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Review Article

The dual role of SLC7A11 in tumor drug resistance: mechanisms, challenges, and therapeutic potential

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Abstract: Tumor drug resistance is a major factor in cancer treatment failure. SLC7A11 is characterized as a light-chain subunit antiporter of the Xc^- system, responsible for exchanging extracellular cystine with intracellular glutamate. SLC7A11 has been shown to critically modulate tumor progression through regulation of intracellular cysteine homeostasis and redox balance, thereby governing ferroptosis and disulfidptosis. Ferroptosis and disulfidptosis are closely associated with tumor drug resistance, and SLC7A11 demonstrates a dual regulatory role in this process. This review summarized the structure and function of SLC7A11 and the mechanisms underlying tumor drug resistance. It then analyzed the potential regulatory effects of SLC7A11 on ferroptosis, disulfidptosis, and autophagy in the context of tumor chemotherapy, targeted therapy, immunotherapy resistance, and prognosis. Finally, this review delineated the therapeutic opportunities and translational challenges in targeting SLC7A11 to overcome tumor drug resistance, serving as a foundation for future mechanistic exploration and clinical development.

Keywords: SLC7A11, drug resistance, ferroptosis, disulfidptosis, autophagy

Introduction

In the 21st century, cancer continues to be among the predominant causes of premature mortality [1]. Recent statistical data indicate that roughly 20 million new cases of cancer were recorded globally in 2022, resulting in approximately 9.7 million deaths. By 2050, this number is anticipated to rise to 35 million [2]. Present cancer therapies primarily include surgery, radiation treatment, chemotherapy, targeted molecular therapies, hormone therapies, and immunotherapies. Nevertheless, approximately 90% of cancer-related mortalities are significantly associated with drug resistance exhibited by tumors [3, 4]. This resistance arises from multiple mechanisms, including genetic mutations, activation of efflux pumps, dysregulation of signaling pathways, and tumor heterogeneity [5]. It constitutes a critical challenge in oncology, and thus far, there remains no highly effective therapeutic strategy to surmount this obstacle.

The cystine/glutamate antiporter SLC7A11 is a pivotal regulator in the processes of ferroptosis, disulfidptosis, and autophagy [6-9]. Extensive research has demonstrated that pro-

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moting ferroptosis through modulation of the SLC7A11-SLC3A2-GPX4 signaling pathway, along with iron and lipid metabolism, notably enhances therapeutic efficacy against cancer and potentially reverses resistance [10]. It is noteworthy that SLC7A11 utilizes nicotinamide adenine dinucleotide phosphate (NADPH) to catalyze the intracellular conversion of cystine to cysteine, thereby preventing ferroptosis. Conversely, aberrant accumulation of cystine can trigger disulfide stress, resulting in disulfidptosis [9, 11]. Furthermore, genes associated with disulfidptosis, including SLC7A11, are correlated with tumor prognosis and drug resistance, positioning them as prospective therapeutic targets [12, 13]. Additionally, SLC7A11 is identified as an autophagy-associated gene, implicated in suppressing paclitaxel resistance in ovarian cancer (OC) through regulation of the autophagic pathway as a competing endogenous RNA (ceRNA) [6].

Thus, this paper systematically reviews recent progress concerning SLC7A11's involvement in tumor drug resistance. Specifically, the review addresses the structural and functional aspects of SLC7A11, underlying mechanisms of resistance in tumors, and the contributions of SLC7A11 to resistance against chemotherapy, targeted therapy, and immunotherapy, as well as its prognostic significance via potential modulation of ferroptosis, disulfidptosis, and autophagy. Finally, the paper discusses current opportunities and challenges in targeting SLC7A11 therapeutically. This review aims to provide novel perspectives to facilitate further investigation into the role of SLC7A11 in tumor drug resistance.

Structure and basic function of the SLC7A11 gene and its encoded protein

The human SLC7A11 gene is located on chromosome 4, comprises 14 exons, and encodes the solute carrier family 7 member 11 protein (also known as xCT). This protein consists of 501 amino acids and is characterized by 12 strongly hydrophobic transmembrane domains, with both amino and carboxyl termini positioned within the cytoplasm [14, 15] (**Figure 1**).

The Xc^- system is formed by SLC7A11, the light-chain subunit, and SLC3A2 (also termed 4F2hc or CD98), the heavy-chain subunit. This complex facilitates the equimolar exchange of extracellular cystine and intracellular glutamate. Specifically, SLC7A11 functions as a multichannel transmembrane protein that directly mediates transport activity, while SLC3A2, a single-transmembrane protein, primarily functions as a chaperone to stabilize SLC7A11's membrane localization and transport efficiency [16, 17]. Thus, extracellular cystine enters the cytoplasm as intracellular glutamate is simultaneously exported [18]. Cytoplasmic cystine is subsequently reduced to cysteine through NADPH and then combined with glycine and glutamate to synthesize glutathione (GSH) [18] (**Figure 1**). As a critical antioxidant, GSH serves as an essential cofactor for glutathione peroxidase 4 (GPX4), which reduces lipid peroxides into lipid alcohols, thus preserving cellular redox homeostasis and inhibiting ferroptotic cell death [16, 19] (**Figure 1**).

Nevertheless, this antioxidant mechanism depends heavily on NADPH availability. Under conditions of NADPH depletion or dysfunction, elevated SLC7A11 expression results in cystine accumulation, leading to aberrant disulfide bond formation within the actin cytoskeleton and consequently inducing disulfidptosis [18, 21] (**Figure 1**). Consequently, SLC7A11 operates as a "double-edged sword" in the regulation of cellular demise. On one hand, SLC7A11 inhibits ferroptosis by balancing intracellular cystine/glutamate homeostasis and enhancing antioxidant activity; on the other hand, excessive expression in the context of NADPH insufficiency induces cystine accumulation and triggers disulfide stress-dependent disulfidptosis (**Figure 1**).

Diverse regulatory mechanisms of tumor drug resistance

Tumor drug resistance is mediated by a complex network of molecular pathways, genetic alterations, cellular processes, and regulatory mechanisms. Specifically, these mechanisms encompass diminished drug uptake, heightened intracellular drug efflux, drug neutralization mediated by GSH, nuclear pore complex alterations, enhanced DNA repair capabilities, modifications of β-tubulin as drug target molecules during mitosis, altered expression of apoptosis-regulatory proteins, epithelial-mes-

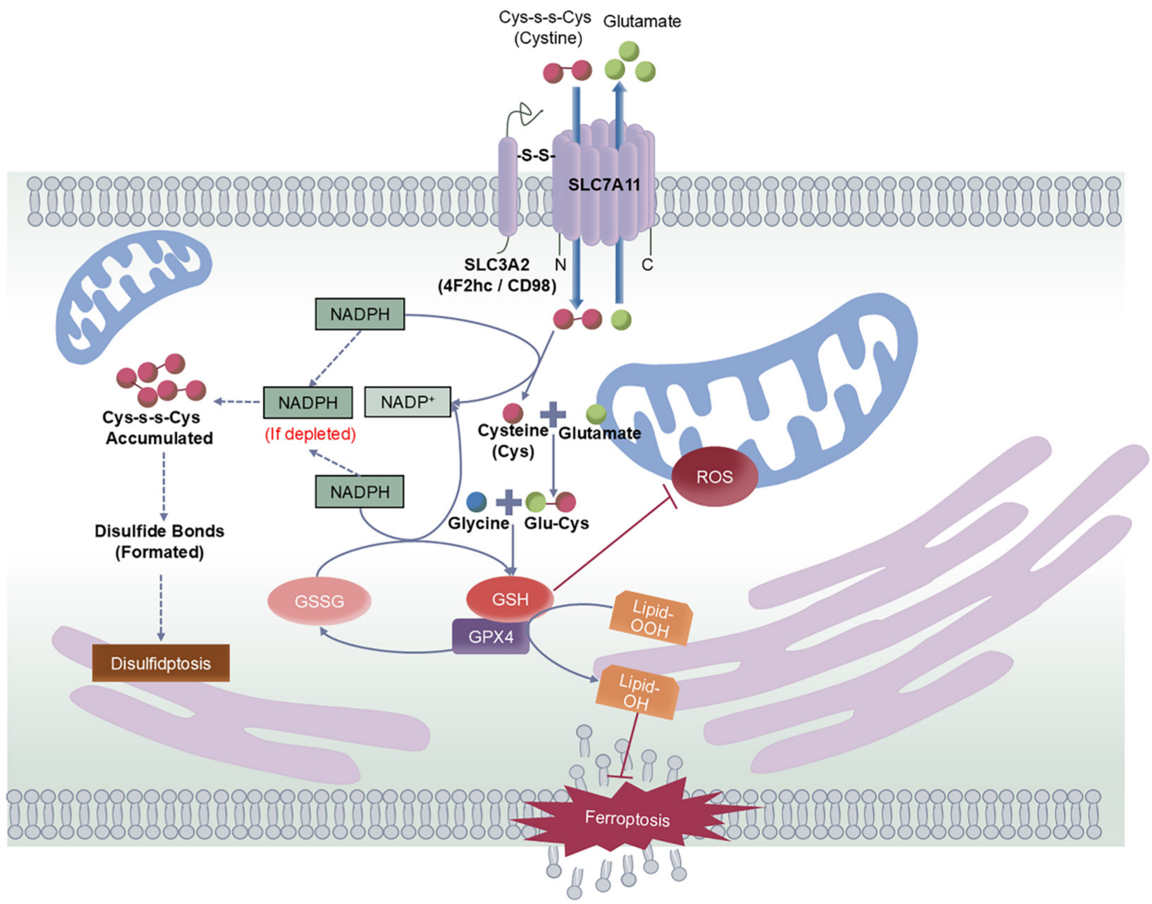

Figure 1. Structure and basic functions of the SLC7A11 gene and its encoded protein. Cytoplasmic cystine is reduced to cysteine by NADPH, serving as a precursor for GSH synthesis alongside glutamate and glycine. GSH acts as a cofactor for GPX4, reducing lipid peroxides to lipid alcohols. This process maintains intracellular redox homeostasis and inhibits ferroptosis. The antioxidant activity mediated by SLC7A11 requires NADPH consumption. If NADPH is deficient or impaired, cystine accumulates in cells overexpressing SLC7A11, causing abnormal disulfide bond formation in the actin cytoskeleton and inducing disulfidptosis.

enchymal transition (EMT), induction of tumor cell dormancy, and dynamic interplay between tumor cells and components of the tumor microenvironment (TME) [21-24] (**Figure 2**).

Water-soluble therapeutic agents gain entry into cells predominantly through active transport processes facilitated by sodium-dependent transporters, copper transport proteins, and organic cation transporters localized at cellular or plasma membranes [21, 25]. Intracellular drug efflux is primarily regulated by six subgroups of the ABC transporter family (ABCA-ABCE, ABCG), among which ABCB1, ABCC1, and ABCG2 are recognized as key mediators of enhanced drug efflux [21, 26]. GSH shows a high affinity for cisplatin, competitively inhibiting cisplatin's binding to DNA. Additionally, blocking the passage of platinum agents through nuclear pore complexes attenuates their ability to induce DNA double-strand breaks [21, 22]. Taxanes exert anticancer effects by modulating the assembly and depolymerization of α-tubulin and β-tubulin subunits forming microtubules [23]. EMT, a transdifferentiation process, provides cancer cells with survival signals, potentially activating ABC transporters, decreasing cell proliferation, and promoting anti-apoptotic pathways [24, 27]. Tumor cell dormancy, characterized by halted cell division, enhances drug resistance by reducing metabolic activity and mRNA synthesis efficiency [21]. The TME provides a microenvironment for direct and indirect interactions, significantly impacting the development of anticancer therapy resistance [21, 28]. These biological processes promote multidrug resistance in chemotherapy by acti-

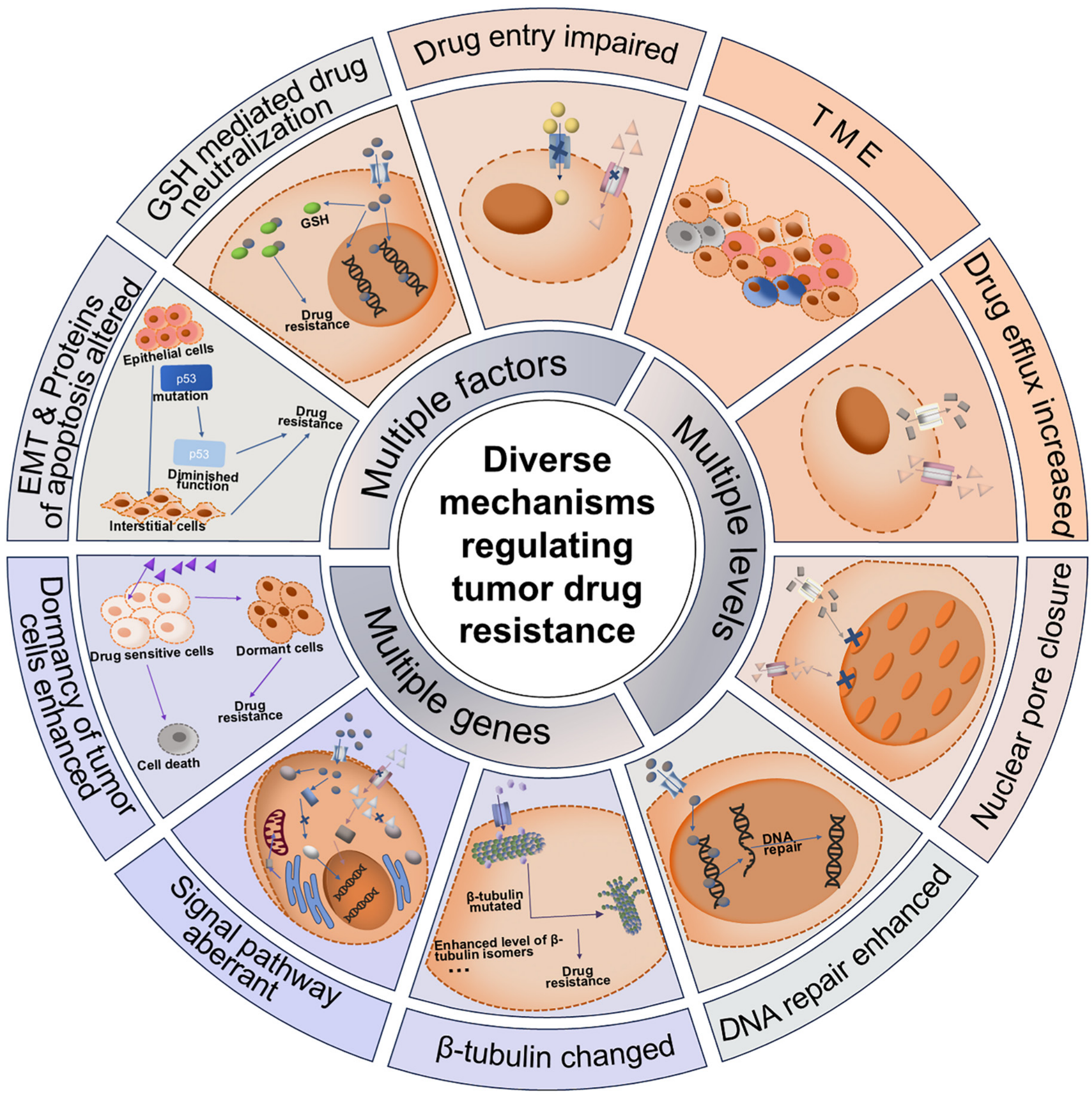

Figure 2. Mechanisms of tumor drug resistance. The regulatory network of tumor drug resistance involves complex, multifaceted, multi-level, and multi-gene biological processes. Key mechanisms include reduced cellular drug uptake, increased intracellular drug efflux, GSH-mediated drug neutralization, nuclear pore closure, enhanced DNA repair, tubulin alterations, EMT, increased tumor cell dormancy, and complex interactions between tumor cells and the TME.

vating apoptosis, cell cycle, autophagy, ferroptosis, and other related signaling pathways [10, 26].

The dual regulatory role of SLC7A11 in tumor drug resistance: definition and molecular basis

Pathways through which SLC7A11 promotes tumor drug resistance

SLC7A11 promotes tumor resistance by inhibiting ferroptosis: Ferroptosis is an iron-dependent cell death modality, clearly distinct from apoptosis, necrosis, and autophagy, and has recently gained attention as a potential strategy to overcome tumor drug resistance [10]. Ferroptosis initiation pathways mainly involve GPX4 regulation, iron metabolism, and lipid metabolism, with SLC7A11 functioning as the critical transporter of the Xc^- system within the GPX4 regulatory pathway [10]. Under regulation by the chaperone protein SLC3A2 (4F2hc/CD98), SLC7A11 translocates to the cell membrane, facilitating cystine transport, glutathione synthesis, GPX4 activity enhancement, and lipid peroxide reduction, thus preventing ferroptosis through the SLC7A11-SLC3A2-GPX4 pathway [16, 19]. Consequently, many studies have focused on the ferroptosis signaling pathway to elucidate SLC7A11's role in chemotherapy, targeted therapy, and immunotherapy resistance.

In paclitaxel-resistant endometrial cancer (EC) and docetaxel-resistant prostate cancer (PC) cells, SLC7A11 knockdown significantly increased ROS, MDA, and Fe^{2+} levels, inducing ferroptosis and enhancing chemotherapy sensitivity [44, 45]. Additionally, SLC7A11 expression was elevated in cisplatin-resistant tissues, cells, or organoids from gastric, bladder, ovarian, and oral squamous cell carcinoma, inhibiting lipid peroxide accumulation and promoting drug resistance [31, 32, 36-39, 65]. Furthermore, baicalin improved oxaliplatin sensitivity in resistant gastric cancer (GC) cells by disrupting iron homeostasis, enhancing antioxidant defense, and activating the p53-mediated SLC7A11/GPX4/ROS ferroptosis pathway [41]. In 5-fluorouracil-resistant GC cells, STAT3 inhibition downregulated ferroptosis-related genes (SLC7A11, GPX4, and FTH1), restoring chemotherapy sensitivity [52].

Ferroptosis is also closely related to resistance in targeted therapy and immunotherapy. In gefitinib- and sorafenib-resistant cells, targeting ABCC5, the NRF2-SLC7A11 axis, FASN/HIF1α/SLC7A11, or SOCE-CaN-NFAT signaling pathways activated ferroptosis, thereby reversing drug resistance [54, 55, 57, 60, 62]. SLC7A11 knockdown or ferroptosis induction by erastin increased MDA, reduced tumor growth, and reversed TKI resistance induced by IL-6-mediated SLC7A11 upregulation via the JAK2/STAT3 pathway in renal cell carcinoma cells [66]. Persistent mTOR/4EBP1/SLC7A11 activity contributed to ferroptosis resistance against MEK inhibitors, which was reversed by AKT-mediated inhibition of SLC7A11 protein synthesis [66]. Additionally, SLC7A11 knockdown in immunotherapy-resistant cells increased ferroptosis sensitivity, decreased myeloid-derived suppressor cell (MDSC)-mediated $CD8^+$ T-cell suppression, and enhanced anti-PD-L1 efficacy, indicating that SLC7A11 regulates immunotherapy resistance via ferroptosis [64] (**Figure 3**).

Regulation of classical multidrug resistance (MDR) pathways: Beyond ferroptosis suppression, SLC7A11 critically modulates classical MDR pathways through interconnected mechanisms, including the synergistic regulation of drug efflux pumps, DNA damage repair, and apoptosis resistance.

The role of synergistic regulation of drug efflux pumps is reflected in the fact that SLC7A11 modulates the thiolation status of P-glycoprotein (P-gp) by sustaining intracellular GSH levels, thereby stabilizing P-gp membrane localization and enhancing its drug efflux function [21, 26]. Concurrently, SLC7A11 supplies GSH as a co-transport substrate for multidrug resistance-associated protein 1 (MRP1/ABCC1), indirectly potentiating the activity of ABC transporter family members and augmenting drug extrusion capacity [21, 26]. Clinical correlative studies demonstrate significantly positive associations between SLC7A11 expression levels and ABC transporter activity in malignancies such as breast and OC [23, 25]. This synergistic interaction may constitute a critical factor underlying the failure of conventional chemotherapy.

SLC7A11 also promotes tumor drug resistance by enhancing DNA damage repair. Recent studies have shown that SLC7A11 can regulate the DNA damage repair system through several mechanisms [21, 22]. At the metabolic regulation level, SLC7A11-mediated cystine uptake provides key raw materials for DNA synthesis and repair. Cysteine produced by cystine metabolism is an essential precursor for dCTP synthesis and maintains nucleotide pool balance to ensure the supply of materials required for DNA damage repair. In cisplatin-resistant cells, SLC7A11 knockdown reduced dCTP levels [22]. In terms of oxidative damage protection, the SLC7A11-GSH system plays an important role: it clears therapy-induced ROS to protect nuclear genome stability and maintains the reduced state of repair enzymes (e.g., PARP1, XRCC1) to ensure their catalytic activity [21, 22, 27]. Regarding repair complex formation, co-immunoprecipitation confirmed a direct interaction between SLC7A11 and XRCC1, promoted the recruitment of repair complexes to damage sites, and enhanced base excision repair and nucleotide excision repair pathway activities. Clinical sample analysis shows elevated expression levels of DNA damage repair markers in SLC7A11-high tumors [22, 27].

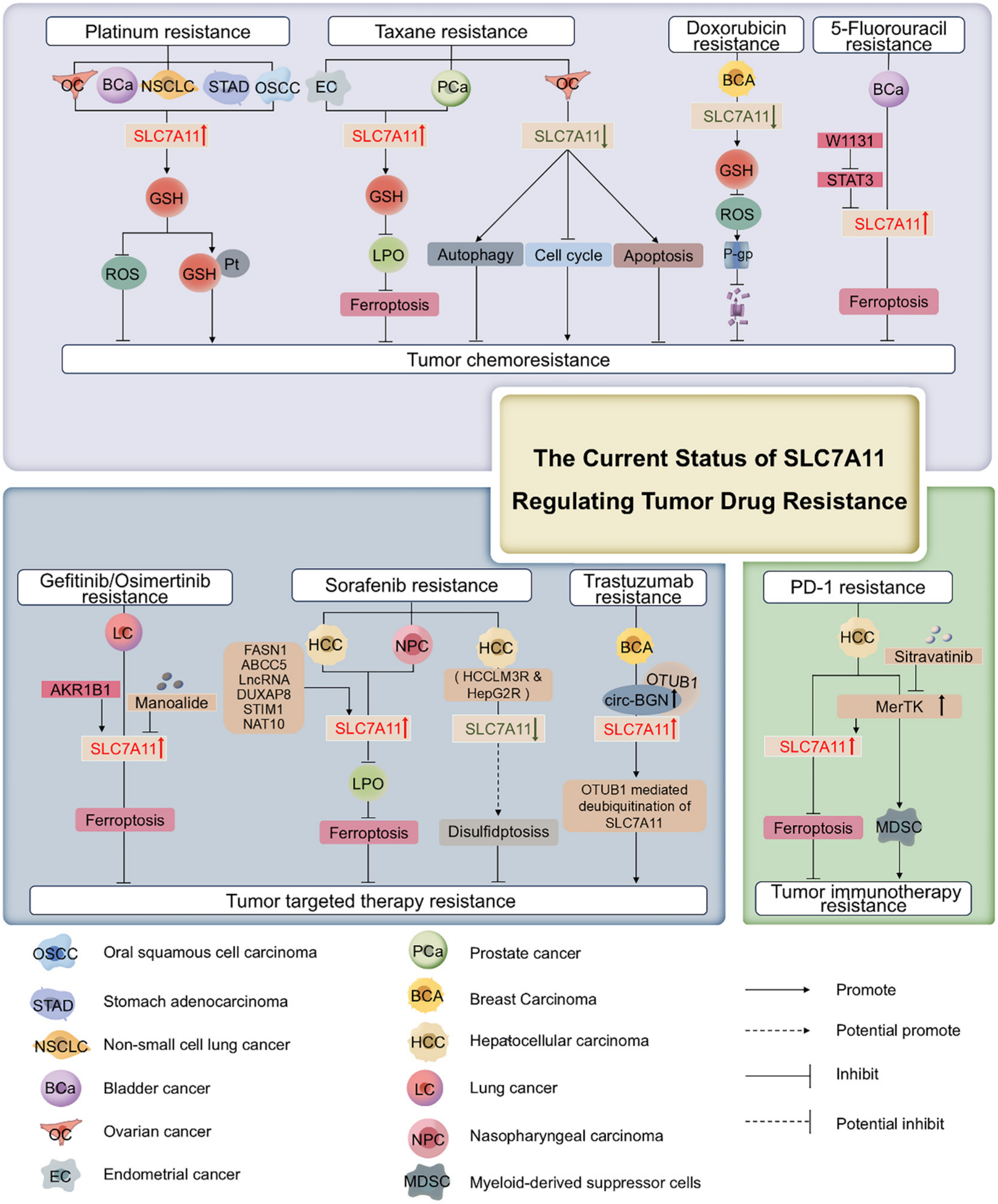

Figure 3. Current status of SLC7A11 in regulating tumor drug resistance. In chemoresistance, SLC7A11 positively regulates platinum resistance. It is highly expressed in platinum-resistant ovarian cancer, bladder cancer, Non-small cell lung cancer, and oral squamous cell carcinoma. It promotes resistance through mechanisms. In taxane resistance, SLC7A11 plays a dual regulatory role. High expression of SLC7A11 in docetaxel-resistant endometrial and prostate cancers enhances resistance by inhibiting ferroptosis. Conversely, low SLC7A11 expression occurs in paclitaxel-resistant ovarian cancer, where overexpression of SLC7A11 suppresses drug resistance. In doxorubicin resistance, low SLC7A11 expression in BC increases ROS levels and enhances P-gp-mediated drug efflux, thus promoting resistance. SLC7A11 positively regulates 5-fluorouracil resistance in gastric cancer; inhibiting the STAT3 signaling pathway decreases SLC7A11 expression, enhancing chemosensitivity. In targeted therapy resistance, SLC7A11 enhances resistance to gefitinib or osimertinib in lung cancer and is positively regulated by AKR1B1 and negatively by manolide. In trastuzumab-resistant bladder cancer, circ-BGN binds SLC7A11 and OTUB1 proteins, facilitating OTUB1-mediated SLC7A11 deubiquitination, thus enhancing resistance. In liver cancer and nasopharyn-

geal carcinoma, resistance to sorafenib, SLC7A11 expression is positively regulated by FASN1, ABCC5, and other genes, promoting drug resistance through ferroptosis inhibition. However, in sorafenib-resistant hepatocellular carcinoma cells (HCCLM3R and HepG2R), SLC7A11 expression is reduced, suggesting its potential involvement in suppressing resistance via disulfidptosis. In immunotherapy resistance, MerTK impairs PD-L1 blockade efficacy by recruiting MDSCs and upregulating SLC7A11, thereby inhibiting ferroptosis.

SLC7A11 promotes tumor drug resistance through apoptosis resistance mechanisms: SLC7A11 enhances tumor cell resistance to apoptosis through multiple molecular mechanisms, involving three key regulatory levels. Firstly, at the mitochondrial level, SLC7A11 stabilizes mitochondrial membrane potential and reduces mitochondrial permeability transition pore opening, effectively inhibiting cytochrome C release from mitochondria to the cytoplasm, thereby blocking initiation of the mitochondrial apoptosis pathway [21]. Secondly, at the apoptosis-related protein regulation level, SLC7A11 upregulates anti-apoptotic proteins Bcl-2 and Bcl-xL while downregulating pro-apoptotic proteins Bax and Bak, leading to an increased Bcl-2/Bax ratio and further reinforcing mitochondrial outer membrane stability [21, 26]. Finally, at the apoptosis execution stage, SLC7A11 inhibits caspase-9 activation, blocks downstream cleavage activation of caspase-3/7, and ultimately suppresses characteristic apoptotic events such as PARP cleavage [21, 24]. These synergistic mechanisms collectively constitute the SLC7A11-mediated apoptosis resistance network, providing tumor cells with a robust survival advantage [21].

Analysis of clinical samples has demonstrated an inverse correlation between SLC7A11 expression and the apoptosis marker cleaved caspase-3, underscoring its critical role in clinical drug resistance [21, 24, 33, 40]. These findings provide a theoretical foundation for developing combination therapeutic strategies targeting the SLC7A11-apoptosis regulatory axis [21, 27].

SLC7A11-mediated tumor microenvironment remodeling mechanisms: SLC7A11 plays a pivotal role in constructing a tumor-promoting ecosystem by regulating metabolic interactions between tumor cells and the microenvironment.

In metabolic reprogramming, glutamate efflux mediated by SLC7A11 is taken up by cancer-associated fibroblasts (CAFs), where it undergoes transamination to generate α-ketoglutarate. This process enhances CAF energy metabolism and cytokine secretion capabilities, thereby establishing a "tumor cell-CAF" metabolic symbiosis network [16, 19]. Such metabolic crosstalk significantly alters the physicochemical properties of the tumor microenvironment, manifesting as decreased extracellular pH and lactate accumulation [16, 19, 28].

Regarding immune microenvironment regulation, SLC7A11 establishes an immunosuppressive barrier through multiple mechanisms [17, 19, 79]: it depletes microenvironmental GSH, reducing natural killer cell cytotoxicity; induces M2-type macrophage polarization [17, 19]; suppresses $CD8^+$ T-cell infiltration [17, 79]; and upregulates PD-L1 expression via the ROS-NF-κB signaling pathway [17]. Single-cell transcriptomic analysis revealed increased proportions of immunosuppressive cells (e.g., MDSCs, Tregs) in SLC7A11-high regions, forming a characteristic "immune desert" phenotype [17].

Additionally, SLC7A11 promotes angiogenesis: effluxed glutamate directly stimulates endothelial cell migration [16, 18], and SLC7A11 upregulates VEGF expression by stabilizing HIF-1α protein, leading to increased microvascular density [16]. Preclinical studies have confirmed that targeted inhibition of SLC7A11 normalizes tumor vasculature and enhances chemotherapeutic drug delivery efficiency [16, 81].

SLC7A11-enhanced pathways for tumor drug sensitization

Although SLC7A11 generally promotes drug resistance, its overexpression can paradoxically enhance tumor cell sensitivity to therapy under specific conditions. This sensitization effect is primarily manifested in:

SLC7A11 may inhibit paclitaxel resistance in OC by promoting autophagy: Autophagy represents a cellular self-degradation mechanism responsible for recycling intracellular materials. This biological process involves sequential steps: phagophore nucleation, autophagosome formation, fusion of autophagosomes with lysosomes, and subsequent degradation within autolysosomes [67]. During tumor development, autophagy exhibits context-dependent dual functionality, described as a "double-edged sword", since it can either promote cell survival or contribute to cell death in drug-resistant tumors [68, 69]. For example, circMAPKBP1 expression is elevated in oral squamous cell carcinoma resistant to cisplatin and augments autophagy, subsequently activating the miR-17-3p/TGFβ2 pathway and leading to increased cisplatin resistance [70]. Conversely, autophagy has been shown to counteract paclitaxel resistance [6, 71]. In nasopharyngeal carcinoma, high levels of CENPN positively correlate with resistance to paclitaxel and inversely correlate with autophagic activity and VAMP8 expression [70]. Silencing CENPN significantly enhances sensitivity to paclitaxel via activation of the CREB-VAMP8 signaling cascade, thereby inducing autophagy [71]. Similarly, a recent study identified SLC7A11 as an autophagy-related gene based on three autophagy-related datasets [6]. This gene is significantly downregulated in paclitaxel-resistant OC tissues and cells and interacts with multiple resistance-related proteins [6]. Furthermore, pan-cancer analysis across 32 tumor types has demonstrated that SLC7A11 positively regulates autophagy pathway proteins STX17, RAB33B, and UVRAG through a ceRNA mechanism [6]. Overexpression of SLC7A11 significantly induces the expression of STX17, RAB33B, and other autophagy-related proteins such as LC3, Atg16L1, and Atg7, which further increase under paclitaxel treatment [6]. These findings suggest that SLC7A11 potentially promotes autophagy to suppress paclitaxel resistance in OC (**Figure 3**).

Triggering disulfidptosis: Under NADPH-depleted conditions, SLC7A11-mediated excessive cystine uptake induces intracellular disulfide stress, leading to aberrant crosslinking of the actin cytoskeleton and consequent cell death [9, 11, 18, 20, 75]. For instance, in sorafenib-resistant hepatocellular carcinoma (HCC) cells, inhibiting NADPH generation converted SLC7A11 from a "pro-survival molecule" to an "executioner of death", thereby restoring drug sensitivity through disulfidptosis [12].

Paradoxically, in doxorubicin-resistant breast cancer, low SLC7A11 expression causes ROS accumulation that activates P-gp-mediated drug efflux [50]. Conversely, SLC7A11 overexpression reverses resistance by maintaining redox homeostasis to suppress P-gp function [16, 19, 50].

Dynamic regulation and microenvironment dependency of dual functions

The dual roles of SLC7A11 are not contradictory but reflect its dynamic responsiveness to the tumor microenvironment [9, 18, 20]. The redox status of NADPH serves as a critical determinant for SLC7A11's functional switch [9, 20]. In reduced microenvironments with high NADPH, SLC7A11 primarily exerts antioxidant effects that promote drug resistance [9, 16, 20]. Under oxidative stress conditions with NADPH depletion, SLC7A11-mediated cystine accumulation triggers disulfidptosis, enhancing therapeutic sensitivity [9, 11, 18, 20, 75]. Notably, tissue-specific regulatory networks - such as the antagonism between autophagy and ferroptosis pathways in OC - further amplify the functional complexity of SLC7A11 [9, 20].

Correlation between SLC7A11 and chemoresistance

SLC7A11 positively regulates platinum-based chemotherapy resistance

Platinum-based chemotherapeutics, such as carboplatin, cisplatin, oxaliplatin, nedaplatin, and lobaplatin, constitute a category of cell cycle non-specific drugs. They primarily exert anti-cancer effects by binding DNA, thereby obstructing processes of replication and transcription essential for cancer cell proliferation [29]. Nevertheless, the clinical efficacy of these platinum agents is severely hindered by persistent issues of chemoresistance [29].

Notably, elevated expression of SLC7A11 is identified in platinum-resistant OC tissues and corresponding cellular models, marking it as a potential indicator of chemoresistance [30, 31]. A retrospective analysis conducted on 192 epithelial OC specimens revealed substantially increased levels of SLC7A11 and GPX4 in platinum-resistant cases [30]. Simultaneously, elevated expression of these two proteins was strongly associated with a 60-fold greater likelihood of resistance to platinum chemotherapy ($P < 0.001$) [30]. Additionally, experiments involving the silencing of SLC7A11 or GPX4 expression in cisplatin-resistant OC cell lines (A2780/CisR and SKOV3/CisR) demonstrated a reversal of resistance phenotypes [30]. A subsequent investigation provided evidence that miR-194-5p directly targets SLC7A11 transcripts in cisplatin-resistant OC cells, while enforced SLC7A11 overexpression counteracted the enhanced cisplatin sensitivity mediated by miR-194-5p [31].

SLC7A11 expression increases significantly in cisplatin-resistant bladder cancer cells or organoids via ceRNA or N6-methylade-nosine (m^6A) mechanisms, potentially enhancing cisplatin resistance by elevating GSH levels [32, 33]. SLC7A11 is highly expressed in cisplatin-resistant bladder cancer tissues as a downstream target of microRNA-27a, promoting resistance by regulating glutathione biosynthesis [33]. m^6A, an RNA modification, dynamically regulates mRNA splicing, transport, stability, and translation via methyltransferases, demethylases, and methylation-reading proteins [34, 35]. In cisplatin-resistant bladder cancer cells, decreased m^6A levels on SLC7A11 mRNA reduced binding with the m^6A reader YTHDF3, increasing mRNA stability and SLC7A11 protein expression [32]. Knockdown of SLC7A11 enhanced cisplatin sensitivity in bladder cancer organoids [32].

In non-small cell lung cancer (NSCLC), SLC7A11 positively regulates cisplatin resistance [36-38]. LncRNA ITGB2-AS1 expression significantly increases in cisplatin-resistant NSCLC cells. Knockdown of ITGB2-AS1 reduced SLC7A11 expression and inhibited NSCLC cell proliferation and cisplatin resistance [36]. Furthermore, both α-Hederin and Dihydroisotanshinone I reversed cisplatin resistance by reducing SLC7A11 protein levels in resistant NSCLC cells [37, 38].

SLC7A11 expression also correlates positively with cisplatin or oxaliplatin resistance in GC [39-41]. SLC7A11 and FAM120A are upregulated, whereas SLC7A11-AS1 is downregulated in cisplatin-resistant GC tissues [39, 40]. SLC7A11-AS1 reduces intracellular GSH and elevates ROS levels by interacting with miR-33a-5p or directly inhibiting SLC7A11 expression [39]. FAM120A stabilizes SLC7A11 mRNA, enhancing cisplatin resistance [40]. One study reported increased SLC7A11 expression in oxaliplatin-resistant GC cells, indicating that Baicalin improves chemosensitivity by activating the p53-mediated SLC7A11/GPX4/ROS pathway [41] (**Figure 3**).

SLC7A11 plays a dual role in taxane chemoresistance

Taxanes, including paclitaxel, docetaxel, and their derivatives, are anticancer substances derived from the bark or needles of Taxus chinensis. These compounds have potent cytotoxic effects and are widely used for targeting tumor microtubules in cancer therapy. However, their effectiveness is limited by chemotherapy resistance [42].

SLC7A11 is identified as a beneficial factor in overcoming paclitaxel resistance in OC [6, 43]. One study demonstrated that SLC7A11 expression was significantly downregulated by 16-fold in paclitaxel-resistant OC cells compared to parental cells, based on microarray analysis [43]. Although it was initially proposed that SLC7A11 had opposite roles in paclitaxel and cisplatin resistance, a detailed investigation was not performed. Moreover, another investigation employed extensive bioinformatic and experimental validation approaches to reveal substantially diminished SLC7A11 mRNA and protein levels in paclitaxel-resistant OC tissues and resistant cell variants (HeyA8-R and SKOV3-R) [6]. Forced expression of SLC7A11 in paclitaxel-resistant HeyA8-R cells led to reduced cell viability, impaired colony formation capacity, cell cycle arrest, increased apoptosis, and significant restoration of sensitivity to paclitaxel, effectively reversing resistance [6].

Conversely, three studies indicated that SLC7A11 functions as an adverse regulator of paclitaxel resistance in EC and docetaxel resistance in PC [44-46]. Lin et al. found that Fanconi anemia complementation group D2 (Fancd2) and SLC7A11 were significantly elevated in paclitaxel-resistant EC cells (Ishikawa/TAX). Knockdown of Fancd2 enhanced paclitaxel sensitivity and markedly reduced SLC7A11 protein levels in Ishikawa/TAX cells [44]. In PC, docetaxel-resistant cells exhibited increased resistance to ferroptosis with elevated expression of PCAT1 and SLC7A11 [45, 46]. Moreover, SLC7A11 expression is positively regulated by PCAT1, and inhibition of SLC7A11 reverses resistance to docetaxel and ferroptosis inducers in PCAT1-overexpressing PC cells [45, 46] (**Figure 3**).

SLC7A11 negatively regulates doxorubicin chemoresistance

Doxorubicin, a widely used anthracycline anticancer drug, causes DNA damage and subsequent cytotoxicity by intercalating DNA strands, inhibits topoisomerase II activity, and promotes ROS accumulation [47-49]. However, its clinical utility is significantly compromised by resistance. A pioneering study demonstrated that increased ROS combined with suppressed cystine uptake via inhibition of SLC7A11 is integral to doxorubicin-induced overexpression of P-gp and subsequent drug resistance [50]. The researchers reported markedly reduced SLC7A11 expression in breast cancer (BC) cell line variants resistant to doxorubicin (MCF-7R) compared to their sensitive counterparts (MCF-7S). Suppression of SLC7A11 expression led to decreased GSH synthesis, elevated ROS levels, and increased drug efflux mediated by P-gp. Conversely, overexpression of SLC7A11 increases doxorubicin sensitivity in both sensitive and resistant BC cells. Additionally, cysteine deprivation increases ROS levels and P-gp expression, while cysteine supplementation decreases both. Collectively, these findings suggest that SLC7A11 and cysteine regulation critically influence P-gp expression and function, identifying SLC7A11 as a potential therapeutic target for overcoming doxorubicin resistance in BC [50] (**Figure 3**).

SLC7A11 positively regulates 5-fluorouracil chemoresistance

5-fluorouracil (5-FU) is an antimetabolite chemotherapy agent. Its active metabolite, fluorouracil deoxynucleotide, inhibits thymidylate synthase and blocks DNA synthesis, thereby exerting antitumor effects. Currently, resistance to 5-FU remains a primary reason for poor chemotherapy outcomes in GC [51]. To date, a single investigation has confirmed increased SLC7A11 expression levels in GC cells and xenograft models resistant to 5-FU. Treatment of resistant GC cells with the STAT3 inhibitor W1131 effectively lowered SLC7A11 expression, thereby restoring their susceptibility to 5-FU [52]. Collectively, these observations suggest a contributory role for SLC7A11 in promoting chemoresistance to 5-FU in GC (**Figure 3**).

Correlation between SLC7A11 and targeted therapy resistance

The rationale behind targeted therapies is to enhance cancer treatment precision through selective inhibition of specific genetic mutations or aberrantly expressed proteins within tumors. Nevertheless, resistance remains a substantial obstacle limiting their clinical benefit. Recent evidence indicates that SLC7A11 may influence resistance to targeted therapies in various malignancies, including breast, lung, liver cancers, and nasopharyngeal carcinoma [12, 53-60].

Mutations in the epidermal growth factor receptor (EGFR) are frequent therapeutic targets in LC; however, acquired resistance substantially restricts the efficacy of EGFR tyrosine kinase inhibitors (TKIs) [53]. Elevated SLC7A11 expression has been observed in lung cancer cells resistant to the EGFR inhibitor gefitinib, possibly contributing to enhanced antioxidant defenses and subsequent gefitinib resistance [55]. Furthermore, manoalide has been shown to restore sensitivity in osimertinib-resistant LC cells by downregulating SLC7A11 expression [54]. Additionally, AKR1B1 activation was reported to elevate SLC7A11 levels, while AKR1B1 inhibition restored EGFR-TKI responsiveness and delayed acquired resistance in LC-derived xenograft models [53].

In BC, human epidermal growth factor receptor 2 serves as a biomarker guiding targeted therapeutic interventions. Research indicates that high circ-BGN expression in trastuzumab-resistant BC cells and tissues stabilizes SLC7A11 through OTUB1-mediated deubiquitination, thereby contributing to trastuzumab resistance [56].

Sorafenib, the first multi-target TKI approved for advanced HCC, encounters significant challenges from acquired resistance that diminish its clinical utility [61]. Previous studies illustrated that elevated SLC7A11 expression in sorafenib-resistant cells of HCC and nasopharyngeal carcinoma is positively regulated by various genes, including FASN1 [60], ABCC5

[62], LncRNA DUXAP8 [60], STIM1 [57], and NAT10 [63]. These genes enhance resistance primarily through decreasing lipid peroxide accumulation. Notably, recent data indicate that increased SLC7A11 in sorafenib-resistant HCC lines (HCCLM3R and HepG2R) may facilitate disulfidptosis, thus suppressing resistance [12]. This highlights a context-dependent, dual regulatory role of SLC7A11 in modulating sorafenib resistance (**Figure 3**).

Correlation between SLC7A11 and tumor immunotherapy resistance

Tumor immunotherapy primarily employs immune checkpoint inhibitors (PD-1/PD-L1 blockers) to boost immune responses against tumors. However, immunotherapy resistance remains a significant challenge [64]. In anti-PD-L1-resistant HCC cells and tissues, levels of SLC7A11 and MerTK were significantly elevated and positively correlated. Knockdown of SLC7A11 and MerTK improved sensitivity to PD-L1 blockade [64]. Additionally, MerTK inhibition reduced SLC7A11 expression, promoted ferroptosis, and decreased MDSC infiltration [64]. These findings suggest that MerTK positively regulates immunotherapy resistance in HCC by upregulating SLC7A11, thereby providing an effective strategy to enhance PD-L1 blockade efficacy (**Figure 3**).

Prognostic value of SLC7A11 in tumor progression and chemoresistance

Treatment failure and poor clinical outcomes in cancer patients frequently result from difficulties in early tumor detection and acquired resistance to chemotherapeutic agents [72, 73]. Remarkably, accumulating evidence indicates that the prognostic significance of SLC7A11 expression varies substantially across diverse cancers and chemoresistant scenarios [6, 30, 32, 33, 40]. For instance, SLC7A11 acts as a negative regulator of paclitaxel resistance in OC [6, 43]. Its low expression correlates significantly with poor overall survival (OS), progression-free survival (PFS), and post-progression survival (PPS) in OC patients [6]. Furthermore, simultaneous high expression of SLC7A11 and positively associated autophagy genes, such as UVRAG or STX17, predicts improved patient prognosis [6]. However, in platinum-resistant OC, increased SLC7A11 levels are associated with adverse clinical outcomes, including poor OS and PFS; notably, concurrent high expression of SLC7A11 and GPX4 is an independent prognostic indicator for poorer OS and PFS [30]. Similarly, SLC7A11 is upregulated in cisplatin-resistant gastric and bladder cancers. Its elevated expression correlates with poor OS, PPS, and first progression (FP) in GC patients, as well as poor OS, disease-specific survival (DSS), and progression-free interval (PFI) in bladder cancer patients [32, 40]. Moreover, increased SLC7A11 expression significantly predicts poorer prognosis in terms of PFS and cancer-specific survival (CSS) among patients with cisplatin-resistant bladder cancer [33] (**Table 1**).

Opportunities for SLC7A11 in regulating tumor drug resistance

Inducing cell death through SLC7A11 inhibitors has significant clinical potential for reversing tumor resistance. Currently, SLC7A11 inhibitors mainly include erastin, sulfasalazine, and sorafenib, which promote ferroptosis by inhibiting the Xc^- system [74, 75]. Studies report that combining erastin with cisplatin or docetaxel enhances cytotoxicity against human OC cells, cisplatin-resistant OC cells, and docetaxel-resistant NSCLC cells [76, 77]. Furthermore, erastin reverses ABCB1-mediated docetaxel resistance in ovarian and PC cells [46, 78]. Sulfasalazine and sorafenib, approved drugs for inflammatory diseases and multi-targeted anticancer therapy, respectively [79], also increase drug sensitivity in resistant cells by inhibiting SLC7A11 activity [33, 58, 80, 81].

SLC7A11 holds promise in suppressing tumor drug resistance as a positive regulator of autophagy or disulfidptosis. Only one study identifies SLC7A11 as positively regulating autophagy to inhibit paclitaxel resistance in OC via ceRNA mechanisms [6]. Disulfidptosis, a recently identified programmed cell death pathway, has drawn considerable research interest [82]. Disulfidptosis is characterized by high SLC7A11 expression, depletion of NADPH synthesized through the pentose phosphate pathway, and subsequent accumulation of intracellular cystine. This cystine accumulation promotes abnormal disulfide bond formation among actin cytoskeletal proteins [75]. Notably, recent research demonstrated that disulfidpto-

Table 1. Summary of SLC7A11 regulation of tumor drug resistance

SLC7A11	Drugs	Tumor Type	Drug-resistant Cell Lines	Relative Indexes	Pathways/ Mechanisms	Prognosis	Ref.
Downregulate	Adriamycin	Adriamycin resistant bladder cancer cells	MCF-7R	ROS increases, P-gp expression increases	-	-	[50]
Downregulate	Paclitaxel	Paclitaxel resistant ovarian cancer cells	W1PR	-	-	-	[43]
Downregulate	Paclitaxel	Paclitaxel resistant tissues and cells of ovarian cancer	HeyA8-R & SKOV3-R	After overexpression of SLC7A11, clonogenic ability decreased, cell cycle arrest and apoptosis increased	Cellular autophagy, ceRNA	Poor prognosis in OS, PFS, PPS	[6]
Upregulate	Paclitaxel	Endometrial cancer paclitaxel-resistant cells	Ishikawa/TAX	ROS, MDA, GSH, Fe^{2+} reduce	Ferroptosis	-	[44]
Upregulate	Docetaxel	Prostate cancer cells are resistant to docetaxel	PC3/DR & 22RV1/DR	After knocking down SLC7A11, ROS levels and total iron content increased	Ferroptosis	-	[45]
Upregulate	Docetaxel	Prostate cancer cells resistant to docetaxel	PC3-DR & DU145-DR	Reduction of lipid peroxides	Ferroptosis	-	[46]
Upregulate	Platinum & Cisplatin	Epithelial ovarian cancer platinum resistant tissue and cisplatin resistant cells	A2780/CisR & SKOV3/CisR	Knocking down SLC7A11 reduces cell viability	-	Poor prognosis in OS, PFS	[30]
Upregulate	Cisplatin	Cisplatin resistant tissue in gastric cancer	-	-	Ferroptosis	-	[39]
Upregulate	Cisplatin	Cisplatin resistant non-small cell lung cancer cells	A549/DDP	-	Ferroptosis	-	[38]
Upregulate	Cisplatin	Cisplatin resistant cells and organoids in bladder cancer	T24R2	Reduction of lipid peroxides	Ferroptosis, m^6A	Poor prognosis in OS, DSS, PFI	[32]
Upregulate	Cisplatin	Cisplatin resistant tissues and cells in ovarian cancer	SKOV3/DDP & A2780/DDP	4-HNE, Fe^{2+} reduce	Ferroptosis, ceRNA	-	[31]
Upregulate	Cisplatin	Cisplatin chemotherapy for bladder cancer	EJ-R, D4-R & G7-R	GSH increase	-	Poor prognosis in PFS, CSS	[33]
Upregulate	Cisplatin	Cisplatin resistant tissues and cells in gastric cancer	SGC7901/DDP	GSH increase, ROS reduction	-	Poor prognosis in OS, FP, PPS	[40]
Upregulate	Oxaliplatin	Gastric cancer oxaliplatin resistant cells	HGC27/L	Reduction of lipid peroxides	Ferroptosis	-	[41]
Upregulate	5-Fluorouracil	5-FU resistant gastric cancer cells	MGC803/5-FU	Reduction of lipid peroxides, Fe^{2+} reduce	Ferroptosis	-	[52]
Upregulate	Gefitinib	Lung cancer cells resistant to gefitinib	HCC827GR	ROS reduction	-	-	[55]
Upregulate	Osimertinib	Osimertinib resistant lung cancer cells	HCC827OR	Reduced synthesis of GSH	Ferroptosis	-	[54]
Upregulate	Sorafenib	Sorafenib resistant hepatocellular carcinoma	Huh7-SR & 7721-SR	Reduction of lipid peroxides	Ferroptosis	-	[59]
Upregulate	Sorafenib	Sorafenib resistant hepatocellular carcinoma	Hep3B-SR & MHCC97H-SR	Reduction of lipid peroxides	Ferroptosis	-	[57]
Upregulate	Sorafenib	Sorafenibresistant hepatocellular carcinoma	HuH7-SR	Reduction of lipid peroxides, Increased expression of ABCC5	Ferroptosis	-	[62]
Downregulate	Sorafenib	Sorafenibresistant hepatocellular carcinoma	HCCLM3R & HepG2R	Cell contraction and F-actin contraction	Disulfidptosis	-	[12]
Upregulate	PD-L1 antibody	Hepatocellular carcinoma and tissues resistant to PD-L1	Res1-6	Reduction of lipid peroxides	Ferroptosis	-	[83]

Note: overall survival, OS; progression-free survival, PFS; post-progression survival, PPS; disease-specific survival, DSS; progression-free interval, PFI; cancer-specific survival, CSS; first progression, FP.

sis-related genes correlate with drug sensitivity. Specifically, inhibition of MYH9 expression increased SLC7A11 expression and induced disulfidptosis, thereby enhancing sorafenib sensitivity in sorafenib-resistant liver cancer cells [12].

Challenges of SLC7A11 in regulating tumor drug resistance

SLC7A11 exhibits dual roles within a complex regulatory network of tumor drug resistance, both enhancing and inhibiting resistance. Specifically, it inhibits ferroptosis to promote resistance, while mediates autophagy and disulfidptosis to enhance drug sensitivity. However, whether these three mechanisms of cell death act antagonistically or synergistically remains unclear and warrants further study. A major challenge lies in the fact that disulfidptosis, induced by high SLC7A11 expression, is a newly identified form of cell death with many unresolved questions. For example, the precise molecular mechanism underlying disulfidptosis is unclear, as is its potential interaction with other redox-related cell death pathways [82]. Current studies primarily associate elevated SLC7A11 expression with poor prognosis across various drug-resistant tumors, as it mainly promotes resistance by inhibiting ferroptosis. Thus, SLC7A11 represents a promising therapeutic target. However, due to tumor heterogeneity, drug-related adverse effects, and toxicity concerns that remain inadequately controlled, development and clinical application of SLC7A11 inhibitors are still limited to the preclinical stage.

Conclusion

SLC7A11 is a critical light-chain subunit of the Xc^- system with transport activity. It influences tumor resistance primarily by regulating ferroptosis and disulfidptosis through controlling intracellular cystine levels and GSH synthesis. Tumor drug resistance involves complex genetic and biological processes, with SLC7A11 playing diverse regulatory roles and demonstrating prognostic significance across different cancer types. Current research predominantly highlights SLC7A11-mediated inhibition of ferroptosis to promote drug resistance. Conversely, limited studies indicate that SLC7A11 may regulate autophagy or disulfidptosis, suppressing paclitaxel resistance in OC, sorafenib resistance in liver cancer, and doxorubicin resistance in BC. However, associations between SLC7A11 and carboplatin resistance remain unexplored, and SLC7A11-targeted inhibitors have not entered clinical practice. In conclusion, SLC7A11 represents both a promising therapeutic target and a prognostic biomarker in tumor drug resistance, with potential implications for improving the efficacy of chemotherapy, targeted therapy, and immunotherapy.

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Disclosure of conflict of interest

None.

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