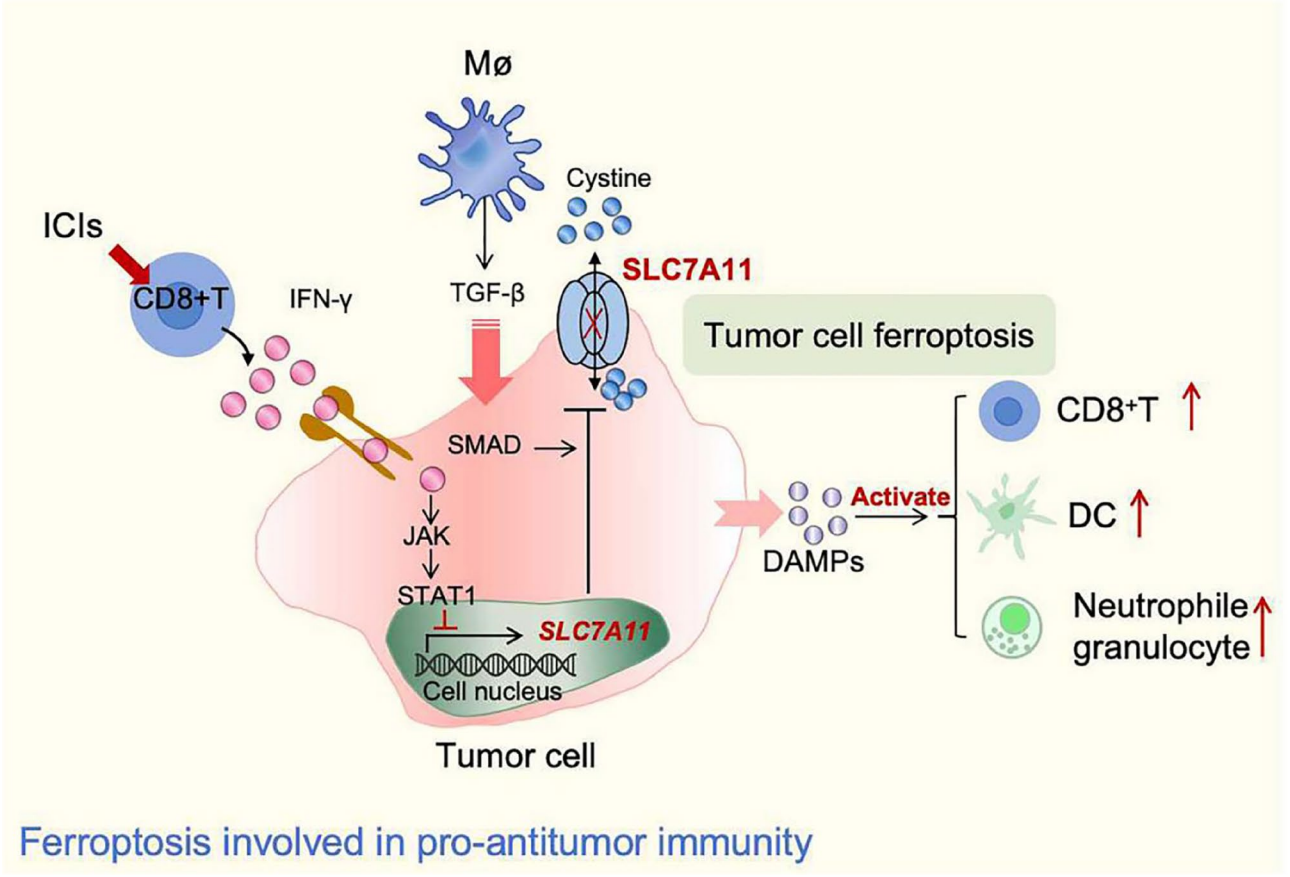


Fig. 4 Ferroptosis and the involvement of SLC7A11 in immunotherapy. The macrophages can suppress the expression of SLC7A11 by releasing TGF-β activating tumor cell SMAD related signal, which likewise promotes ferroptosis of tumor cells; the $CD8^+$ T cells inhibit tumor cell cystine uptake by downregulating SLC7A11 by releasing IFN-γ, and at the same time assisting immune checkpoint inhibitor PD-L1, which can synergistically enhance T cell-mediated anti-tumor immunity and induce tumor cell ferroptosis. The DAMPs released in *vitro* by tumor cells undergoing ferroptosis can induce the maturation of DCs, cross-induction of $CD8^+$ T cells, and production of Neutrophilgranulocyte.

autophagy inhibitor (CQ) were all unable to attenuate cell death induced by high SLC7A11expression after glucose starvation. Similarly, knocking out genes associated with ferroptosis (ACSL4) and apoptosis (BAX and BAK) also did not affect this form of cell death.

Interestingly, thiol oxidants (diamines and diethyl maleate) significantly promote the rapid death of SLC7A11-expressing cells after glucose starvation. Additionally, reducing agents that can mitigate disulfide stress (DTT, 2ME, and TCEP) also appear to inhibit this form of death. Further mechanistic studies have shown that intracellular disulfide stress can activate the Rac-WRC-Arp2/3 signaling pathway, leading to abnormal crosslinking of disulfide bonds among actin cytoskeleton proteins and inducing the collapse of the F-actin network, all of which have deepened our understanding of disulfidptosis.

The combination of immune checkpoint inhibitors with ferroptosis inducers can effectively amplify antitumor immunotherapy. Whether disulfidptosis similarly affects the immune microenvironment is an important question that needs to be addressed.

Notably, although both H_2O_2 treatment and glucose starvation can cause cell death in $SLC7A11^{deficient}$ and $SLC7A11^{low}$ cells, their death is significantly delayed and involves different modes of death, such as apoptosis and necrotic apoptosis. Nevertheless, under metabolic stress conditions, $SLC7A11^{high}$ tumor cells and tumor tissues are more sensitive to glucose transporter (GLUT) inhibitors, and the administration of GLUTs can in turn lead to more intense cell death in $SLC7A11^{high}$ tumor cells and tumor tissues [10, 77–79] (Fig. 3). These studies revealed that the interactions among the expression level of SLC7A11, the cellular redox balance and the cell death pathways increase the complexity of the regulatory mechanisms that control cell fate.

The application of disulfidptosis in tumor treatment

Current studies have shown that the combined use of ICIs and ferroptosis inducers effectively enhances the efficacy of antitumor immunotherapy. Whether the phenomenon of disulfide bond cleavage death also benefits the immune therapy against cancer, is still an important

issue that needs to be addressed. Studying the release of DAMPs during the disulfide bond cleavage death process may provide interesting insights into the potential synergistic effects of immunotherapy [80]. Recent studies have shown the metabolic fragility of SLC7A11^{high} tumor cells, revealing potential therapeutic avenues to keep patients alive by targeting SLC7A11 in a manner dependent on NADPH and glucose. Furthermore, Koppula et al. [9] reported that lung cancer cells with Keap1 mutations or Keap1 deletion have an increased dependence on glucose and abnormally accumulate disulfide molecules due to SLC7A11-mediated upregulation of cysteine uptake under glucose-deficient conditions. This susceptibility makes Keap1 mutant lung cancer cells sensitive to GLUT inhibition, suggesting potential treatments against disulfidptosis for this type of lung cancer.

Recent studies have shown that disdulfidptosis is also closely related to the prognosis of cancer [81, 82]. For example, prognostic models using disulfidptosis genes and long noncoding RNA (lncRNAs) indicate improved predictive efficacy, and reveal the potential relationship between disulfidptosis and tumor immune infiltration to a certain extent [83]. For instance, Xia et al. reported that lncRNAs associated with disulfidptosis in breast cancer can accurately predict breast cancer subtypes [84]. Among the basic subtypes, the expression level of LINC02188 was the highest overall, and that of LINC00511 was the highest in the Her-2 positive subtype. Moreover the greater the degree to which the lncRNA index is associated with disulfidptosis, the greater the sensitivity of patients to immunotherapy [85].

Notably, cystine, glutamine, glucose, fatty acids are crucial raw materials for disulfidptosis and play important roles in the immune microenvironment and affect various immune interactions within the tumor milieu [86, 87]. For example, cystine is an indispensable source of nutrients for tumor cells, and tumor cells consume cystine in large quantities, making it difficult for $CD8^+$ T cells in the TME to obtain enough cystine. The difference of cystine uptake between tumor cells and T cells indicates that an increase in cystine levels in the TME can promote not only the growth of T cells but also the disulfidptosis of tumor cells [72].

In summary, disulfidptosis is closely connected to the occurrence and development of tumors. Therefore, a comprehensive study on the regulatory mechanism and application of disulfidptosis may lead to innovative ideas for cancer treatment.

Table 2 Different modes of ferroptosis and disulfidptosis

Feature	Ferroptosis	Disulfidptosis
Morphological Features	a. Cellular membrane bubbling b. Chromatin decondensation c. Normal nuclear size d. Increased mitochondrial membrane density and reduction in cristae	a. Lamellipodial protrusions b. The skeleton contracted violently, causing damage to its structure and composition
Biochemical Characteristics	a. Lipid peroxidation b. The accumulation of ROS c. The depletion of Glutathione (GSH)	a. The depletion of NADPH b. The abnormal accumulation of cystine and other disulfides
Molecular Markers	GPX4, SLC7A11, ACSL4, Nrf2	SLC7A11, NADPH-generating enzymes
Trigger Conditions	Lipid peroxidation (GPX4 loss)	Glucose starvation + cystine
Signaling Pathways	a. System Xc-/GPX4 pathway b. Lipid metabolism pathway c. Iron metabolism pathway	RAC1-WAVE-Arp2/3
Biomarkers	Lipid peroxidation, iron staining	Disulfide accumulation, NADPH/$NADP^+$ratio
NADPH Need	High	Low
Clinical Strategies	Ferroptosis inducers combined with immunotherapy	SLC7A11 inhibitors, glucose restriction + cystine loading
Clinical Challenges	Organ toxicity, tumor resistance	Metabolic dependency, precise targeting
References	[7, 12]	[7, 10, 12, 14, 90]

Summary and prospects

A recent series of studies have shown promising prospects for ferroptosis and disulfidptosis in tumorigenesis and therapy. As a pivotal molecule mediating these two forms of death, SLC7A11 plays a dominant role in both forms of death through its involvement in cystine transport, indicating that it connects the two forms of RCD (Tables 1 and 2). However, there are still some prominent scientific issues that need to be further clarified, which will not only provide a new basis for analyzing the relationship between the two death forms of ferroptosis and disulfidptosis, but also lay a solid foundation for the development of tumor therapeutic targets in the future (Fig. 5).

First, the intrinsic relationship between disulfidptosis and ferroptosis remains to be fully elucidated. SLC7A11 is involved in regulating both the disulfidptosis and ferroptosis of tumor cells, with a double-edged sword effect, i.e., tumor-promoting and. tumor-inhibiting effects. Essentially, cells with SLC7A11^{high} are more prone to disulfidptosis under the conditions of glucose starvation, whereas, high expression of SLC7A11 inhibits cellular ferroptosis. This evidence suggests that distinct metabolite levels could operate through SLC7A11, as a hub, to induce different forms of RCD. However, how metabolic interventions can differentially affect SLC7A11-mediated outcomes remains unclear. The exact mechanism is still unknown. Notably, SLC3A2 is part of the Xc- system.

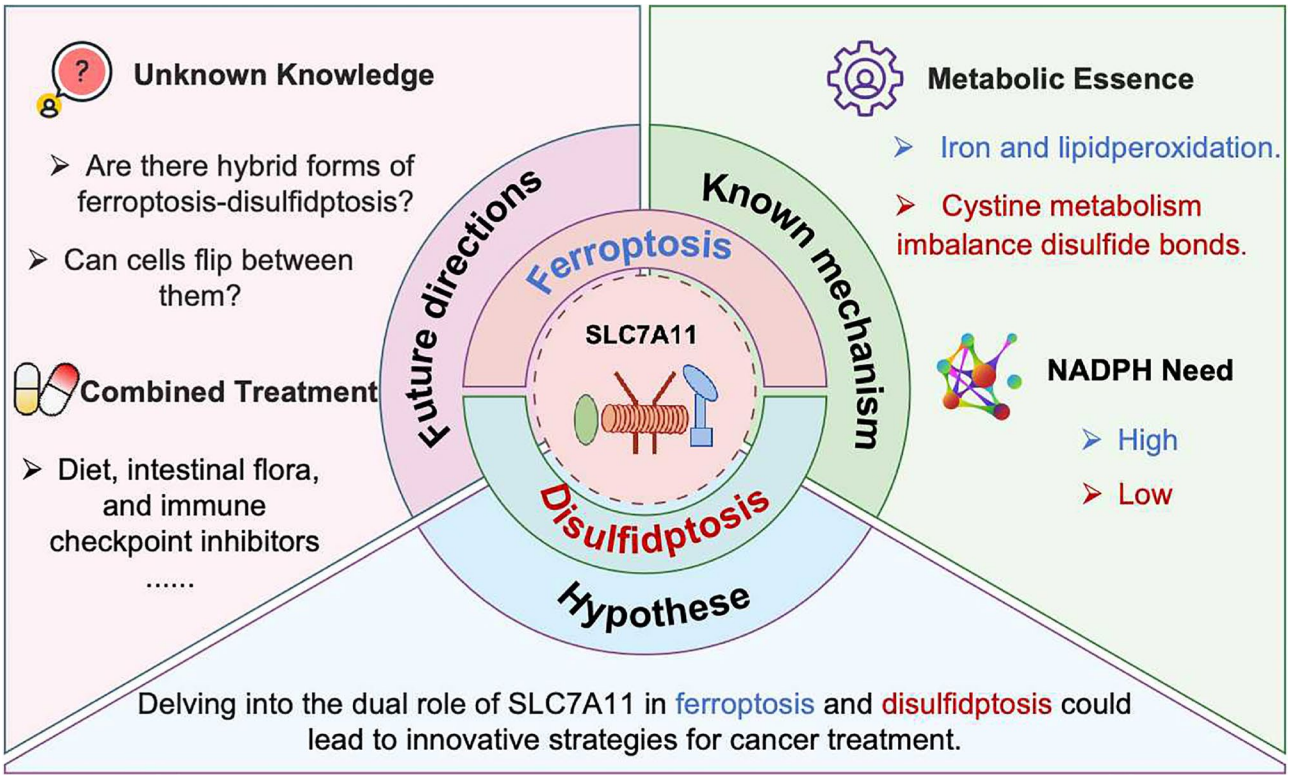


Fig. 5 A diagram about the pending issues on SLC7A11 in the relationship between ferroptosis and disulfidptosis in the future.(The blue font represents ferroptosis, and the red font represents disulfidptosis.)

Current evidence suggests that SLC3A2 has pleiotropic functions beyond the function of system Xc-, such as regulating large neutral amino acid transporters (LAT1, LAT2, etc.) and glucose transporters (GLUT1, GLUT4, etc.) [8]. Therefore, the potential role of other factors and their connections with SLC7A11, such as SLC3A2, need further research. Finally, in the metabolic network, the perception of different metabolic stress is crucial for tumor cell survival. Therefore, it is necessary to study the exact connection between disulfidptosis and ferroptosis in the exact metabolic conditions, which is critical for elucidating the mechanisms of these different RCDs and their roles in tumorigenesis in the future. In addition, there are some key unknowns here, e.g. Are there hybrid forms of ferroptosis-disulfidptosis? Can cells flip between them? All these issues are worthy of further in-depth discussion and research.

Second, SLC7A11-mediated cysteine metabolism plays a vital role in tumor ferroptosis and disulfidptosis, which is reflected not only in the importance of amino acid metabolism but also in processes such as lipid peroxidation. Current research indicates that regulating the metabolic substrates and enzymes in the Cys metabolic network may be an attractive new direction for future research to achieve intervention effects on tumors [91]. However, given the complexity of cellular metabolism, whether it is also related to other metabolic pathways, such as fat metabolism or nucleotide metabolism, remains to be determined. What is more noteworthy is that the $NADP^+$/NADPH reduction reaction is also involved in cysteine metabolism and fat metabolism, indicating the importance of redox balance. What about these different metabolism and stress homeostasis intrinsic relationship between in tumor cell ferroptosis and disulfidptosis? Additionally, disulfide bond is a familiar protein posttranslational modifications (PTMs), and relevant studies have reported that PTMs such as glycosylation and ubiquitination of GPX4 are also involved in the regulation of ferroptosis [13]. Could these PTMs be associated with disulfidptosis? And how? Exploring these questions in depth will provide important clues and insights into the relationship between the two types of cell death.

Finally, methods for developing precision therapeutic strategies against tumors are needed. Studies have shown that SLC7A11 connects the regulation of both forms of death, indicating that SLC7A11 has great value in targeted therapy for tumors. However, since the local TME is very complex, different TMEs have different effects on tumor treatment. For example, genetic mutations and environmental factors (hypoxia, acidosis, and nutrient deficiency) are important driving factors for promoting

the metabolic reprogramming of tumor cells. Moreover, immune factors might also modify the TME, affecting the metabolic characteristics of the TME. For example, the lipid metabolic reprogramming of tumor-associated macrophages (TAMs) plays an important role in forming a tumor immunosuppressive microenvironment [88]. Notably, recent evidence has further shown that dietary intervention can alter the metabolic product levels in the TME by reshaping the intestinal microbiota, thereby influencing the metabolism of cancer cells and modifying tumor growth and treatment [89, 92]. Therefore, the complexity of tumor metabolism suggests that a single-target treatment based on targeting SLC7A11 may have difficulty achieving the desired effect. Future research needs to pay more attention to combination therapies that target different factors and the issues that arise during targeted therapy, such as side effects and tumor selectivity.

Overall, in this article, we provide an up-to-date review of current research advances in ferroptosis and disulfidptosis, especially SLC7A11, a pivotal molecule that mediates these two forms of death, including its structure, expression and regulatory mechanisms. More importantly, we discuss some of the riddles caused by SLC7A11 bridging ferroptosis and disulfidptosis, hoping to stimulate further thinking and provide insights and assistance for future research.

Abbreviations

ACSL4	Acyl-CoA synthetase long chain family member 4
ALOX12	Arachidonic acid 12-lipoxygenase
ASCT1/2	Alanine-serine-cysteine transporter 1/2
ATF4	Activating transcription factor 4
BAP1	BRCA1 associated protein 1
CD44v	CD44 variant
Gln	Glutamine
EAAT 3	Excitatory amino acid transporter 3
GLS	Glutaminase
GPX4	Glutathione peroxidase 4
H2Aub	Histone 2A ubiquitination
ICIs	Immune checkpoint inhibitors
IGF2BP	IGF2 mRNA-binding protein
ORF	Open reading frame
PPP	Glucose-pentose phosphate pathway
PUFA	Polyunsaturated fatty acids
RCD	Regulatory cell death
SLC7A11	Solute carrier family 7 member 11
UFM1	The ubiquitin-fold modifier 1
USP7	Ubiquitin-specific processing protease 7

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

Conflict of interest
No potential conflicts of interest are disclosed.

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