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SLC7A11 Inhibitors Represent a Promising Therapeutic Target by Facilitating the Induction of Ferroptosis in Breast Cancer

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Review Article

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It is predicted with near certainty that an estimated 310,720 women will be diagnosed with invasive breast carcinoma in 2024, while the number of men will be significantly lower at around 2,800, highlighting the alarming prevalence of this cancer across the sexes. The Solute Carrier Family 7 Member 11(SLC7A11) gene is vital for the exchange of extracellular cystine for glutamate at a 1:1 ratio and its expression is significantly increased in various tumors. Numerous research studies have shown that SLC7A11 expression is fine-tuned at several levels, contributing to its pharmacological functions in tumors, such as maintaining cellular redox balance, promoting cell proliferation, and influencing ferroptosis. Many studies suggest that reducing SLC7A11 expression and activity may be beneficial for cancer treatment, making it a promising target for therapy. However, recent findings also suggest that inhibiting SLC7A11 in certain scenarios may increase the survival of cancer cells and promote drug resistance. This review begins with a brief overview of the properties of SLC7A11, including its structural features and physiological functions, followed by a summary of its potential regulators. We then delve deeper into its role in cancer, particularly breast cancer, and explore the relationships between SLC7A11 and ferroptosis, proliferation, metastasis, and therapeutic resistance. Consequently, more customized therapeutic approaches should be considered when targeting SLC7A11 in the context of breast cancer. Thus, high expression of SLC7A11 is associated with poor prognosis in breast cancer, and various inhibitors have been identified that can effectively target this transporter. Innovative therapeutic strategies, including immunotherapies targeting SLC7A11, can potentially reduce tumor growth and metastasis in breast cancer models.

Keywords: SLC7A11, tumor, breast cancer, ferroptosis, therapeutic resistance, inhibitors

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Introduction

In the year 2022, there were 2.3 million cases of breast cancer diagnosed among women, which led to 670,000 deaths around the world. Breast cancer can impact women in every nation worldwide, occurring at any age after puberty, with a greater frequency noted in older populations. In 2024, it is estimated that around 310,720 women and 2,800 men will be identified with invasive breast cancer. Approximately 66% of breast cancer cases are detected at a localized stage-before the cancer spreads beyond the breast-which is when treatment is most effective (1, 2).

Metabolic reprogramming plays a vital role in providing tumors with the necessary nutrients to support their rapid and often uncontrolled growth and proliferation, thus significantly contributing to energy production and biosynthesis. This alteration in metabolic processes is likely a significant contributing factor to the progression of tumors as well as the failure of various therapeutic interventions, which further emphasizes the critical need for innovative therapeutic strategies that specifically target metabolic reprogramming in cancer treatment (3, 4). Among the myriad of metabolic pathways being explored, glutamine metabolism has emerged as a prominent area of interest, as cancer cells often exhibit a high level of dependence on this most prevalent and non-essential amino acid, which serves as a vital source of nutrition that fuels the relentless and aggressive growth of cancerous cells (4).

The metabolism of glutamine and its related metabolic pathways, which include the expression of pertinent amino acid transporters, are crucial for the survival of cancer cells. Cancer cells that proliferate rapidly absorb glutamine through these amino acid transporters and then convert it into glutamate via glutaminase, a process referred to as glutaminolysis (3, 5). The altercation of intracellular glutamate for extracellular cystine, which is the oxidized dimer of cysteine, occurs at a 1:1 ratio through the solute carrier family 7 member 11 (SLC7A11). This transporter is characterized as a sodium-independent, chloride-dependent anionic antiporter for L-cystine and L-glutamate situated on the cell membrane. Normally, cysteine is synthesized within the cell either from scratch or recycled from protein breakdown. However, during oxidative stress, the production of cysteine or its supply from catabolism often does not meet the increased demand for antioxidants in cancer cells. Consequently, many of these cells rely on transporters like SLC7A11 to import extracellular cystine, facilitating metabolic reprogramming that supports the energy needs associated with their altered metabolism (4, 6).

The uptake of cysteine mediated by SLC7A11 is beneficial yet serves as a bottleneck in the synthesis of glutathione (GSH), which is integral to cancer development. In this context, GSH activates the antioxidant defense system that safeguards cancer cells from apoptosis, oxidative stress, and ferroptosis. While SLC7A11 is present in low amounts in normal cells, it functions as a primary transporter in cancer cells that depend heavily on extracellular cystine for their survival, particularly in liver, glioma, and lung cancers, influencing disease endurance (7). The contrasting expression levels of SLC7A11 in normal versus cancer cells indicate that it could be a viable target for cancer therapies. In breast cancer, SLC7A11 is believed to influence cancer stem cells, affecting metastasis significantly. In triple-negative breast cancer (TNBC), recognized as the most aggressive subtype with dismal survival rates, it also plays a vital role in the progression and proliferation of the disease (6-8).

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Up to the present time, a plethora of ongoing research has consistently demonstrated that SLC7A11 is intricately linked to a wide array of significant aspects of breast cancer, which encompasses vital processes such as tumourigenesis, cellular proliferation, metastasis, prognostic outcomes, and resistance to chemotherapy (9). However, it is important to note that an intricate level of complexity has surfaced concerning the involvement of SLC7A11 in cancer, whereby notable inconsistencies between its pro-tumourigenic and anti-tumourigenic effects become apparent when contrasting observations made in cell culture studies with those obtained from in vivo models of malignancy (8). Moreover, SLC7A11 possesses the potential to serve as a crucial target for drug development, as its activity can be successfully influenced and adjusted through the application of various classes of pharmacological compounds. In this review article, we will provide a concise overview of the biological characteristics and properties associated with SLC7A11 inhibitory for the treatment of breast cancer (8, 9). Our main focus will be to clarify and comprehensively understand the intricate dynamics and multi-layered relationship between SLC7A11, the regulated form of cell death known as ferroptosis, and the complex pathology of breast cancer. At the same time, we will investigate the specific molecular and biochemical mechanisms by which these critical biological processes and entities are intimately linked and influence each other in different physiological and pathological contexts. In addition, we will address the promising prospects for therapeutic modulation of SLC7A11 activity in the context of cancer treatment, emphasizing its importance for the advancement of cancer therapy (10, 11).

Literature Search and Selection of Articles

A thorough investigation of the current literature regarding recent advancements in SLC7A11 inhibitory therapeutic agents for breast cancer was undertaken. The eligibility criteria encompassed articles that were in English, fully accessible, thorough, and closely related to the researched topic. The exploration commenced in November 2023 and concluded in February 2024, utilizing specified keywords in PubMed, Google Scholar, and Scopus databases utilizing keywords associated with Breast cancer, Pathways, Ferroptosis, SLC7A11, Therapeutic, and Inhibitory. Totally, 280 articles were initially identified based on their titles, abstracts, and publication dates. Following the elimination of duplicates, 65 distinct articles were retained. Subsequently, in April 2024, supplementary searches were carried out through Google Scholar, PubMed, and Scopus, resulting in the inclusion of 4 more articles pertinent to the subject.

SLC7A11 and Ferroptosis

Cancer cells exhibit a greater demand for iron compared to normal cells, which is crucial for their growth and development. This reliance on iron influences various cell death mechanisms, particularly ferroptosis, a type of cell death that is dependent on iron levels. Interestingly, both an excess and a deficiency of iron can be leveraged in cancer treatment strategies. The processes of iron absorption, transport, storage, and utilization are facilitated by membrane proteins such as transferrin receptor 1 (TFR1), the ferrireductase activity of STEAP3, divalent metal transporter 1 (SLC11A2), and ferritin, an iron-storing protein complex, all of which play a role in determining the sensitivity to ferroptosis (6, 9). In situations of iron deficiency, ferritinophagy helps to regulate iron levels by degrading the iron-storage protein ferritin through autophagy. This process involves the specific cargo receptor nuclear receptor coactivator 4, which directs ferritin to autophagosomes for lysosomal degradation, thereby releasing free iron. Furthermore, iron metabolism is also

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influenced by mitochondria, which are responsible for heme synthesis and the production of iron-sulfur clusters. Given that iron is a vital trace element for cellular function, investigating its physiological roles and mechanisms could unveil new therapeutic avenues for combating cancer and other diseases (12, 13).

The reliance of cancer cells on iron renders them more vulnerable to iron-induced necrosis, referred to as ferroptosis. This concept was introduced by Stockwell as a new form of regulated cell death. In contrast to alternative mechanisms of cellular demise like autophagy and apoptosis, ferroptosis is distinguished by its reliance on iron and reactive oxygen species (ROS), resulting in unique cytological modifications (14). These changes include a reduction or complete loss of mitochondrial cristae, damage to the outer mitochondrial membranes, and condensation of mitochondrial membranes. Ferroptosis has been linked to various diseases, particularly tumors, and targeting this process to eradicate tumors is emerging as a promising strategy in cancer therapy. The biological relevance of ferroptosis is rapidly increasing, especially with the identification of GPX4 and system xc− as essential regulators of this process, along with the application of ferrostatins to inhibit ferroptosis in various scenarios (15). A significant challenge in preventing ferroptosis is the availability of GSH, which acts as a redox equivalent for GPXs, including GPX4. The synthesis of GSH is contingent upon the availability of intracellular cysteine, which is derived from cystine transported from the extracellular environment through the sodium-independent cystine/glutamate antiporter system (14, 16, 17).

The system xc− transporter, which is responsible for cysteine and glutamate transport, is a heterodimer composed of a heavy chain (4F2, gene name SLC3A2) and a light chain (xCT, gene name SLC7A11) (18). Notably, xCT is frequently overexpressed in various cancers, presenting a potential vulnerability for cancer treatment through the induction of ferroptosis. Several FDA-approved medications have been discovered to induce ferroptosis across different cancer types. Furthermore, a range of ferroptosis-inducing agents and mechanisms has been classified such as system xc− inhibitors (Erastin, Sulfasalazine (SAS), and Sorafenib), GSH depleters (FIN56), direct GPX4 inhibitors (RSL3), and iron chelators (Deferoxamine) (19-21). Among these agents, SAS, which is widely used for managing rheumatoid arthritis, has been recognized as an inhibitor of SLC7A11 transporter function. Additionally, SLC7A11 knockout mice exhibit viability without any significant phenotypic changes. Consequently, SLC7A11 may serve as a more favorable therapeutic target for cancer treatment compared to GPX4, as inhibiting SLC7A11 is likely to result in reduced toxicity for patients compared to targeting GPX4 (7, 9, 20).

The metabolism of amino acids is significantly altered in various cancers, indicating the unique uptake and metabolic requirements of cancer cells. This has led to an increasing interest in targeting these metabolic pathways for therapeutic interventions. Cysteine, an essential amino acid, is crucial for protein synthesis and the maintenance of redox homeostasis. Intracellular cysteine can be synthesized de novo or obtained through the degradation of proteins. However, during oxidative stress conditions, such as those found in cancer, the endogenous production or catabolic supply of cysteine often falls short of the elevated demand for antioxidants (22-24). Consequently, many cancer cells depend on nutrient transporters to import extracellular cystine, the oxidized form of cysteine. SLC7A11, referred to as xCT, serves as the light chain component of this transport mechanism, functioning as a sodium-independent, chloride-dependent antiporter for L-cystine and L-glutamate at the cellular membrane. The SLC7A11 protein requires one of the two heavy chain subunits of SLC3A2 to facilitate the exchange of extracellular cystine for intracellular glutamate at a 1:1

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molar ratio. The SLC7A11 gene is located on chromosome 4 in humans, and its protein has orthologs across all vertebrate species. Comprising 12 transmembrane domains, both the N- and C-termini of the SLC7A11 protein are situated in the cytoplasm. Unlike SLC3A2, which serves as a chaperone for various light subunits in heterotrimeric amino acid transport systems, SLC7A11 is specific to its system, making it the primary transporter for cystine and glutamate (19-21).

Extracellular cysteine enters the cell through the SLC7A11 transporter, where it undergoes a reduction reaction that consumes nicotinamide adenine dinucleotide phosphate, taking place in the cytosol's highly reducing environment. This cysteine is then utilized in a two-step synthesis of GSH, a tripeptide (8). The first step involves the formation of γ-glutamylcysteine from cysteine and glutamate, catalyzed by γ-glutamylcysteine synthetase, followed by the conversion of γ-glutamylcysteine into GSH, facilitated by GSH synthetase. SLC7A11 plays a crucial role in metabolic reprogramming in both normal and cancerous cells, influencing nutrient dependency, particularly in glucose and glutamine metabolism, as well as maintaining intracellular redox balance (25). Additionally, cysteine can be imported via an alanine-serine-cysteine transporter or synthesized de novo through a trans-sulfuration pathway in certain tissues, such as the liver,

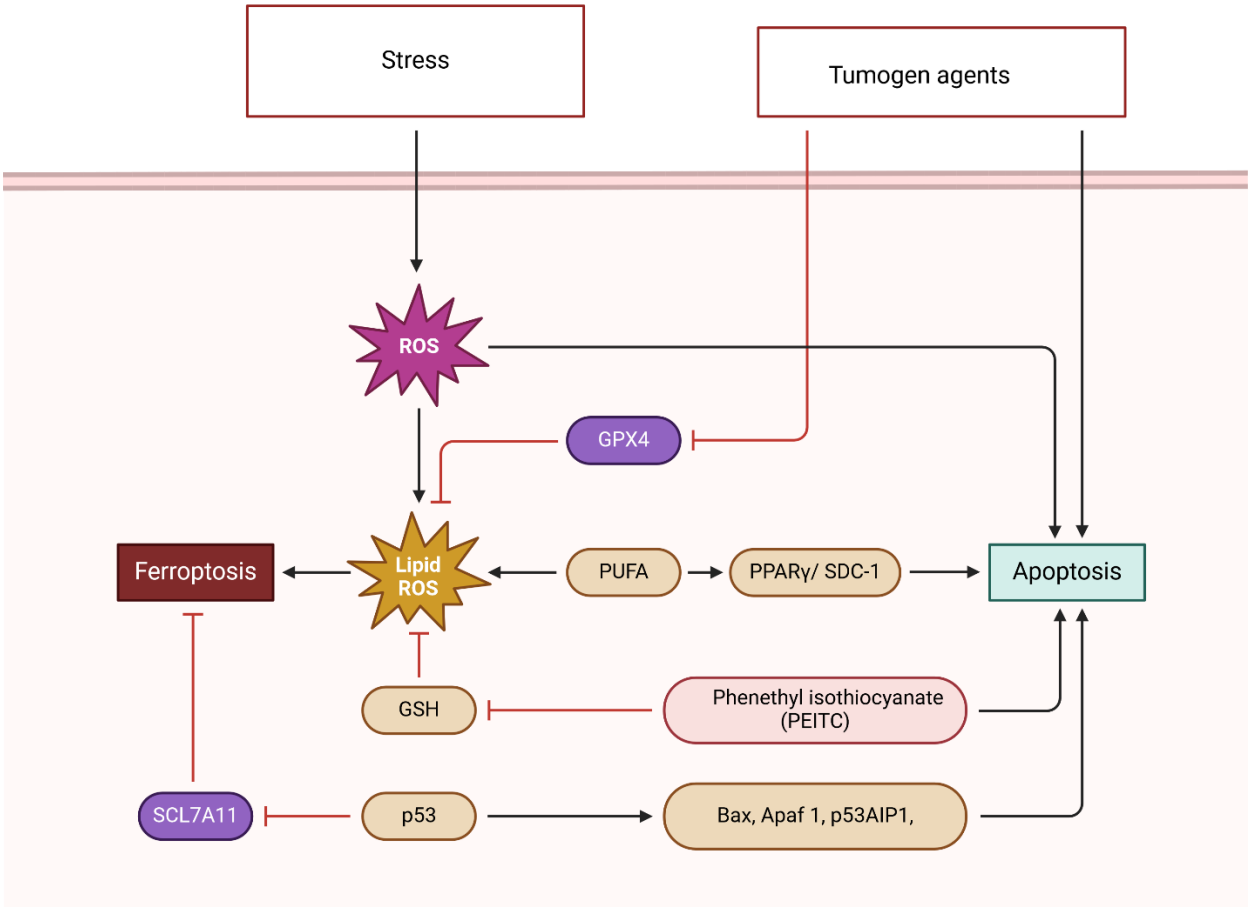


Fig. 1. The SCL7A11 and GPX4 pathways of ferroptosis and apoptosis.

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kidney, and pancreas. Nevertheless, SLC7A11 remains a key transporter for cancer cells that heavily rely on extracellular cystine for their survival. In normal tissues, SLC7A11 is predominantly expressed in the brain, with minimal expression in other tissues (26). Mice that do not possess the SLC7A11 gene can still survive without any issues, successfully reproduce and produce offspring, and seem to maintain a healthy appearance overall, showing no notable adverse phenotypic characteristics, while also being able to lead lives that are comparable in duration to those of typical mice. SLC7A11 is often found to be upregulated in various human cancers. Normal cells are probably capable of fulfilling their intracellular cysteine requirements through de novo synthesis or other transport mechanisms, even without SLC7A11. As a result, the non-essential role of SLC7A11 in typical physiological processes, along with its heightened expression in various cancers, makes it an attractive target for cancer treatment (9, 19) (Figure 1).

The expression of SLC7A11 is influenced by a variety of stress-related factors, including metabolic stress, amino acid deprivation, genotoxic stress, hypoxia, and viral infections. This modulation occurs through several mechanisms such as transcription factors, epigenetic modifications, protein stability, interactions with other proteins, and both post-transcriptional and post-translational regulations, as well as transporter activity (26).

Research has highlighted two key transcription factors, nuclear factor erythroid 2-related factor 2 (Nrf2) and activating transcription factor 4 (ATF4), which play significant roles in the transcriptional regulation of SLC7A11 under stress conditions. When cells experience stress, the degradation of NRF2 by the proteasome is inhibited, leading to its stabilization and movement into the nucleus. Upon entering the nucleus, NRF2 interacts with antioxidant response elements (AREs) located within the promoter regions of numerous genes, such as SLC7A11, consequently facilitating the transcription of genes linked to the antioxidant response (27).

Meanwhile, the translation of ATF4 mRNA is typically suppressed due to the presence of untranslated open reading frames (uORFs) in its 5' untranslated region, but under stress conditions, this translation is enhanced. Stressors such as amino acid deprivation activate phosphorylated eukaryotic initiation factor 2α, which inhibits the translation of many mRNAs, including those containing ATF4 uORFs, thus facilitating the translation of ATF4 and increasing its protein levels. ATF4 subsequently binds to amino acid response elements in the promoter regions of genes like SLC7A11, enabling cellular adaptation to stress (28).

For instance, studies have shown that pancreatic cancer cells increase SLC7A11 expression in response to cystine starvation. In these scenarios, NRF2 and ATF4 work together to regulate SLC7A11 expression. Conversely, p53 has been identified as a repressor of SLC7A11 expression, although the underlying mechanism remains unclear. Recent findings indicate that the absence of NRF2 and ATF4 leads to decreased SLC7A11 levels, which in turn enhances cancer cell survival in low glucose environments (8, 19, 28).

The factors affecting SLC7A11 regulation

Cell stress

Reactive oxygen species, commonly abbreviated as ROS, refer to a diverse group of chemically reactive molecules that include various free radicals, such as superoxide anion, the highly reactive hydroxyl radical (OH-), and the relatively stable hydrogen peroxide (H2O2), all of which are produced as a consequence of intricate reduction-oxidation (redox) reactions taking place within biological systems. These reactive species, along with their many derivatives, possess the capacity to function as crucial signaling intermediates, thereby

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playing a pivotal role in modulating molecular pathways that are integral to a wide range of biological processes, which encompass fundamental activities such as the maintenance of stem cell pluripotency, the orchestration of immune responses, and the regulation of insulin synthesis and secretion by pancreatic beta-cells (19).

Nevertheless, it is important to note that an overabundance of ROS can severely compromise normal physiological functions, leading to detrimental effects that include the incurrence of significant damage to critical biomolecules such as DNA, RNA, proteins, and various cellular organelles, primarily through mechanisms like lipid peroxidation, which can ultimately culminate in cellular apoptosis or necrosis. This pathological state of imbalance is frequently the result of inadequate or overwhelmed detoxification pathways, which may include diminished levels of the tripeptide GSH and a deficiency of key antioxidant enzymes that are essential for the neutralization of oxidative stress (29). The Kelch-like ECH-associated protein 1/Nrf2 (Keap1-Nrf2) signaling pathway plays a crucial role in regulating the cytoprotective response to both endogenous and exogenous stress induced by ROS. Central to this pathway is Nrf2. We have reviewed the existing literature on the Keap1-Nrf2 signaling pathway, focusing on three key areas: its structure, functional mechanisms, and implications in cancer and clinical applications. This pathway can be likened to a double-edged sword; while Nrf2 activation offers protection against oxidative and electrophilic stress, heightened Nrf2 activity may also promote the survival and proliferation of cancer cells. Furthermore, oxidative stress is recognized as a significant marker of cancer in humans. The Keap1-Nrf2 signaling pathway, recognized as a primary antioxidant stress pathway, exhibits abnormalities in various human malignancies, including lung, liver, and thyroid cancers. Recent years have seen a surge in detailed research concerning the Keap1-Nrf2 signaling pathway (Figure 2) (10, 11).

The dysregulation between ROS generation and antioxidant defenses has been linked to numerous diseases, including cancer, pulmonary hypertension, retinal damage, and asthma. SLC7A11 contributes to antioxidant defense by facilitating the import of cystine, which supports the synthesis of GSH. GSH is crucial for various cellular functions, including maintaining intracellular redox balance, reducing hydrogen peroxide and oxygen radicals, detoxifying electrophiles, storing cysteine, and regulating numerous other cellular activities (7). Malignant cells are typically distinguished by a substantial elevation in the concentrations of ROS relative to their non-malignant cellular equivalents, a phenomenon that can considerably enhance the tumorigenesis process; however, it is crucial to recognize that an excess of intracellular ROS may also activate apoptotic signaling pathways, resulting in cellular demise and consequently obstructing tumor advancement. The elevation of ROS levels within these malignant cells may be attributed to a variety of factors including, but not limited to, exposure to ionizing radiation, the administration of cytotoxic pharmacological agents, or the impairment of antioxidant mechanisms along with the overall antioxidant defense system that is typically present within healthy cells. Within the microenvironment of tumors, the modulation of oxidative stress is critically influenced by a transporter known as SLC7A11, which plays a crucial role in maintaining the delicate balance of the cystine/cysteine redox cycle across the cellular membrane (11, 30). The residual cysteine that is produced as a byproduct during the synthesis of GSH is subsequently exported from the cell and is rapidly oxidized to form cystine, while concurrently, SLC7A11 facilitates the continuous influx of extracellular cystine into the cellular environment. This intricate process

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effectively establishes a dynamic cystine/cysteine redox cycle that operates across the cellular membrane, thereby creating a reducing extracellular milieu that is conducive to the growth, proliferation, and ultimate survival of cancer cells. Consequently, understanding the mechanisms by which ROS levels are regulated and the role of SLC7A11 in this context is of paramount importance for the development of novel therapeutic strategies aimed at targeting these pathways in the treatment of cancer. Such insights could potentially lead to more effective interventions that not only inhibit tumor growth but also induce selective apoptosis in cancerous cells while sparing normal tissues from collateral damage (7, 8, 29).

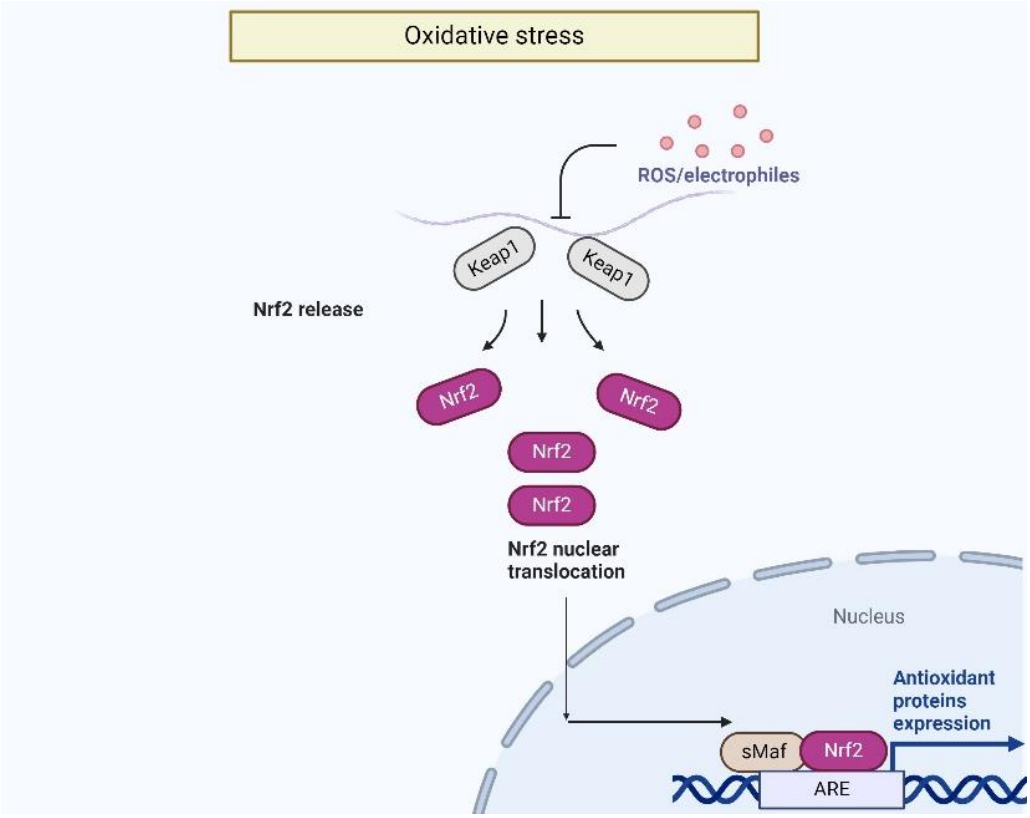


Fig. 2. Keap1-Nrf2 signaling pathway oxidative stress; Keap 1: Kelch-like ECH-associated protein 1; Nrf 2: Nuclear factor erythroid 2-related factor 2; sMaf: The small Maf.

Nutrient Reliance and Metabolic Adaptability

Interactions with other proteins and post-translational modifications can influence the expression and functionality of SLC7A11. For instance, the presence of SLC3A2 is essential for the stability of SLC7A11. In cancer cells, isoforms of the CD44 variant interact with and help stabilize SLC7A11 (31). A deficiency in CD44v leads to compromised localization of SLC7A11 on the cell surface, which induces ROS and inhibits tumor formation. Research utilizing stable isotope labeling in cell culture (SILAC) alongside mass spectrometry on glioblastoma cells engineered to overexpress SLC7A11 revealed that mTORC2 (mammalian target of rapamycin complex 2) binds to the N-terminal cytoplasmic tail of SLC7A11, inhibiting its transport activity through phosphorylation at serine (7, 9).

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Additionally, the epidermal growth factor receptor (EGFR) has been shown to interact with SLC7A11, aiding in its membrane localization; this interaction correlates with increased cystine uptake and enhanced glutamate export, which are associated with tumor growth and invasiveness in EGFR-expressing glioma cells. Cancer cells exhibit a distinct reliance on specific nutrients for their survival and proliferation compared to normal cells (32). In nutrient-deficient environments, cancer cells may undergo cell death, while healthy cells often endure due to their greater metabolic flexibility. Gaining insights into the mechanisms that limit the metabolic adaptability or nutrient dependency of cancer cells could lead to targeted approaches that effectively eliminate cancer cells while preserving healthy ones. Glucose and glutamine serve as primary nutrients that fuel the biosynthetic machinery and various metabolic functions in most cells. For instance, in conditions where glucose is scarce, cells frequently increase their reliance on glutamine metabolism to sustain survival (33, 34).

The uptake of cystine mediated by SLC7A11 is essential for maintaining redox homeostasis and incorporating biomass in cells. Cancer cells elevate SLC7A11 expression to boost cystine import and sustain ROS balance. Unlike glucose and glutamine, which utilize specific transporters for uptake, cystine must be reduced to cysteine after import. The exchange of cystine and glutamate across the cell membrane occurs in a 1:1 ratio, resulting in significant glutamate export when SLC7A11 is upregulated. Glutamine, the most prevalent amino acid in plasma, is converted into glutamate through the action of glutaminase and acts as a precursor for GSH synthesis, as well as participating in the tricarboxylic acid cycle by converting to α-ketoglutarate (7, 34).

Notably, elevated cystine levels in the culture medium have been shown to stimulate cystine uptake in cancer cells, leading to increased glutamate export and heightened dependency on glutamine. Research indicates that basal and claudin-low TNBC cell lines exhibit a greater reliance on glutamine, characterized by high SLC7A11 expression and enhanced cystine import compared to other breast cancer subtypes (35, 36). Treatment with SAS, a SLC7A11 inhibitor, reduces the growth of xenograft tumors derived from these cell lines, indicating that SLC7A11-high cancers, such as TNBCs, are more reliant on glutamine. This dependency likely arises from the need for increased glutamate to facilitate cystine exchange due to elevated SLC7A11 levels. Similarly, various pancreatic cancer cell lines, including PANC-1, BxPC-3, and HPAC, demonstrate glutamine dependence, with findings from Badgley et al. revealing that these glutamine-dependent pancreatic cancer cells are more susceptible to both pharmacological and genetic inhibition of SLC7A11 (26).

Ferroptosis

Ferroptosis is a form of cell death that relies on iron and is characterized by the accumulation of iron and lipid peroxidation. The reduction in antioxidant capacity associated with ferroptosis, along with the buildup of lipid ROS in cells, results in oxidative cell death. This process is distinct from other types of cell death, as cells undergoing ferroptosis exhibit shrunken, dense mitochondria without the typical signs of plasma membrane blebbing, DNA fragmentation, or Caspase-3 activation. In recent years, ferroptosis has been linked to various diseases, including cancer, neurological disorders, and ischemia (37, 38).

The overexpression of SLC7A11 provides cancer cells with resistance to ferroptosis by facilitating the import of cystine, which is essential for GSH synthesis, and by alleviating lipid ROS stress through the

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activation of GSH peroxidase 4 (GPX4). GPX4 plays a crucial role in reducing hydrogen and lipid peroxides, thereby safeguarding cells against oxidative damage. When GPX4 is inactivated, lipid peroxides accumulate, leading to ferroptosis (7). Consequently, SLC7A11 helps prevent ferroptosis by importing cystine and enhancing GSH production. In cases of acute liver failure, SLC7A11 overexpression serves a protective function by regulating lipopolysaccharide-D-galactosamine-induced hepatocyte injury primarily through the inhibition of ferroptosis (39, 40).

GPX4 is an antioxidant enzyme that safeguards cells and membranes from peroxidation by utilizing GSH as a cofactor, thereby preventing lipid peroxidation. GSH can transition between its reduced (GSH) and oxidized (GSSG) forms, allowing it to engage in redox biochemical processes. ChaC GSH-specific γ-glutamylcyclotransferase 1 (CHAC1) can lower intracellular GSH levels, triggering ferroptosis in prostate cancer cells and enhancing their sensitivity to docetaxel. The inhibition of GPX4 results in the accumulation of ROS and lipid peroxidation, ultimately leading to ferroptosis. Additionally, GPX4 is capable of converting harmful lipid peroxides (such as R–OOH) into less toxic lipid alcohols (like R–OH). RSL3 can irreversibly inactivate GPX4 by binding to the selenocysteine residue in its active site. GPX4 serves as a fundamental inhibitor of ferroptosis. Iron serves as a crucial cofactor in various biological processes. Excessive iron accumulation can result in harmful ROS production and lipid peroxidation (41). The TFR1 is a transmembrane glycoprotein that facilitates the import of iron, which is primarily stored and transported as an iron-protein complex, predominantly ferritin. The enzyme STEAP3 reduces ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}). Subsequently, Fe^{2+} is released from the endosome into the cytoplasm's unstable iron pool via the divalent metal transporter 1 (DMT1). As a significant contributor to ROS formation through both enzymatic and non-enzymatic pathways, iron is vital in making cells more susceptible to ferroptosis. Research by Bordini et al. indicated that high iron concentrations can impede the proliferation of prostate cancer cells by inducing oxidative damage. In cells resistant to bicalutamide, iron exhibited a synergistic effect with the drug. Recent studies have investigated the mechanisms underlying ferroptosis triggered by various inducers, with potential signaling pathways and targets illustrated in Figure 3 (42).

One of the defining characteristics of cancer is the ability to evade cell death. Research by Li et al. in 2012 revealed that a particular mutation in p53, known as the 3KR mutant, which cannot be acetylated at specific lysine residues, leads cancer cells to forfeit their capacity to trigger cell cycle arrest or apoptosis. Nevertheless, this mutation can still inhibit tumor formation *in vivo*. Subsequently, researchers found that this mutation helps maintain the tumor-suppressive functions of p53, in part by downregulating SLC7A11 expression and promoting ferroptosis. Additional mutations in p53 have also been associated with its regulation of SLC7A11 and ferroptosis in cancer (43).

Another tumor suppressor, BAP1, which is often lost or mutated in various cancers, has been shown to inhibit SLC7A11 expression, thereby reducing cystine uptake and facilitating ferroptosis in cancer cells. Moreover, the overexpression of SLC7A11 or the use of ferroptosis inhibitors can partially counteract the tumor growth suppression observed with BAP1 restoration. Beyond ferroptosis, the inhibition of SLC7A11 has been associated with apoptosis in murine melanocytes and cancer cells, depending on the context. In contrast to erastin, the SLC7A11 inhibitor HG106 primarily induces apoptosis, likely through the depletion of GSH (44). The precise mechanisms that differentiate GSH depletion-induced ferroptosis from apoptosis

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are still not fully understood, and there may be variations based on cell type and context, as well as potential off-target effects of the two compounds. Therefore, examining the same cell line after treatment with either erastin or HG106 could shed light on the mechanisms that govern these cell death pathways. Investigating cells deficient in apoptosis or ferroptosis following SLC7A11 inhibition may help clarify some of these unresolved issues (26, 44-46).

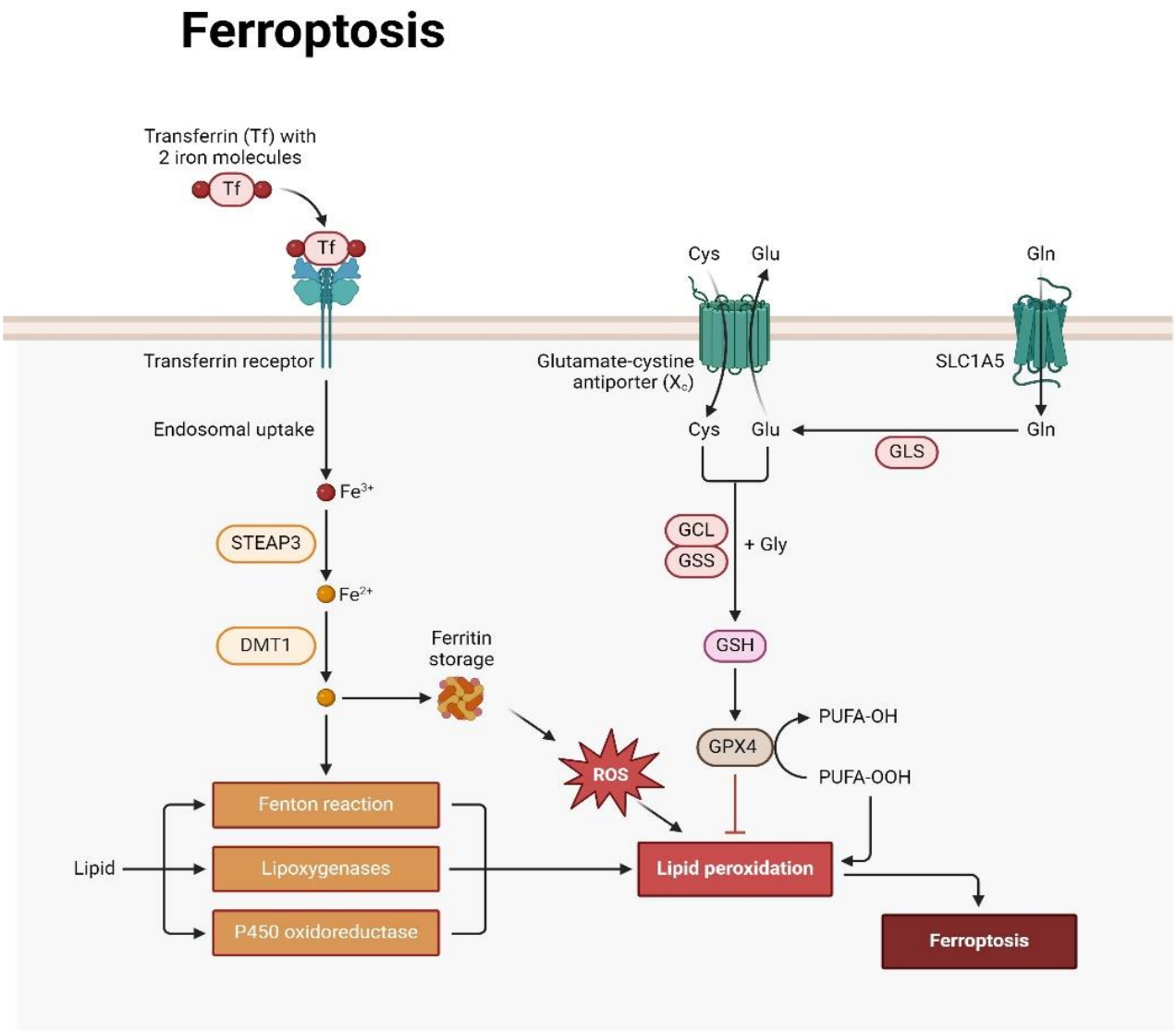


Fig. 3. Ferroptosis pathway; STEAP: Six-Transmembrane Epithelial Antigen of Prostate 3; DMT1: Divalent metal transporter 1; GLS: glutaminase; GCL: glutamate-cysteine ligase; GSH: glutathione; GPX4: Glutathione peroxidase 4; ROS: robot operating system.

Cancer Immunity and SLC7A11: Their Interrelationship

Numerous cancer immunotherapies have shown the capability to suppress the activity of SLC7A11, which subsequently initiates ferroptosis in cancer cells. For example, therapies that inhibit programmed death

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ligand-1 (PD-L1) and activate CD8+ T cells increase ROS levels by inducing the release of interferon-gamma (IFNγ). This release promotes the attachment of the transcription factor STAT1 to the transcriptional initiation site of SLC7A11, resulting in a reduction of its expression (47). Moreover, the upregulation of interferon regulatory factor 1 by IFNγ reduces SLC7A11 transcription via the Janus kinase pathway. Additionally, radiotherapy applied after immunotherapy works cooperatively with IFNγ to amplify ferroptosis by inhibiting SLC7A11. The downregulation of SLC7A11 is also linked to enhanced immune responses associated with T-cell memory. As a result, targeting SLC7A11 in combination with immunotherapy could represent a promising treatment strategy for certain types of cancer (9).

Resistance to Cancer Therapy

The overexpression of SLC7A11 is linked to resistance against immunotherapy, chemotherapy, and radiotherapy, including resistance to agents like gemcitabine and cisplatin. It is thought that increased synthesis of GSH and the inhibition of ferroptosis contribute to the drug and radio-resistance associated with SLC7A11. For instance, SLC7A11 confers resistance to BRAF and MEK inhibitors in BRAFV600E mutant melanoma, as well as to geldanamycin in lung cancer, cisplatin in gastric cancer, temozolomide in glioma, and gemcitabine in pancreatic cancer. Numerous studies indicate that this therapeutic resistance can be mitigated by directly targeting SLC7A11. For example, in head and neck cancer, treatments with erastin or SAS have been shown to re-sensitize cancer cells to cisplatin (26).

While elevated levels of SLC7A11 may negatively impact cancer patient outcomes, it also plays a beneficial role in tissue repair. For instance, reduced SLC7A11 expression in cardiomyocytes leads to lower GSH levels and increased ferroptosis and is linked to cardiomyopathy and heart failure in mouse models. Additionally, overexpression of STAT3 enhances SLC7A11 levels, providing a protective effect in a mouse model of acute lung injury induced by intestinal ischemia/reperfusion by reducing ferroptosis. The stabilization of SLC7A11 by CD44v9 facilitates increased cystine uptake in chief cells following the loss of parietal cells during gastric injury. Furthermore, SLC7A11 is significantly upregulated during liver regeneration, and its overexpression in hepatocytes promotes repopulation and recovery after toxic liver damage (48).

Current strategies for targeting SLC7A11 involve either the direct inhibition of its transporter activity or the indirect targeting of metabolic vulnerabilities and pathways linked to SLC7A11 in cancer. Direct approaches include the use of inhibitors such as SAS, erastin, imidazole ketone erastin (IKE), sorafenib, and HG106. These agents promote ferroptosis by obstructing cystine uptake through SLC7A11 and are classified as class I ferroptosis inducers. Each inhibitor presents distinct advantages and disadvantages. For instance, SAS has shown limited efficacy in Phase I/II clinical trials due to its unfavorable pharmacological characteristics (49). When developed as a zinc oxide-SAS nanoparticle, it exhibits increased retention in tumors and greater cytotoxic effects while preserving the integrity of healthy cells. Erastin, recognized for its potential as a system inhibitor and ferroptosis inducer, has been effective across various cancer types, including breast cancer. Nonetheless, its poor solubility and metabolic instability in vivo hinder its clinical application. In contrast, IKE is metabolically stable and has shown efficacy in genetically engineered mouse models of pancreatic ductal adenocarcinoma, although it has yet to be evaluated in clinical settings. Both sorafenib and SAS are FDA-approved and have been demonstrated to induce ferroptosis and suppress tumor

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growth. However, sorafenib also functions as a multi-kinase inhibitor, while SAS inhibits prostaglandin synthesis, leading to potential adverse clinical effects. Consequently, exploring metabolic vulnerabilities associated with SLC7A11 may represent a more effective therapeutic approach to cancer treatment (50).

Breast Cancer

Several glutamate analogs, including L-Homocysteate, L-Quisqualate, 4-bromo-homoibotenate, and S-4-Carboxy-phenylglycine (CPG), have been demonstrated to influence the exchange of L-cystine and glutamate across the cell membrane via the SLC7A11 system (18). The activity of SLC7A11 can also be modulated indirectly by targeting its upstream regulators. For instance, the MEK inhibitor AZD6244 and BAY-11-7085 inhibit NRF2, while JQ-1 targets BD4 and focuses on the receptor tyrosine kinase TrkA (26), all of which lead to a reduction in SLC7A11 expression (51). Additionally, Paclitaxel promotes ferroptosis by suppressing SLC7A11 transcription. Various immunotherapeutic strategies aimed at decreasing SLC7A11 expression in vivo show potential (52). For example, anti-SLC7A11 DNA vaccines that use plasmids to express the full-length SLC7A11 have been effective in inducing regression of lung metastases in mice with 4T1 tumors (53). Furthermore, virus-like particles (AX09-0M6) that present the sixth extracellular loop of SLC7A11, which is conserved between mice and humans, have been shown to impair the self-renewal capacity of breast cancer stem cells (54). Lastly, a bovine herpesvirus 4-based vector that delivers full-length SLC7A11 DNA has been found to protect mice from breast cancer metastases by targeting cancer stem cells (55).

Therapeutic approaches by SLC7A11 inhibitors

The multifaceted roles and functionalities of SLC7A11 can be systematically classified into two distinct categories, namely the direct effects and the indirect effects, each of which plays a critical role in the overall physiological and biochemical processes. In particular, both cystine and glutamate emerge as highly significant endogenous compounds that possess the capacity to exert notable pharmacological effects directly, thereby influencing various biological systems and mechanisms. The indirect effects, on the other hand, are derived from biotransformation products that utilize glutamate or cystine as essential substrates; these two substrates are integral to a myriad of metabolic pathways, which subsequently lead to the generation of bioactive metabolites that exhibit a wide array of biological and pharmacological functions. Consequently, the interplay between these substrates and their resultant metabolites underscores the complexity of SLC7A11's role in cellular metabolism and its potential implications in therapeutic contexts (35, 36).

The role of SLC7A11 in therapeutic resistance is linked to various factors, including the antioxidant stress response, ferroptosis, nutrient scarcity, autophagy, and multidrug resistance. A microarray analysis examining the gene expression of transporter proteins across 60 human cancer cell lines revealed a correlation between SLC7A11 expression and the effectiveness of 1400 potential anticancer agents. Additionally, SLC7A11 enhances the cellular uptake of L-alanosine, an amino acid analog known for its anticancer properties (56). This transporter also plays a crucial role in maintaining GSH levels by providing cystine, while exhibiting a negative correlation with the effectiveness of certain anticancer drugs, such as geldanamycin. Thus, SLC7A11 exerts a multifaceted impact on the efficacy of antitumor medications, which varies depending on the specific context (57).

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Since its initial identification by Bannai and Kitamura in 1980, SLC7A11 has been the subject of numerous studies highlighting its widespread expression across different types of cancers and its significant influence on cancer growth, invasion, metastasis, and poor prognosis (58). Generally, SLC7A11 provides cancer cells with resistance to ferroptosis, a form of regulated cell death. For example, in lung cancer cells, SLC7A11 is upregulated to mitigate ferroptosis and protect against radiation damage. Consequently, the overexpression of SLC7A11 enhances radioresistance in lung cancer cells that naturally express lower levels of this protein. In lung cancer cells with KEAP1 mutations, where Nrf2 is continuously activated, a high level of SLC7A11 expression markedly reduces ferroptosis induced by radiation, and the application of SLC7A11 inhibitors has been shown to make these cancer cells more susceptible to radiotherapy in both laboratory and animal studies (18). Overall, the overexpression of SLC7A11 provides cancer cells with a survival edge, while its inhibition can impede tumor growth and present new avenues for cancer treatment. To date, a variety of anticancer strategies have been investigated to alleviate tumor burden, including surgical intervention, chemotherapy, immunotherapy, radiotherapy, and other methods targeting angiogenesis, cell death mechanisms, altered cancer metabolism, and nutrient availability. 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 of the dilemma (56).

SAS is a medication approved by the FDA that is commonly used in the treatment of rheumatoid arthritis (59). It is known to specifically inhibit cystine transport mediated by SLC7A11 and has been shown to hinder the growth, invasion, and metastasis of a variety of cancer types. Our studies demonstrate that SAS significantly boosts levels of ferroptosis and enhances the anti-cancer effects of metformin in both laboratory and live models; however, the likelihood of metformin in combination with SAS triggering other types of cell death is still unclear and requires more research. Notably, we found that the pairing of SAS and metformin effectively suppressed the proliferation of MDAMB231 cancer cells, which generally show resistance to metformin. In support of our results, a recent investigation underscored the effectiveness of metformin used alongside hemin for treating breast cancer (60).

Hence, investigating new drug combinations involving metformin could offer a promising strategy to enhance its anti-cancer efficacy. It is critical to pinpoint appropriate molecular targets and determine which patients are most likely to reap the benefits of metformin therapy (61). Previous investigations revealed a notable negative correlation between SLC7A11 expression and the prognosis of breast cancer patients. Therefore, we propose that breast cancer patients with heightened SLC7A11 levels may be prime candidates for targeted therapies, and exploring the mechanisms by which SLC7A11 safeguards certain breast cancer cells could pave the way for new research opportunities. The anti-cancer mechanisms of metformin are closely associated with pathways related to apoptosis, autophagy, and other regulated forms of cell death. A recent study by X Tang et al. demonstrated that the deprivation of cystine led to necrosis in TNBC cells (62). Additionally, research conducted previously revealed that doxorubicin enhanced the expression of SLC7A11 in TNBC and that inhibiting the SLC7A11 antiporter system made TNBC cells more sensitive to ADR (63). The results indicate that SLC7A11 may represent a valuable target for enhancing the efficacy of conventional treatments in patients with TNBC. In contrast, some investigation revealed that ADR reduced cystine influx

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and downregulated the activity of the SLC7A11 transporter in MCF-7 cells, while also significantly increasing the expression and function of P-glycoprotein (62).

Adriamycin (ADR) has been demonstrated to enhance the over-expression of P-glycoprotein (P-gp) and play a role in the development of multidrug resistance in breast cancer cells, although the precise biochemical pathways and mechanisms involved are still not well comprehended. Earlier studies suggested that ADR causes an increase in ROS and a decrease in the synthesis of GSH, with N-acetylcysteine, known for scavenging ROS, effectively reversing the over-expression of P-gp (63). The present study revealed that ADR hinders the uptake of cystine, crucial for GSH synthesis, by blocking the SLC7A11 transporter in MCF-7 cells. The reduction of SLC7A11 significantly increased the over-expression of P-glycoprotein (P-gp) induced by ROS and enhanced drug resistance (64). Furthermore, the simultaneous inhibition of SLC7A11 or deprivation of cystine, in conjunction with elevated ROS levels, led to a substantial rise in P-gp expression. This effect could be alleviated by the administration of N-acetylcysteine. In contrast, over-expressing SLC7A11, supplying adequate cystine, or administering N-acetylcysteine resulted in a significant decrease in P-gp expression and activity. These results indicate that ROS and the SLC7A11/cystine pathway are vital components affecting P-gp expression and function, suggesting that SLC7A11 might be a promising target for addressing resistance to ADR (63).

In a thorough high-throughput screening designed to pinpoint synthetic lethal agents that target engineered tumorigenic cells, erastin was first identified for its capacity to selectively cause cell death in BJ fibroblast cells expressing small T (ST) oncoproteins and mutated RAS, utilizing a mechanism of non-apoptotic cell death. Further research showed that erastin operates by inhibiting system Xc- and initiating ferroptosis; its use in tumor cells results in diminished cystine uptake while promoting sustained iron-dependent ROS) production, culminating in cell death with morphological traits characteristic of ferroptosis (65). Numerous investigations have confirmed that erastin effectively interferes with SLC7A11 activity, inducing ferroptotic cell death across various cancer types, including human breast cancer. Moreover, two erastin analogs, specifically IKE and piperazine erastin (PE), which demonstrate improved water solubility, potency, and metabolic stability, have also been proven to effectively elicit ferroptosis in mouse models of fibrosarcoma and diffuse large B cell lymphoma (DLBCL) (66).

Sorafenib, a multi-kinase inhibitor approved by the FDA, induces ferroptosis in a range of human cancer cell lines, including those associated with kidney cancer. This process occurs independently of its activity in inhibiting kinases and is not influenced by the oncogenic status of RAF, PIK3CA, RAS, or TP53 in the cancer cells. Notably, the ferroptosis triggered by sorafenib is specifically dependent on the inhibition of system Xc- and is associated with distinct clinical adverse effects that differentiate it from other kinase inhibitors. As of now, the potential of sorafenib in clinical settings to target system Xc- remains unexplored (67).

In a thorough screening designed to uncover compounds that obstruct glutamate release in TNBC cells, capsazepine (CPZ) was found to hinder the function of SLC7A11. The results demonstrated that CPZ treatment notably decreases cystine uptake, increases intracellular ROS levels, and induces cell death, even with an upregulation of SLC7A11 mRNA levels (68). In a different study that aimed to inhibit GSH production in KRAS mutant lung adenocarcinoma cells, HG106 was recognized as a specific inhibitor of SLC7A11 activity in vitro, resulting in a decreased tumor burden in vivo. While HG106 effectively prevents

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cystine uptake and GSH production, it also elevates intracellular ROS levels and encourages apoptosis in tumor cells, which is linked to mitochondrial dysfunction and endoplasmic reticulum (ER) stress (45, 68).

The pVAX1-SLC7A11 plasmid, containing the full mouse SLC7A11 sequence (NM_011990.2) and driven by the CMV promoter, is being used for the first time in an in vivo setting to evaluate its efficacy in a TNBC mouse model. Administration of pVAX1-SLC7A11 induces a humoral immune response in BALB/c mice, with the resultant IgG capable of inhibiting the development of TUBO tumor spheres and decreasing the population of cells that exhibit cancer stem cell (CSC) markers (69). Moreover, in mice with tumors, this vaccination results in tumor shrinkage and a reduction in lung metastases due to antibodies that specifically target SLC7A11 on CSCs. Furthermore, the anti-SLC7A11 vaccination demonstrates a protective effect against spontaneous lung metastases induced by 4T1 cells. Despite the elicitation of a humoral response, a T-cell response is absent, likely due to the depletion of high-avidity T-cell clones within the thymus (53).

A groundbreaking immunotherapy employing virus-like particles, named AX09-0M6, is administered to female BALB/c mice, incorporating the fully homologous sixth extracellular loop (ECD6) of SLC7A11 derived from both murine and human origins (54). Post-treatment with AX09-0M6, a notable rise in antibody titers is detected in the serum of the mice, which effectively hinders the self-renewal ability of breast cancer stem cells and boosts ROS levels across various cancer cell lines, including TUBO, 4T1, HCC-1806, and MDA-MB-231. Remarkably, AX09-0M6 triggers a strong IgG2a antibody response, which amplifies antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity against SLC7A11-positive tumor cells in both localized and metastatic settings (54, 55).

The administration of lidocaine resulted in the accumulation of Fe^{2+}, iron, and lipid ROS within ovarian and breast cancer cells. In vitro investigations demonstrated that lidocaine effectively inhibited the proliferation of ovarian and breast cancer cells while concurrently inducing apoptosis. Additionally, lidocaine diminished the invasion and migration capabilities of these cancer cells (70). In terms of the underlying mechanism, our findings indicated that lidocaine downregulated the expression of SLC7A11 by upregulating microRNA-382-5p within the cells. The suppression of miR-382-5p effectively impeded the ferroptosis induced by lidocaine in ovarian and breast cancer cells. The miR-382-5p/SLC7A11 signaling axis played a significant role in the lidocaine-mediated suppression of ovarian and breast cancer cell proliferation in vitro. Notably, clinical samples of ovarian and breast cancer exhibited downregulation of miR-382-5p alongside upregulation of SLC7A11 expression. Therefore, lidocaine facilitates ferroptosis through the miR-382-5p/SLC7A11 axis in ovarian and breast cancer cells. The potential clinical implications of lidocaine in the management of ovarian and breast cancer warrant comprehensive investigation (71).

Sculponeatin A (stA), a novel diterpenoid derived from Isodon sculponeatus, has not yet been associated with any known antitumor mechanisms. However, based on studies, stA demonstrates significant therapeutic potential in breast cancer by triggering SLC7A11/xCT-dependent ferroptosis. It reduces the expression of ETS1, a key factor in xCT-dependent ferroptosis in breast cancer). Furthermore, stA facilitates the proteasomal degradation of ETS1 by activating ubiquitin ligase synoviolin 1 (SYVN1) to mediate ubiquitination. The K318 site on ETS1 is crucial for its ubiquitination by SYVN1. Overall, these findings indicate that stA enhances the interaction between ETS1 and SYVN1, leading to ferroptosis in breast cancer

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through the degradation of ETS1. This positions stA as a promising candidate for further research in drug development targeting breast cancer and for designing therapies based on the degradation of ETS1 (72).

Breast cancer encompasses various tumor subtypes that exhibit significant heterogeneity, making them particularly difficult to treat due to their resistance to conventional therapies and a high likelihood of recurrence. Over the last five years, there has been an increase in research examining the role of ferroptosis in breast cancer. These studies have enhanced our comprehension of ferroptosis, which is characterized by a complex system that governs iron metabolism, lipid peroxidation, and antioxidant defense, utilizing specialized mechanisms found in the plasma membrane, mitochondria, and cytosol. The insights gained have been leveraged to advance prevention and treatment strategies for this malignancy. For example, emerging preclinical data suggest that inducing ferroptosis could serve as a promising therapeutic approach to mitigate acquired resistance to various cancer treatments and enhance the efficacy of immunotherapy. Notably, clinical trials are currently underway to evaluate ferroptosis-inducing agents in breast cancer patients. Consequently, ongoing research in this area is expected to further clarify the physiological and pathological implications of ferroptosis, paving the way for the development of innovative anticancer strategies. Investigating biomarkers for accurately monitoring ferroptosis in cancer patients, along with the creation and implementation of new ferroptosis-based therapies, will be crucial in the coming years.

Future Directions in SLC7A11 and Ferroptosis Research

The paper discusses several future directions for research related to SLC7A11 and its role in ferroptosis, particularly in the context of breast cancer. Here are the key suggestions:

1. Biomarker Development: There is a need to investigate biomarkers that can accurately monitor ferroptosis in cancer patients. This will help in understanding the effectiveness of therapies targeting ferroptosis and SLC7A11.

2. Ferroptosis-Based Therapies: The creation and implementation of new therapies that induce ferroptosis are crucial. This includes exploring various pharmacological compounds that can modulate SLC7A11 activity effectively.

3. Customized Therapeutic Approaches: The paper emphasizes the importance of developing more tailored therapeutic strategies when targeting SLC7A11 in breast cancer. This is essential due to the complex nature of cancer and the varying responses to treatment.

4. Understanding Mechanisms: Additional investigation is required to clarify the mechanisms by which SLC7A11 affects ferroptosis, cell growth, and resistance to therapy. This understanding could lead to more effective treatment strategies.

5. Clinical Trials: The ongoing clinical trials evaluating ferroptosis-inducing agents in breast cancer patients are highlighted as a significant step forward. Continued research in this area is expected to clarify the physiological and pathological implications of ferroptosis, paving the way for innovative anticancer strategies.

6. Exploration of Tumor Heterogeneity: Given the heterogeneity of breast cancer subtypes, future studies should focus on how different tumor types respond to SLC7A11 inhibition and ferroptosis induction. This could help in understanding resistance mechanisms and improving treatment outcomes.

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These future directions aim to enhance the understanding and therapeutic potential of SLC7A11 inhibitors in breast cancer, ultimately contributing to better patient outcomes and more effective cancer treatments.

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