

Review Article

SLC7A11/xCT in cancer: biological functions and therapeutic implications

Wenyu Lin¹, Chaoqun Wang², Guangping Liu³, Chao Bi⁴, Xian Wang⁵, Qiyin Zhou⁵, Hongchuan Jin¹

¹Laboratory of Cancer Biology, Key Lab of Biotherapy in Zhejiang, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou 310016, Zhejiang, China; ²Department of Pathology, Affiliated Dongyang Hospital of Wenzhou Medical University, Dongyang 322100, Zhejiang, China; ³College of Life Sciences, Yan'an University, Yan'an 716000, Shaanxi, China; ⁴Institute of Translational Medicine, Zhejiang University School of Medicine, Hangzhou 310029, Zhejiang, China; ⁵Department of Medical Oncology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou 310016, Zhejiang, China

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Abstract: Amino acid transporters mediate substrates across cellular membranes and their fine-tuned regulations are critical to cellular metabolism, growth, and death. As the functional component of system Xc⁻, which imports extracellular cystine with intracellular glutamate release at a ratio of 1:1, SLC7A11 has diverse functional roles in regulating many pathophysiological processes such as cellular redox homeostasis, ferroptosis, and drug resistance in cancer. Notably, accumulated evidence demonstrated that SLC7A11 is overexpressed in many types of cancers and is associated with patients' poor prognosis. As a result, SLC7A11 becomes a new potential target for cancer therapy. In this review, we first briefly introduce the structure and function of SLC7A11, then discuss its pathological role in cancer. We next summarize current available data of how SLC7A11 is subjected to fine regulations at multiple levels. We further describe the potential inhibitors of the SLC7A11 and their roles in human cancer cells. Finally, we propose novel insights for future perspectives on the modulation of SLC7A11, as well as possible targeted strategies for SLC7A11-based anti-cancer therapies.

Keywords: SLC7A11, cellular metabolism, redox homeostasis, ferroptosis, drug resistance, cancer

Introduction

In all living organisms, amino acids are essential for cellular growth by involving in energy production, macromolecule synthesis, redox homeostasis and many other cellular processes [1, 2]. Cells shuttle amino acids across membranes through transporters, are located in plasma membrane or intracellular organelles, to ensure their survival [1, 3]. In tumor cells, dysregulated transporters facilitate their high demand of amino acids. Moreover, amino acid transporters are closely related with patients' prognosis [1, 4].

Glutathione is a key cofactor for the activation or induction of antioxidant enzymes. In addition, it maintains proper functions of proteins and neutralizes the cytotoxic drugs [5]. Cysteine, the reduced product of cystine, is a rate-limiting precursor for glutathione synthesis.

Intracellular cystine imported through system Xc⁻ is the predominant source of cysteine in most cancer cells [6]. SLC7A11 is the functional subunit of system Xc⁻, and acts as an important oncogenic protein not only in defending oxidative stress and ferroptosis, but also in affecting malignant cancer behaviors, tumor microenvironment, immune system, cancer-associated syndromes and therapeutic sensitivity. Moreover, exploring the regulatory mechanisms of SLC7A11 has been a focus with significant importance, and targeting SLC7A11 has been implicated in multiple studies. In this review, we summarize the biological functions of SLC7A11 and its relevance to cancer, and then discuss potential clinical implications of SLC7A11.

The structure and function of system Xc⁻

System Xc⁻ is a Na⁺-independent, chloride-dependent anionic L-cystine/L-glutamate anti-

porter on the cell surface and mediates the uptake of extracellular cystine in exchange for the intracellular glutamate at an obligatory molar ratio of 1:1 [7]. System Xc⁻ consists of light chain subunit SLC7A11 (xCT) and heavy chain subunit SLC3A2 (CD98hc or 4F2hc). SLC7A11 is identified as the seventh member of light subunits of heterodimeric amino acid transporters (LSHAT) family, which requires either of the two heavy chain, 4F2hc or rBAT, to induce amino acid transportation [8]. The human SLC7A11 gene is located on 4q28.3 and SLC7A11 protein has orthologs in all vertebrates [5]. SLC7A11 has 12 transmembrane domains composed of 501 amino acids in human, with its N- and C-termini located in the cytoplasm [9]. SLC3A2, a type II membrane glycoprotein, has a single transmembrane domain, with its N-terminus in the cytoplasm and heavily glycosylated C-terminus on the cell surface [10]. SLC7A11 is linked to SLC3A2 by a disulfide bridge between the conserved residue Cys¹⁵⁸ of SLC7A11 and Cys¹⁰⁹ of SLC3A2 [9, 11]. Importantly, SLC7A11 is specific for System Xc⁻, while SLC3A2 is the chaperone protein of several members of LSHAT family, including LAT1, LAT2, asc-1, y+LAT1, y+LAT2, and xCT [8, 12]. The substrate specificity of System Xc⁻, therefore, is primarily mediated by SLC7A11, and SLC3A2 aids to regulate the trafficking of SLC7A11 to the cell membrane or potentially enhances the stability of SLC7A11 protein [8, 13, 14]. Besides, CD44 variant isoform (CD44v) also interacts with and stabilizes SLC7A11 on the cell surface in cancer cells [15].

The imported cystine is reduced to cysteine in the cell and serves as the precursor for glutathione (GSH) synthesis. As a tripeptide, GSH synthesis involves two enzymatic steps. Cysteine and glutamate are firstly catalyzed into γ-glutamyl-L-cysteine by glutamate cysteine ligase (GCL), and then glycine is added to synthesize GSH by GSH synthase (GS). GSH is involved in several vital cellular functions including detoxification of electrophiles, maintaining intracellular redox balance, reducing hydrogen peroxide or oxygen radicals with selenium-dependent GSH peroxidase, preserving the thiol status of proteins, storing cysteine and regulating multiple cellular processes [16, 17].

Cysteine is also imported directly via other transporters such as system alanine-serine-

cysteine (ASC) or synthesized via transsulfuration pathway, and some studies showed that deficient cysteine could be compensated when lacking system Xc⁻ [6]. However, system Xc⁻, especially SLC7A11, is still valued as an important transporter for cystine in cancer. Given its specificity in system Xc⁻, in the following sections we mainly focus on the role of SLC7A11 in tumorigenesis.

SLC7A11 expression and cancer

Since SLC7A11 was firstly identified in 1980 by Bannai and Kitamura [18], there has been a surge of reports demonstrating its pervasive expression in various cancers and multiple effects on cancer growth, invasion, metastasis and unfavorable prognosis (**Table 1**).

SLC7A11 expression is related to tumor invasion and metastasis by affecting redox status or via exported glutamate in tumor microenvironment (TME). One study showed that in prostate cancer, SLC7A11 expression is increased in the metastatic stromal area and is related to low survival rate [19]. SLC7A11 knockdown leads to an oxidized redox status including increase of intracellular ROS/RNS levels, extracellular redox couples Cys/CySS, H₂O₂ and nitrite levels, which ultimately inhibits tumor invasion when co-cultured with tumor stromal cells [19]. Moreover, SLC7A11 is essential to elicit tumor formation and maintain tumorigenicity by relieving oxidative stress in some oncogenic KRAS-mutant cancers, such as pancreatic ductal adenocarcinoma (PDAC), colorectal adenocarcinoma (COAD) and lung adenocarcinoma (LUAD) [20].

Tumors are considered to be hierarchically organized, and cancer stem cells (CSCs) are a special subpopulation of tumor cells that sustain tumor initiation and progression through continuous self-renewal and differentiation. CSCs generate multi-lineage cancer cells with unlimited proliferative potential, and demonstrate multiple phenotypes relating to angiogenesis, immune evasion, metastasis, tumor recurrence and chemo- or radio-resistance [21]. One essential property of CSCs, which enables CSCs to be spared from oxidation stress and to maintain proper functions, is the upregulation of antioxidant genes and decrease of intracellular ROS levels in contrast to non-tumorigenic cells (NTCs) [22]. CD44v, a

Table 1. The role of overexpressed SLC7A11 in cancer

Tumor types	Characteristics
Acute myeloid leukemia [132]	Independent poor prognostic factor
Breast cancer [23, 51, 133]	Carcinogenesis, CSC state and biology, poor prognosis, therapeutic target
Ovarian cancer [134]	Independent risk prognostic factor for overall survival
Colorectal cancer [135]	Independent prognostic predictor of disease recurrence, depth of tumor invasion, lymph node metastasis and venous invasion
Non-small cell lung cancer (NSCLC) [136]	Increased tumor growth and development, advanced cancer stage, shorter 5-year survival
Prostate cancer [19]	Low survival rate, resistance to radiation therapy, increased tumor invasion and metastasis, decreased intracellular ROS and extracellular H ₂ O ₂ levels, and value of the redox couples Cys/CySS
Hepatocellular carcinoma (HCC) [137-139]	Poor differentiation, advanced pathological stages, independent unfavorable prognostic factor for overall survival and disease-free survival, potential therapeutic target
Glioma [24, 54]	Accelerated tumor growth, decreased migration and invasion, increased CSC-like phenotype and potential chemoresistance, complicated clinical course with peritumoral seizures, shorter overall survival
Melanoma [140]	Enhanced tumor proliferation and progression, larger xenograft tumors
Papillary thyroid carcinoma (PTC) [141]	Poor survival, higher mortality, advanced cancer stage
Oral cavity squamous cell carcinoma (SCC) [142]	Advanced T cell classification, perineural invasion, lymphovascular invasion, independent prognostic factor for poor recurrence-free survival, disease-specific survival, and overall survival

major CSC marker, interacts with and stabilizes SLC7A11, thereby contributing to ROS elimination by promoting cystine uptake for GSH synthesis [15]. SLC7A11 is important to stemness maintenance of breast cancer stem cells and it correlates with poor prognosis of breast cancer patients. Depleting SLC7A11 expression hampers tumor sphere formation and increases oxidative stress [23], while overexpression of SLC7A11 endows glioblastoma multiforme (GBM) with cancer stem cell-like properties, which facilitates chemoresistance [24].

Given the intimate relevance of SLC7A11 to the pathological processes in multiple types of cancers, mechanistic insights into how SLC7A11 contributes to tumor development could be valuable for their translational implications in clinical settings, such as the development of effective and preventive or therapeutic approaches by targeting SLC7A11.

The role of SLC7A11 in cancer

The physiological activity of SLC7A11 is mainly involved in regulating redox status, ferroptosis and intercellular signaling. Pathologically, SLC7A11 overexpression or upregulation is frequently seen in tumor cells, especially in cancers that are resistant to therapeutic treatment such as chemotherapy and radiotherapy. Here we summarize the above specific functions of SLC7A11 in cancer (**Figure 1**).

SLC7A11 regulates antioxidant system

ROS is a group of highly reactive ions and molecules including superoxide anion (O₂⁻), hydrogen peroxide (H₂O₂), and hydroxyl radicals (OH⁻). To date, ROS has been found to be involved in various intracellular signaling pathways and physiological events such as stem cell renewal, immune response, insulin synthesis and vascular tones [25]. However, an unbalanced or excessive level of ROS, together with nitrogen species, induces oxidative stress and triggers pathophysiological processes by triggering lipid peroxidation, protein malfunction and DNA damage. Cancer cells have higher levels of intracellular ROS than normal cells to stimulate tumorigenesis and promote tumor progression. However, increased ROS confers intrinsic weakness in cancer cells, as a lethal level of ROS, either induced by exogenous cytotoxic compounds, irradiation or by the inhibition of antioxidant system, triggers cell death and inhibits tumor progression. Cancer cells initiate the antioxidant defense system to mitigate extravagant ROS and maintain redox balance. SLC7A11 serves an essential antioxidant role by supporting GSH generation with imported cystine, and targeting SLC7A11 has caught attention in many studies [26].

Oncogenic RAS is known for protecting tumor cells from diverse cytotoxic stress. In cancer cells with mutant KRAS, transcription factor

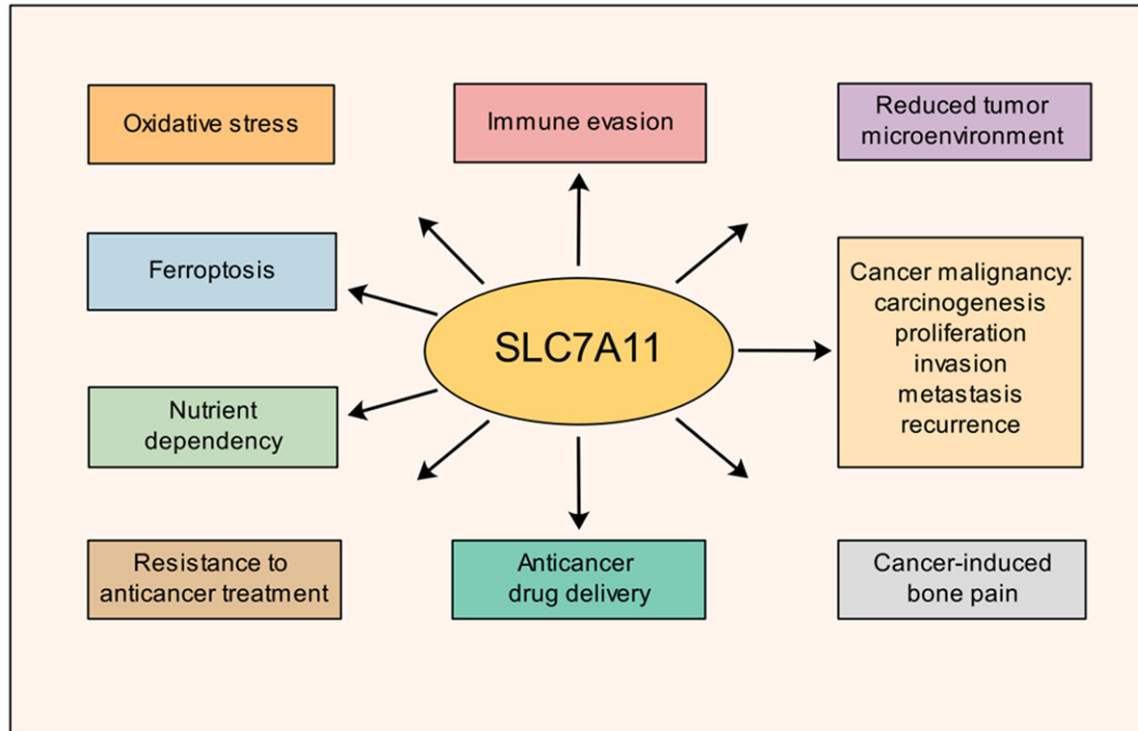


Figure 1. Potential roles of SLC7A11 in cancer cells. SLC7A11 exerts a variety of roles in cancer cells through different mechanisms.

Ets-1 in synergy with ATF4 enhances GSH synthesis by activating SLC7A11 transcription. Besides, Nrf2 is also increased downstream of oncogenic K-RAS signaling axis, offering an additional driving force in promoting SLC7A11 expression independent of Ets-1 and ATF4. As a result, high SLC7A11 expression supports oncogenic K-RAS-driven tumorigenicity [20]. Moreover, in esophageal cancer cells, SLC7A11 expression is increased in response to elevated ROS after Oridonin treatment, and blocking SLC7A11 further sensitizes cancer cells to Oridonin, especially in p53-mutant cancer cells [27]. Thus, K-RAS or p53-mutant cancer cells maintain intracellular redox balance and support their oncogenic survival through upregulation of SLC7A11.

SLC7A11 also mitigates oxidative stress in tumor microenvironment. Once imported into the cell, cystine is rapidly reduced to cysteine. Except for GSH synthesis, some cysteine is also exported out of the cell through neutral amino acid transporters. The extracellular cysteine is rapidly oxidized to cystine which continues to be imported via system Xc-, thereby forming a cystine/cysteine redox cycle and creating a

reducing extracellular environment to support cancer cell survival and proliferation [28].

In addition, increased intracellular ROS with SLC7A11 inhibition triggers cancer cell death in different contexts. For example, p53 degradation is reduced due to ROS accumulation. In human lung cancer cells harboring mutated K-RAS and WT p53, p53 is kept at low level due to decreased phosphorylation on serine 15 and increased proteasomal degradation mediated by MDM2. The phosphorylation of p53 requires ROS to activate phosphorylation kinase ATM, while K-RAS and its downstream NFκB pathway transcriptionally induce the expression of Nrf2 and Nrf2-mediated antioxidant system, including SLC7A11 and NQO1, thus decreasing ROS levels and inhibiting p53 phosphorylation. Depletion of K-RAS, or inactivation of NFκB pathway using BAY 117085, an inhibitor of NFκB pathway, hence exert an inhibitory effect in a ROS-dependent manner [29]. Moreover, cell death is triggered directly due to excessive ROS accumulation. In melanoma cells resistant to BRAF and MEK inhibitors, sequential treatment with vorinostat, a histone deacetylase inhibitor (HDACi), induces tumor cell apoptosis by sup-

pressing SLC7A11 and increasing intracellular ROS to a lethal level, which is validated in the clinical trial [30]. When inhibiting SLC7A11 alone is not sufficient for intracellular ROS to achieve a lethal level, combination therapy is often explored. In GSH-depletion resistant cancer cells, Oxyfedrine (OXY) treatment resensitizes cancer cells to xCT inhibitor sulfasalazine (SSZ) or radiotherapy by inhibiting the activity of ALDH and accumulating 4-HNE, a highly reactive lipid peroxidation product that inactivates thiol-containing proteins in the antioxidant process [31].

Contrary to the oncogenic roles described above, SLC7A11 overexpression also triggers cancer cell death in some special settings. For example, in glioblastoma with glucose deprivation, SLC7A11 expression induces ROS production and oxidative stress by consuming intracellular NADPH during the reduction of imported L-cystine into L-cysteine [32]. Moreover, supplementation of alpha-ketoglutarate (α -KG), a downstream metabolite of glutamate, fully rescues SLC7A11-overexpressing cancer cells under glucose deprivation, indicating that the exported glutamate may additionally contribute to cancer cell death [33]. Another work substantiates that the conversion of glutamate into α -KG is essential for cancer cell survival under glucose starvation, and SLC7A11 thereby modulates nutrient flexibility in cancer cells. Specifically, cancer cells with high SLC7A11 expression level are addicted to glucose, while low-SLC7A11 expressing cancer cells have enhanced OXPHOS activity [13]. This contradiction may occur in a cell line or context dependent manner. In another study where glioblastoma cells are also deprived of glucose, SLC7A11 inhibits cell death and increases cell viability by inducing the phosphorylation of EphA2 at serine 897 [34]. Since only limited experiments were conducted, whether there are other mechanisms or limitations behind this contradiction awaits further investigations.

Together, the seemingly paradox role of SLC7A11 in redox maintenance may be attributed to the quality, quantity and duration of the intracellular ROS.

SLC7A11 functions in ferroptosis

Ferroptosis is an iron-dependent regulated cell death due to excessive accumulation of peroxi-

dated polyunsaturated fatty acids (PUFAs). PUFAs is oxidized either by ROS, which is mainly produced in Fenton or Fenton-like reactions, or by lipoxygenase (LOX) family that catalyzes PUFAs to generate lipid hydroperoxides [35]. Glutathione peroxidases (GPXs) are enzymes that utilize GSH to reduce hydroperoxides, and among them, GPX4 is the only lipid hydroperoxidase capable of detoxifying large and complex phospholipid hydroperoxides in the membranes, thereby hindering the propagation of ferroptosis. Effective GPX4 activity requires sufficient cofactor GSH to reduce GPX4 into active form, and activated GPX4 then catalyzes the reduction of lipid hydroperoxides. Thus, GSH is critical for GPX4-mediated ferroptosis inhibition [36]. Inhibition of SLC7A11 indirectly inactivates GPX4 and increases toxic lipid ROS by decreasing cystine import and limiting GSH synthesis. Moreover, system Xc- could be inhibited by small molecules including erastin or its derivatives, sulfasalazine (SSZ), sorafenib and extracellular glutamate or its analogues [35]. So far, SLC7A11 expression has been found to be associated with ferroptosis sensitivity and myriad studies have explored its role in ferroptosis.

In general, SLC7A11 confers resistance to ferroptosis in cancer cells. For instance, SLC7A11 is adaptively expressed to reduce ferroptosis and buffer irradiation damages in lung cancer cells. As a result, overexpression of SLC7A11 promotes radioresistance in lung cancer cells with low-expression level of SLC7A11. In KEAP1-mutant lung cancer cells where Nrf2 is constitutively activated, high intrinsic expression of SLC7A11 significantly inhibits irradiation-induced ferroptosis, and the use of SLC7A11 inhibitors sensitizes cancer cells to radiotherapy in both in vitro and in vivo settings [37].

SLC7A11 level could be inhibited by different stimuli to induce ferroptosis. One study shows that p53-mediated ferroptosis is specifically induced by ROS. p53, especially p53 3KR mutant that abrogates p53-mediated cell-cycle arrest, apoptosis and senescence, binds to the promoter of SLC7A11 gene and represses SLC7A11 expression, thus inhibiting cystine uptake and promoting ferroptosis [38]. Upon treatment of system Xc- inhibitors, the protein level of BECN1, a key regulator of macroautophagy/autophagy, is increased. BECN1 directly

binds to SLC7A11 protein to form a complex that inhibits SLC7A11 activity, depending on the phosphorylation of BECN1 at serine 90, 93 and 96 mediated by AMPK. Overexpression of BECN1 also enhances the efficacy of erastin in vivo by inducing ferroptosis [39].

In addition to system Xc- inhibitors, other anti-cancer therapies, including anti-cancer immunotherapies, were reported to induce tumor cell ferroptosis by inhibiting SLC7A11. In tumor cells, activated CD8+ T cells following PD-L1 blockade therapy increase lipid ROS by releasing Interferon gamma (IFN γ), which then promotes downstream transcription factor STAT1 to bind with the transcriptional start site of SLC7A11, and downregulate SLC7A11 expression. Interferon regulatory factor 1 (IRF1) upregulated by IFN γ also transcriptionally reduces SLC7A11 expression through Janus kinase (JAK) [40]. Another study showed that radiotherapy reduces SLC7A11 transcription possibly through activating ATM, a DNA damage response serine/threonine kinase. Radiotherapy synergizes with IFN γ either produced from PD-L1 blockade or anti-CTLA-4 checkpoint blockade immunotherapy, to promote ferroptosis. Besides, SLC7A11 deficiency also contributes to the establishment of T cell memory and durable immune responses [41]. Thus, repressing SLC7A11 may enhance the efficacy of immunotherapy and contribute to effective combination therapy against cancer.

It was found that using system Xc-inhibitors augmented the efficacy of other therapies. One study showed that photodynamic therapy (PDT) exerts anticancer effect by selectively delivering photosensitizers to the tumor and triggering cytotoxic intracellular ROS through irradiation. However, this process is frequently dampened, as tumor cells fail to produce lethal levels of ROS due to the hypoxic tumor microenvironment [42]. In oral tongue squamous cell carcinoma (OTSCC), erastin treatment overturns tumor resistance to photodynamic therapy (PDT) as well as enhances therapeutic efficacy by producing O₂ through the Fenton reaction and also by accumulating intracellular ROS via the suppression of SLC7A11 [42]. It is also discovered that class I HDAC inhibitors exacerbate erastin-induced ferroptosis in neuroblastoma, hepatomas and fibrosarcoma cells, while neuron cells are protected from erastin-induced

ferroptosis, indicating a potential combination therapy of erastin and class I HDAC inhibitors for cancer inhibition with additional benefit of neuroprotection [43].

In summary, SLC7A11 overexpression confers resistance to ferroptosis in cancer cells by importing cystine for the synthesis of GSH, and indirectly relieving lipid ROS stress by activating the essential enzyme GPX4 for reducing lipid hydroperoxides. SLC7A11 expression is adaptively elevated to mitigate ferroptosis-induced lipid ROS, while ferroptosis is induced by various stimuli via inhibiting the effective function of SLC7A11. Therefore, SLC7A11 is an intriguing target for enhancing anticancer therapeutic efficacy through ferroptosis elicitation.

SLC7A11 involves in autocrine/paracrine glutamate signaling

SLC7A11 not only affects redox status and ferroptosis sensitivity by importing cystine, but also affects tumor microenvironment through exporting glutamate. Consistent with the expression pattern of SLC7A11 on cancer cells, multiple lines of cancer cells have been proved to release glutamate via system Xc- [44, 45]. Glutamate receptors have two groups: metabotropic glutamate receptors (mGluRs) and ionotropic glutamate receptors (iGluRs). mGluRs are classified into three subgroups, including group I consists of mGluR1 and mGluR5, group II contains mGluR2 and mGluR3, and group III comprises mGluR4, mGluR6, mGluR7 and mGluR8. And iGluRs also have three subgroups: amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptors (AMPA receptors), N-methyl-D-aspartate receptors (NMDARs), and 2-carboxy-3-carboxy-methyl-4-isopropenylpyrrolidine receptors (KARs) [46]. In physiological settings, glutamate contributes to neuronal propagation, migration and neurotoxicity. However, in cancer cells, glutamate serves as an important oncogenic signaling molecule for promoting malignant transformation, tumor proliferation, invasion and metastasis as well as inhibiting immune system by acting on the glutamate receptors on cancer and non-cancerous cells [46].

Glutamate released from glioma cells not only kills brain cells for tumor enlargement through its excitotoxic effect, but also promotes cell migration and invasion in an autocrine- or paracrine-dependent manner. The released glutamate

mate acts on the Ca^{2+} -permeable AMPA receptors expressed on glioma cells and the surrounding cancer cells, inducing intracellular Ca^{2+} oscillations that are related to the migration and invasion ability of cancer cells [47, 48]. In breast cancer, glutamate released through system Xc⁻ contributes to tumor invasiveness by acting on the mGluR3 expressed on breast cancer cells. Activated mGluR3 then accelerates GTPase Rab27-dependent recycling of MT1-MMP, a transmembrane matrix metalloprotease, to the plasma membrane and promotes the degradation of basement membranes, thereby enabling cancer cells to invade into the surrounding extracellular matrix (ECM) [49].

Glutamate also inhibits immune activity and induces tumor evasion. In glioblastoma, SLC7A11 is transcriptionally elevated after anti-VEGF treatment and consequently increases glutamate release. Glutamate then acts on the mGluR1 in Tregs and promotes the expansion, activation and immunosuppressive function of Tregs. As a result, glutamate antagonizes the efficacy of VEGF blockade in glioblastoma [50].

Glutamate not only acts on glutamate receptors, but also inhibits SLC7A11 activity in a paracrine fashion. In triple-negative breast cancer, the high level of extracellular glutamate secreted from cancer cells inhibits cystine uptake via SLC7A11 in other cancer cells. Decreased intracellular cysteine levels lead to auto-oxidation of specific cysteine residues in the EglN1 catalytic domain and results in EglN1 self-inactivation, which prevents HIF1 α degradation under normoxia and ultimately promotes tumor growth. Therefore, in this context, SLC7A11 inhibition did not inhibit cancer cell proliferation [51].

It is recently discovered that glutamate availability confers dependency on exogenous non-essential amino acids (NEAAs) to cancers with KEAP1 loss and Nrf2 activation. Glutamate is an important precursor for the synthesis of intracellular NEAAs. When extracellular serine or asparagine is depleted or when cancer cells are treated with L-asparaginase, system Xc⁻ blockage with erastin efficiently protects Keap1 mutant cells from death by increasing intracellular glutamate levels [52]. This unprecedented finding adds another interpretation of how SLC7A11 functions in different cancers and

offers a special angle of tumor suppression. Moreover, glutamate elicits cancer-associated symptoms, such as bone pain in breast cancer and seizures in glioma, which may complicate clinical courses and worsen prognosis [53, 54].

Therefore, SLC7A11 plays a complex role extending from its basic functions. Targeting SLC7A11 is a hot focus either in unveiling new therapeutic potential or in digging unexplored molecular events out of the known mechanisms.

SLC7A11 involves in resistance to anticancer treatments

Generally, overexpression of SLC7A11 endows cancer cells with survival advantages, while inhibiting SLC7A11 proves to hamper tumor progression and offers alternatives for anticancer treatment. So far, various anticancer approaches to disburden tumor load have been explored, including surgery, chemotherapy, immunotherapy, radiotherapy, and other therapies relating to angiogenesis, cell death pathways, altered cancer metabolism, nutrient availability and so on [55]. However, one main hindrance against efficient therapy is the intrinsic or adaptive resistance to anticancer treatments. Thus, summarizing what SLC7A11 has brought to the obstacles may provide alternatives to step out the dilemma (**Table 2**).

SLC7A11 overexpression leads to therapeutic resistance largely by promoting intracellular GSH synthesis. For example, SLC7A11 confers resistance to BRAF and MEK inhibitor in BRAF^{V600E} mutant melanoma by increasing intracellular GSH contents, while its suppression by histone deacetylase inhibitor dramatically induces tumor regression [30, 56]. By alleviating oxidative stress, SLC7A11 pervasively confers chemoresistance in various cancer types, including cisplatin resistance in gastric cancer [57], geldanamycin resistance in lung cancer [58], temozolomide resistance in glioma [59] and gemcitabine resistance in pancreatic cancer [60]. In addition, SLC7A11 mediates therapeutic resistance by enhancing the suppressive function of Tregs through exported glutamate [50].

It is confirmed by multiple studies that therapeutic resistance can be reversed by directly targeting SLC7A11. For example, SLC7A11

Table 2. The role of SLC7A11 inhibition in reduced resistance to anticancer treatment

Mechanism	Cancer type	Treatment
ROS decrease, GSH increase	BRAF ^{V600E} mutant melanoma	Vorinostat [30]
	CDDP-resistant hepatocellular carcinoma	Combination of CDDP and sulfasalazine [139]
	CDDP-resistant lung cancer	Combination of CDDP and salazosulapyridine [143]
	CDDP-resistant head and neck cancer	Combination of cisplatin, aspirin and sorafenib [144]
	CDDP-resistant bladder cancer	Combination of CDDP and sulfasalazine [94]
	5-fluorouracil-resistant gastric cancer	Combination of 5-fluorouracil and sulfasalazine [145]
	Celastrol-resistant glioma	Combination of celastrol and sulfasalazine [146]
	Cannabidiol-resistant glioblastoma	Combination of cannabidiol and sulfasalazine [147]
	Tumor cells resistant to cold plasma	Combination of sulfasalazine and cold plasma [61]
	Doxorubicin-resistant breast cancer stem cells	Combination of anti-xCT vaccination and doxorubicin [23]
Ferroptosis	CDDP-resistant head and neck cancer	Combination of CDDP and sulfasalazine [62]

repression resensitizes tumor cells to cold plasma treatment, a therapy works by increasing intracellular ROS [61]. Erastin or sulfasalazine treatment resensitizes cisplatin-resistant head and neck cancer cells by inducing ferroptosis [62]. Indirectly targeting upstream regulators of SLC7A11 also impairs therapeutic resistance. One study showed that increased Nrf2, downstream of activated mTORC signaling pathway, upregulates SLC7A11 at transcriptional level and antagonizes ROS accumulation after radiation, which partially leads to radioresistance. Inhibiting mTOR, therefore, reverses radioresistance and increases radiosensitivity in cancer cells [63].

Some studies also found that inhibition of SLC7A11 counteracts therapeutic efficacy through different mechanisms. SLC7A11 is discovered to import small anticancer molecules including L-alanosine [64] and certain anticancer drugs such as selenium [65]. Selenium uptake into cancer cells relies on the reduced tumor microenvironment mainly mediated by extracellular cysteine, which is firstly amplified intracellularly from cystine imported through SLC7A11, and then exported via multidrug resistance proteins [65]. Another study also showed that the down-regulation of SLC7A11 is responsible for multidrug resistance induced by adriamycin in MCF-7 breast cancer cells [66]. Therefore, what roles SLC7A11 exactly plays in therapeutic resistance are in a context-dependent manners, and detailed underlying mechanisms are subjected to future investigation.

In brief, by relating to therapeutic resistance and exploring new regimens for cancer cells, SLC7A11 hence serves as an additional focus in anticancer treatment.

Regulation of SLC7A11 in cancer

Pioneering works have found that SLC7A11 expression is regulated by various stimuli such as oxygen [67] and electrophilic agents [68]. Later, emerging studies reveal that under various cellular stresses in a host of cancers, SLC7A11 is mostly adaptively upregulated to mitigate intracellular ROS and replenish GSH, thereby antagonizing cell death and resisting anticancer therapies (Figure 2).

Transcriptional regulation

Transcriptional factor Nrf2 regulates numerous antioxidant and detoxification genes [69], and Nrf2 directly binds to the antioxidant response element (ARE) in the promoter of SLC7A11 [70]. ARID1A, a gene frequently mutated in various cancer types, encodes a subunit of the SWI/SNF chromatin-remodeling complex, which facilitates chromatin remodeling at the transcriptional start site of SLC7A11 and enables SLC7A11 transcription by Nrf2 and RNA polymerase II, while deleterious ARID1A mutations markedly attenuate Nrf2 localization and suppress SLC7A11 expression, thus sensitizing cancer cells to glutathione deficiency [71]. In addition, mutant p53 also binds to Nrf2 and impairs Nrf2-mediated activation of SLC7A11 transcription [72].

In addition to Nrf2, transcription factor ATF4 regulates SLC7A11 by binding to the amino acid response element (AARE) within its promoter [73]. In response to integrated stress response (ISR), such as hypoxia, endoplasmic reticulum (ER) stress, amino acid deprivation and glucose deprivation, the phosphorylated eukaryotic translation initiation factor 2 (eIF2 α) enhances ATF4 translation and indirectly increases

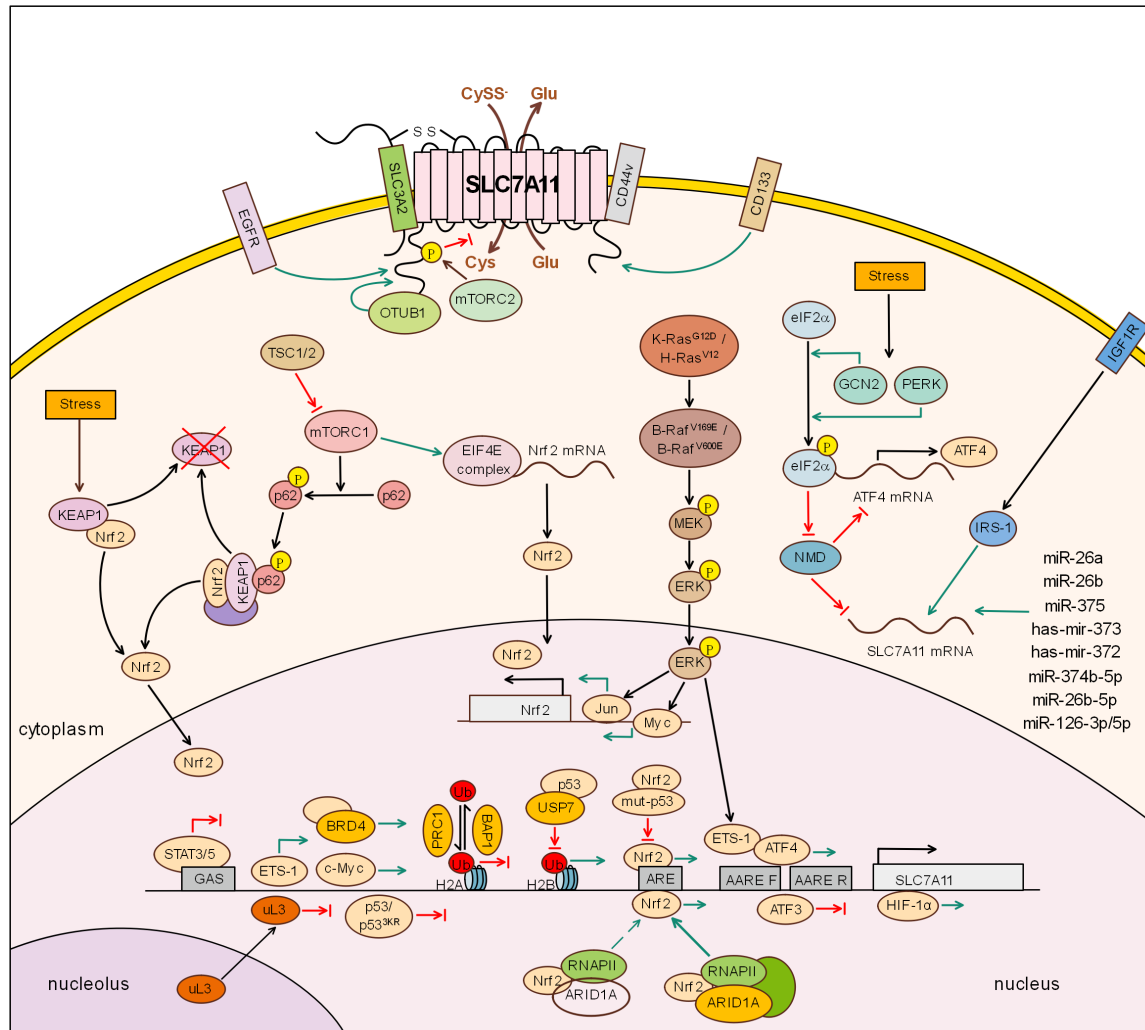


Figure 2. The functions and mechanisms of regulating SLC7A11 activity in cancer. SLC7A11 is regulated by multi-faceted mechanisms from transcription, post-transcription, to post-translational modification, and SLC7A11 is then involved in many cellular processes.

SLC7A11 transcription [74]. Moreover, the p-eIF2 α /ATF4/SLC7A11 axis is found in mouse embryonic fibroblasts [75]. In triple-negative breast cancer, paclitaxel treatment induces ISR and promotes eIF2 α phosphorylation by eIF2 α kinase PKR-like ER kinase (PERK) and general control nonderepressible 2 (GCN2), thereby activating p-eIF2 α /ATF4/SLC7A11 axis and increasing cancer resistance to paclitaxel [76]. Salubrinal, an inhibitor of eIF2 α dephosphorylation, also activates p-eIF2 α /ATF4/SLC7A11 axis and mediates cisplatin resistance in gastric cancer [57]. In addition, in KRAS mutant tumor cells, oncogenic transcriptional factor Ets-1 downstream of RAS-RAF-MEK-ERK pathway synergizes with ATF4 to induce SLC7A11 expression

[20]. Besides, overexpressing Ets-1 also upregulates SLC7A11 protein level in chemoresistant ovarian cancer cells [77].

The TSC1/TSC2 complex (TSC1/2) is a negative upstream regulator of mTOR pathway [78]. In tuberous sclerosis complex (TSC) syndrome, TSC1 or TSC2 gene mutations (loss of function) activate mTOR signaling and the downstream transcription factor Oct1, which upregulates SLC7A11 expression, causing hypopigmented pheomelanin production and tumorigenesis. In addition, PTEN mutations (loss of function) upstream of the mTOR pathway activate the same cascade [79]. HIF-1 α , another transcription factor induced upon chemotherapy treatment in

triple negative breast cancer, also directly binds to the third intron of SLC7A11 and increases SLC7A11 mRNA level [80]. Moreover, by using human promoter microarrays and CHIP assay, c-Myc is found to directly bind to SLC7A11 promoter and induce its expression [81].

Besides the above transcription factors, SLC7A11 transcription is also enhanced by bromodomain protein BRD4, a member of the bromodomain and extraterminal domain (BET) family that helps recruiting transcription factors [82]. In estrogen receptor-positive breast cancer cells, SLC7A11 mRNA is upregulated by IGF receptor substrate-1 (IRS-1) downstream of activated insulin-like growth factor (IGF) signaling pathway [83]. In p53-defect lung cancer cells, loss of ribosomal protein uL3 decreases its binding to SLC7A11 promoter and depresses SLC7A11 transcription, thus increasing SLC7A11 mRNA expression and mediating resistance to 5-FU [84].

Studies also found other transcription factors that genetically suppress SLC7A11 expression. One study indicated that both WT p53 and acetylation-defective mutant p53^{3KR} (R117, R161, and R162) inhibit SLC7A11 expression [38]. In addition, signal transducer and activator of transcription 3/5 (STAT3/5) binds to the gamma-activated site (GAS) in the distal promoter of SLC7A11 and represses its transcription [85]. Moreover, activation transcription factor 3 (ATF3) binds to the SLC7A11 promoter at BS-2 and BS-1 sites and represses SLC7A11 expression [86].

Apart from the regulation by transcription factors, epigenetic modifications on histone also modulate SLC7A11 expression. Tumor suppressor gene BRCA1-associated protein 1 (BAP1) encodes a deubiquitinase in the nucleus and forms polycomb repressive deubiquitinase (PR-DUB) complex with other transcriptional factors and chromatin-modifying factors, which reduces monoubiquitination of histone 2A at lysine 119 (H2A-ub). Deubiquitinated H2A reduces its occupancy on SLC7A11 promoter and represses SLC7A11 expression [87]. Further study reveals that another ubiquitin ligase, polycomb repressive complex 1 (PRC1), mono-ubiquitinates H2A at lysine 119 to represses SLC7A11 expression, indicating that a dynamic regulation of H2A-ub by BAP1 and PRC1 may be important for SLC7A11 inhibition [88]. In addition,

H2Bub1 activates SLC7A11 transcription and sensitizes cancer cells to ferroptosis, while deubiquitinase USP7 translocates into the nucleus through its interaction with p53, and binds to H2Bub1, causing reduced H2B ubiquitination and inhibiting SLC7A11 expression [89].

Post-transcriptional regulation

Nonsense-mediated RNA decay (NMD) mediates the constant degradation of both mutated and nonmutated mRNAs. It is shown that various cellular stresses inhibit NMD through the phosphorylated translation initiation factor eIF2 α [90]. Inhibition of NMD leads to the stabilization and upregulation of SLC7A11 mRNA and protein levels, which is dependent on the phosphorylation of eIF2 α . Moreover, eIF2 α phosphorylation inhibits NMD-induced ATF4 mRNA degradation and indirectly promotes SLC7A11 expression, thereby regulating cystine import and intracellular GSH levels [91].

MicroRNAs (miRNAs), a family of small non-coding RNAs with 20-25 nucleotides, bind to the 3' untranslated region of target mRNAs and mediate gene silencing by inhibiting translation and increasing mRNA degradation [92]. Accumulating evidence demonstrates that SLC7A11 mRNA is derepressed by decreased miR-26b in human breast cancer, miR-27a in bladder cancer and miR-375 in oral squamous cell carcinoma [93-95]. And bioinformatic analysis predicted that SLC7A11 is targeted by different miRNAs, including has-mir-373 and has-mir-372 relating to B cell infiltration in lung adenocarcinoma [96], miR-374b-5p and miR-26b-5p in collecting duct carcinoma [97], and miRNA-126-3p/5p in lung adenocarcinoma [98], but whether and how these miRNAs regulate SLC7A11 are not clear.

Post-translational regulation

As mentioned above, CD44v and SLC3A2 interact with SLC7A11 protein on the plasma membrane and maintain its stability. OTUB1, a deubiquitinase of the ovarian tumor (OTU) family, directly interacts with the N-terminal domain of SLC7A11 protein and stabilizes SLC7A11 protein. Besides, the standard CD44 isoform (CD44s) also stabilizes SLC7A11 protein by binding to its C-terminal domain. Moreover, CD44s has a weak binding affinity with OTUB1 and

facilitates the binding between OTUB1 and SLC7A11, indicating that OTUB1, CD44s and SLC7A11 may form a complex for more efficient stabilization. OTUB1 and CD44 are overexpressed in many cancers, and inactivation of either OTUB1 or CD44 induces ferroptosis by promoting SLC7A11 degradation both in vitro and in vivo [99]. Another study shows that inhibition of CD133, a surface marker of CSCs, decreases SLC7A11 protein stability, though the exact mechanism was not explored [100].

Mammalian target of rapamycin complex 2 (mTORC2) is a multiprotein complex with serine/threonine kinase activity. mTORC2 is activated downstream of mutated growth factor receptor signaling pathways, such as EGFRvIII, PTEN loss and nutrient availability in tumor microenvironment. Activated mTORC2 promotes tumorigenesis and drug resistance by phosphorylating downstream targets [101]. mTORC2 phosphorylates the cytosolic N-terminus of SLC7A11 protein at serine residue 26 and inhibits SLC7A11 function. When pharmacologically inhibiting mTORC2 or depleting glucose, mTORC2 is inactivated, and increased SLC7A11 activity contributes to cancer cell survival [102]. Moreover, the N-terminal intracellular domain of EGFR interacts with the central portion of SLC7A11 protein and stabilizes SLC7A11 on the cell surface in glioma cells [103].

To date, accumulating evidence indicates that SLC7A11 is specifically regulated in different settings. However, the underlying mechanisms of its function and/or stability remain largely unclear. Though the regulation of SLC7A11 is diverse in response to different cellular stresses and therapies, the ultimate goal is to explore the possibility of targeting either the upstream regulating pathways or SLC7A11 itself on the road to develop efficient anticancer treatment.

Small molecules targeting SLC7A11

Inhibitors of system Xc-

Sulfasalazine: Sulfasalazine is firstly identified as an immunosuppressant to treat chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease, while expanded research indicates that it inhibits SLC7A11 and induces ferroptosis in many cancers including lymphoma and bladder cancer

[104-106]. However, due to the unfavorable pharmacological properties, sulfasalazine does not have better outcomes in a phase I/II clinical trials [107, 108]. Later, one study reports a more effective way to deliver sulfasalazine by using ultra-small SASP/ZnO nanoparicles (NPs), which are composed of carrier ZnO NPs, stabilizer DSPE-PEG and sulfasalazine. The SASP/ZnO NPs effectively increase ROS and deplete GSH in cancer cells, and have greater cytotoxicity than sulfasalazine alone. Moreover, *in vivo* experiment finds that SASP/ZnO NPs effectively oxidize cancer cells and decrease CSCs with enhanced tumor retention, and show no evident damage to normal tissues [109]. This may pave the way for exploring novel sulfasalazine derivatives of clinical significance against cancer.

Erastin: In a high-throughput screening of synthetic lethal compounds targeting engineered tumorigenic cells, erastin is firstly identified to selectively kill BJ fibroblast cells expressing small T (ST) oncoproteins and mutated RAS through non-apoptotic cell death [110]. Later, it is found that erastin inhibits system Xc- and induces ferroptosis, as its treatment in tumor cells inhibits cystine uptake and promotes continuous iron-dependent ROS formation that causes cell death with cell morphology identical to the characteristics of ferroptosis [105]. To date, multiple studies have validated that erastin treatment inhibits SLC7A11 function and causes ferroptotic cell death in various cancer types including human breast cancer [111]. In addition, two erastin analogues imidazole ketone erastin (IKE) and piperazine erastin (PE) with improved water solubility, potency and metabolic stability also efficiently induce ferroptosis in mouse models of fibrosarcoma and diffuse large B cell lymphoma (DLBCL) [112-114].

Sorafenib: Sorafenib, an FDA-approved inhibitor of multiple oncogenic kinases, elicits ferroptosis in various human cancer cell lines such as kidney cancer, which is neither dependent on its kinase inhibition activity nor related to the status of oncogenes RAF, PIK3CA, RAS and TP53 in cancer cells [115, 116]. However, sorafenib-induced ferroptosis uniquely relies on system Xc- inhibition and manifests special clinical adverse events in contrast to other kinase inhibitors [106]. Currently, the clinical applica-

tion of sorafenib in targeting system Xc- is still untested.

Competitive and newly identified inhibitors of SLC7A11

An earlier study revealed that SLC7A11 activity is restricted by its substrate availability [7]. By using fluorometric efflux assays, several glutamate and cyclic glutamate analogues were found to inhibit the exchange of L-cystine and L-glutamate through system Xc-, including L-Homocysteate, (RS)-4-Bromo-homoibotenate, L-Serine-O-sulphate, L-Quisqualate and (S)-4-Carboxy-phenylglycine (CPG), among which CPG has the most competitive inhibitory effect and the least substrate activity [117].

In a high throughput screening for compounds inhibiting glutamate release in triple-negative breast cancer cells, capsazepine (CPZ) was found to inhibit SLC7A11 activity. The study showed that CPZ treatment effectively decreases cystine uptake, increases intracellular ROS contents and induces cell death, though SLC7A11 mRNA level is upregulated [118]. Another study screened the compounds to inhibit glutathione production in KRAS mutant LUAD cells, and found that HG106 specifically inhibits SLC7A11 function *in vitro* and decreases tumor burden *in vivo*. Although HG106 effectively inhibits cystine import and GSH production, it also increases intracellular ROS and induces apoptosis in tumor cells because of mitochondrial dysfunction and ER stress [119].

Moreover, a new mouse model is established to evaluate the efficacy of SLC7A11 inhibitors *in vivo*, which is based on measuring cystathionine levels in the mouse thymus and spleen after inhibiting cystathionine γ -lyase. A compound named Compound A shows much higher inhibitory efficacy on SLC7A11 than erastin in this mouse model, but the more detailed information of Compound A is not reported [120].

Inhibitors targeting SLC7A11 upstream regulators

In light of multiple regulating pathways upstream of SLC7A11, it is conceivable that SLC7A11 could be indirectly inhibited by compounds targeting upstream suppressors or stimulators.

One study showed that Pseudolaric acid B (PAB) activates p53 and promotes p53-mediated inhibition of SLC7A11 in glioma, causing ferroptotic cell death [121]. In hypopharyngeal squamous carcinoma, low-concentration paclitaxel (PTX) upregulates the expression of mtp53 (R175H, R248L) but does not affect K98 acetylation of p53, which is required for p53 to inhibit SLC7A11 transcription. Thus, low-concentration PTX enhances RSL3-induced ferroptosis by inhibiting SLC7A11 expression [122]. It is also indicated that receptor tyrosine kinase TrkA activated by neurotrophin nerve growth factor (NGF) transcriptionally activates SLC7A11 expression via RAS-MAPK signaling pathway [123]. In triple-negative breast cancer, TrkA inhibitor AG879 effectively inhibits SLC7A11 activity and expression both *in vitro* and *in vivo*, which inhibits tumor invasion and attenuates cancer-induced bone pain *in vivo* [123]. Moreover, MEK inhibitor AZD6244 antagonizes mutant KRAS induced activation of Nrf2 transcription to inhibits SLC7A11 expression in MEFs, which synergizes with statin to elicit stronger antitumor effect [124]. Similarly, BAY 11-7085 mediates Nrf2 inhibition and inhibits SLC7A11 expression [125], and JQ-1 inhibits SLC7A11 transcription by targeting BRD4 [82].

Immunotargeting SLC7A11

In vivo depletion of SLC7A11 is found to inhibit tumor growth without compromising antitumor immune responses, which not only enables the adoption of combination therapy with the immunotherapeutic agent anti-CTLA-4, but also supports the potential use of SLC7A11-targeted immunotherapies [126].

DNA-based vaccines

pVAX1-SLC7A11 plasmid, cloned with full-length mouse SLC7A11 (NM_011990.2) and transcriptionally controlled by CMV promoter, is firstly used *in vivo* to explore its efficacy in TNBC mouse model. On the one hand, pVAX1-SLC7A11 vaccination induces humoral response in BALB/c mice, and IgG purified from the mice impairs TUBO tumor sphere generation and lowers the amounts of CSC markers-positive cells. On the other hand, pVAX1-SLC7A11 vaccination in tumor-bearing mice induces tumor regression and reduces lung metastases by antibodies specifically targeting SLC7A11 on CSCs. Besides, anti-SLC7A11 vaccination also

exerts a preventive effect against spontaneous lung metastasis induced by 4T1 cells. Though humoral response is elicited, no T-cell response is found, which is possibly due to thymic depletion of high-avidity T-cell clones [23].

VLP-based vaccines

A virus-like particle (VLP) based immunotherapy named AX09-OM6, which displays the fully homologous sixth extracellular loop (ECD6) of both mouse and human SLC7A11, is applied in female BALB/c mice. The high titer of antibodies in sera from AX09-OM6 treated mice disables the self-renewal ability of breast cancer stem cells and increases ROS content in TUBO, 4T1, HCC-1806, and MDA-MB-231 cells. In particular, a strong IgG2a antibody response is induced by AX09-OM6, which confers high ADCC and CDC activity to SLC7A11 positive tumor cells in both in situ and metastatic tissues. AX09-OM6 treatment in mice also slows tumor growth and attenuates lung metastasis preventively or therapeutically. In addition, mouse spleen myeloid cells and CNS are barely affected by AX09-OM6 treatment, indicating that the potential of autoimmune activation is limited [127].

BoHV-4-based vaccines

A viral vector based on Bovine Herpes Virus-4 (BoHV-4), with open reading frame (ORF) expressing full-length mouse SLC7A11 protein (BoHV-4-mSLC7A11), is used to vaccinate mice. Sera collected from BoHV-4-mSLC7A11 treated mice contain antibodies recognizing both mouse and human SLC7A11 proteins. CSCs specifically targeted by and bound with antibodies from BoHV-4-mSLC7A11 treated mice are then cleared through antibody-dependent cell cytotoxicity (ADCC), or are disabled by impaired self-renewal ability and accumulated intracellular ROS levels. In addition, this effect is reproducible among TUBO, 4T1, and HER2⁺ SKBR3 cells. *In vivo* study reveals that BoHV-4-mSLC7A11 vaccination in mice significantly inhibits breast cancer growth, and lung metastasis is reduced both preventively and therapeutically. Moreover, increased content of CD4⁺ and CD8⁺ T cells, and increased PD1 expression are found in the lungs of vaccinated mice, indicating the potential of better prognosis and combination therapy with immune checkpoint inhibitors [128].

Future perspectives and conclusions

Oxidative stress is the most frequent cellular event in cancer due to its tumorigenic nature and the challenging tumor microenvironment. The redox status in cancer often correlates with its malignancy and therapeutic sensitivity. In order to cope with the increased cellular ROS stress, cancer cells invoke antioxidant defense system, which not only mitigates intracellular ROS and enables cancer cell survival, but also enhances cancer malignancy by promoting proliferation, metastasis, invasion and so on. SLC7A11 is pervasively overexpressed or upregulated to defense oxidative stress, and confer resistance to anticancer treatments. In addition to modulate ROS levels, SLC7A11 has a broader range of actions including ferroptosis, intercellular signaling, drug transportation, nutrient preference, immune response, and cancer-induced bone pain. Therefore, targeting SLC7A11 is an important focus in exploring effective anticancer therapies. Multiple studies have found increased therapeutic efficacy by inhibiting SLC7A11 alone or in combination [42, 120]. As the efficacy of SLC7A11 inhibition is closely related to SLC7A11 expression levels, it is of premier importance to measure SLC7A11 activity in tumors. Positron emission tomography (PET) based on ¹⁸F-fluoroaminosuberic acid (¹⁸F-FASu) [129] or (S)-4-(3-[¹⁸F] fluoropropyl)-L-Glutamic Acid ([¹⁸F] FSPG) is used to image SLC7A11 activity in mouse models, and [¹⁸F] FSPG PET has been used in pilot clinical trials [130], which may offer a practicable visualized measurement to facilitate better clinical assessment in the future.

Although pioneering studies in SLC7A11 have advanced our understanding of its fundamental functions and pathophysiological roles, there are still several questions to be answered. First, many studies have investigated SLC7A11 regulation both at transcriptional and post-transcriptional levels, while studies of post-translational modifications of SLC7A11, such as ubiquitylation, are still lacking. Thus, further studies are needed to investigate the diverse post-translational modifications of SLC7A11 that control its biological functions in pathophysiological conditions. Second, though lethal levels of ROS contribute to cell death, a moderate content of ROS drives tumorigenesis. Indeed, SLC7A11-deficient mice display increased incidence

ce of chemically induced tumorigenesis due to excessive oxidative stress and inflammation [131], indicating alternative mechanisms to maintain intracellular redox status. Third, SLC7A11 inhibition was reported to conversely favor cancer cell survival in certain settings. Thus, much research vacancy is left waiting for future exploration. Fourth, some compounds directly targeting SLC7A11 have undesirable pharmacological properties and the mechanistic insight into their detailed mechanisms is not fully explored. As for compounds that indirectly target SLC7A11, the application range has to be paid special attention as the targeted molecules may also engage in other signaling pathways and elicit unwanted side effects. Finally, though immunotargeting SLC7A11 exhibits effective outcomes *in vivo*, the experiment model is primarily based on breast cancer, and other cancer types are not explored. Thus, further mechanisms and improvements are required for this prospective therapeutic approach.

In summary, SLC7A11 is involved in the pathogenesis of various cancers. The biological function and upstream regulation of SLC7A11 will cause great attention in the field of cancer research and targeting SLC7A11 may provide a novel and effective therapeutic approach for anticancer treatment.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Qiyin Zhou, Department of Medical Oncology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou 310016, Zhejiang, China. E-mail: zhouqiyin@zju.edu.cn; Dr. Hongchuan Jin, Laboratory of Cancer Biology, Key Lab of Biotherapy in Zhejiang, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou 310016, Zhejiang, China. E-mail: jinhc@zju.edu.cn

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