

Biological Functions and Therapeutic Potential of SLC7A11 Across Diseases

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Abstract: SLC7A11, a key component of the cystine/glutamate antiporter System Xc⁻, regulates redox balance and ferroptosis. Its dysregulation is linked to cancer, metabolic, neurodegenerative, immune, and kidney diseases. In tumors, SLC7A11 promotes growth and therapy resistance, while in non-cancerous tissues, it offers antioxidant protection. This review outlines the biological functions of SLC7A11, its dual disease roles, and therapeutic strategies including small molecule inhibitors, exosome delivery, and metabolic interventions. Though promising, clinical translation faces challenges in tissue specificity and metabolic compensation. Advances in precision targeting may help realize its full therapeutic potential.

Keywords: SLC7A11; System Xc⁻; Ferroptosis; Redox Homeostasis; Cancer Metabolism; Oxidative Stress; Disulfidptosis; Therapeutic Resistance; Exosome Delivery; Metabolic Reprogramming.

1. Introduction

In recent years, with the deepening research on metabolic reprogramming and cell death mechanisms, the solute carrier family member SLC7A11 (also known as xCT) has gradually become a research focus across various disease fields. As the core functional subunit of the cystine/glutamate antiporter system (System Xc⁻), SLC7A11 plays a central role in maintaining intracellular redox homeostasis, regulating ferroptosis, and metabolic adaptation by mediating cystine uptake and glutamate export. Dysregulation of SLC7A11 is not only closely associated with tumor initiation, metastasis, and drug resistance but also implicated in the pathological processes of various non-cancer diseases, such as intracerebral hemorrhage, neurodegenerative diseases, liver injury, and metabolic syndrome [1,8,12,13]. This review aims to systematically summarize the biological functions of SLC7A11, its therapeutic potential in cancer and other diseases, and discuss the progress and challenges of targeted intervention strategies.

2. Biological Functions and Mechanistic Diversity of SLC7A11

SLC7A11, together with the heavy chain subunit SLC3A2 (4F2hc), forms the System Xc⁻ antiporter complex at a 1:1 ratio, mediating the intracellular uptake of cystine and the export of glutamate. Once inside the cell, cystine is reduced to cysteine, which participates in the synthesis of glutathione (GSH), a key antioxidant that neutralizes reactive oxygen species (ROS) and is essential for maintaining cellular redox balance. Moreover, the function of SLC7A11 extends to the regulation of ferroptosis: decreased activity of SLC7A11 leads to GSH depletion, thereby impairing the ability of glutathione peroxidase 4 (GPX4) to clear lipid peroxides, ultimately triggering iron-dependent cell death. This mechanism has attracted considerable attention in cancer therapy, while also suggesting a potential protective role in other oxidative stress-related diseases [4, 6, 8].

Notably, the expression of SLC7A11 is regulated by multiple signaling pathways. For instance, hypoxia-inducible

factor HIF-1 α upregulates SLC7A11 in laryngeal cancer, enhancing cancer cell resistance to oxidative stress, while mutant p53 (e.g., R175H) interacts with the transcription factor BACH1 to relieve its repression of SLC7A11, thereby promoting tumor metastasis and inhibiting ferroptosis. In addition, epigenetic modifications such as O-GlcNAcylation mediated by OGT and ubiquitination regulation via the USP8-OGT pathway have been shown to affect the stability and function of SLC7A11. This multilayered regulatory network endows SLC7A11 with complex roles in disease [4, 5, 7].

3. Dual Roles and Therapeutic Potential of SLC7A11 in Cancer

In the tumor microenvironment, high expression of SLC7A11 is often associated with poor prognosis. It promotes tumor progression through the following mechanisms:

1. Inhibition of ferroptosis: SLC7A11-mediated cystine uptake maintains GSH levels, protecting cancer cells from lipid peroxide-driven ferroptosis. For example, in hepatocellular carcinoma, USP8 promotes SLC7A11 glycosylation by stabilizing OGT protein, thereby inhibiting ferroptosis and facilitating tumor growth [5, 7].

2. Metabolic reprogramming: Tumor cells depend on SLC7A11 to adapt to nutrient-deprived microenvironments. Under glucose starvation, elevated SLC7A11 expression leads to NADPH depletion, triggering a novel cell death mode called disulfidptosis. This new form of cell death provides a therapeutic window for metabolically abnormal tumors [6, 17].

3. Immune evasion: SLC7A11 modulates glutamate release, affecting the tumor microenvironment. For instance, in a colorectal cancer liver metastasis model, activation of ferroptosis enhances T cell antitumor activity. Combining PD-1 inhibitors with ferroptosis inducers significantly suppresses tumor progression [8, 17].

3.1. The Role of SLC7A11 in Gastric Cancer

3.1.1. Promotion of Tumor Growth and Drug Resistance

SLC7A11 mediates cystine uptake through the System Xc⁻, promoting glutathione (GSH) synthesis and thereby

enhancing gastric cancer cells' resistance to oxidative stress. Yan et al. found that in cancer cells with high SLC7A11 expression, combined with H₂O₂ treatment, the increased cystine uptake leads to toxic accumulation of intracellular cystine and other disulfide-bonded molecules, NADPH depletion, collapse of redox homeostasis, and rapid cell death, possibly through disulfidptosis. Further studies indicate that while high SLC7A11 expression promotes tumor growth, it inhibits tumor metastasis, possibly because metastatic cancer cells with high SLC7A11 expression are particularly susceptible to oxidative stress [1]. Other research also shows that SLC7A11 is overexpressed in gastric cancer tissues and correlates with poor patient prognosis. This mechanism may relate to maintaining redox balance in tumor cells and inhibiting chemotherapy-induced apoptosis. The team led by Liu Xianghua and Sun Ming at Nanjing Medical University revealed that the HCP5-132aa microprotein acts as a scaffold promoting the interaction between YBX1 and ELAVL1. YBX1, as an m5C reader protein, maintains the stability of target gene mRNAs. MeRIP and RNA pull-down experiments demonstrated that YBX1 recognizes m5C modifications on ferroptosis-related gene mRNAs such as SLC7A11 and G6PD. Knockout of HCP5-132aa inhibits YBX1's recognition of m5C, reducing the stability of SLC7A11/G6PD mRNAs. KEGG enrichment analysis of RNA-seq data from HCP5 knockout cells showed involvement in ferroptosis regulation, suggesting that HCP5-132aa may inhibit ferroptosis in gastric cancer cells by modulating SLC7A11 and G6PD [2]. Furthermore, while high SLC7A11 expression promotes tumor growth, it may inhibit metastasis by increasing sensitivity to oxidative stress [1].

3.1.2. Regulation of Ferroptosis and Disulfidptosis

Ferroptosis is an iron-dependent form of cell death driven by lipid peroxidation. In gastric cancer, SLC7A11 inhibits ferroptosis and promotes tumor progression by stabilizing its own mRNA expression, regulated by factors such as the microprotein HCP5-132aa encoded by lncRNA-HCP5, which also prevents degradation of ferroptosis-related genes like G6PD. On the other hand, under glucose deprivation, high expression of SLC7A11 accelerates NADPH depletion, leading to abnormal disulfide accumulation and triggering disulfidptosis. This metabolism-dependent cell death pathway offers a therapeutic window for targeting gastric cancers with elevated SLC7A11 expression.

3.2. The Role of SLC7A11 in Hepatocellular Carcinoma

3.2.1. Resistance to Ferroptosis

SLC7A11 inhibits lipid peroxidation by maintaining GSH levels, thereby protecting hepatocellular carcinoma (HCC) cells from ferroptosis. In radiation-resistant HCC cells, decreased expression of suppressor of cytokine signaling 2 (SOCS2) leads to accumulation of SLC7A11 protein, inhibiting ferroptosis and enhancing radiotherapy resistance. Professor Shao Chunlin's team revealed SOCS2 as a potential radiosensitizing target in HCC; SOCS2 overexpression promotes K48-linked ubiquitination and degradation of the ferroptosis-related protein SLC7A11, thus regulating ferroptosis [3].

The ATF4-SLC7A11 signaling axis suppresses ferroptosis, reducing compensatory proliferation and carcinogenesis risk after chronic liver injury. Researchers at the University of California San Diego (UCSD) found that activating transcription factor 4 (ATF4) protects the liver from

hepatocyte death and subsequent tumor formation by promoting SLC7A11 expression. By decreasing ferroptosis, the ATF4-SLC7A11 pathway protects hepatocytes and slows progression from liver injury to HCC. Ferroptosis inhibitors or ATF4 activators may have clinical utility in preventing nonalcoholic steatohepatitis and its progression to cancer [4].

3.2.2. Metabolic Reprogramming

HCC cells rely on SLC7A11-mediated cystine metabolism to adapt to highly oxidative microenvironments. High SLC7A11 expression causes NADPH depletion, triggering disulfidptosis under glucose starvation, offering new therapeutic strategies for metabolically aberrant HCC. Additionally, glutamate efflux activates glutamate receptors in the tumor microenvironment, promoting infiltration of immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs), which dampens antitumor immune responses.[5]

3.2.3. Chemotherapy and Radiotherapy Resistance

Overexpression of SLC7A11 reduces ROS accumulation, decreasing sensitivity of HCC cells to radiotherapy (e.g., photon irradiation) and chemotherapy agents such as cisplatin. Clinical studies have shown that high SLC7A11 expression significantly correlates with increased postoperative recurrence risk and reduced survival in HCC patient.

3.3. The Role of SLC7A11 in Glioma

3.3.1. Resistance to Radiotherapy and Chemotherapy

Under low-glucose microenvironment conditions, overexpression of SLC7A11 suppresses the mismatch repair (MMR) pathway, resulting in defective DNA damage repair but may paradoxically increase radiosensitivity. Preclinical studies have reported that SLC7A11 is expressed at higher levels in glioblastoma multiforme (GBM) compared to normal brain tissue but shows a negative correlation with tumor grade and a positive impact on survival according to bioinformatic analyses of the TCGA and CGGA databases. Pearson correlation analysis identified a negative correlation between SLC7A11 and MMR gene expression. In GBM cells cultured under glucose-restricted conditions, SLC7A11 overexpression significantly reduced expression of MMR genes, including MLH1, MSH6, and EXO1. GBM cells overexpressing SLC7A11 exhibited increased levels of double-strand breaks (DSBs) and heightened sensitivity to radiation therapy [6].

SLC7A11 reduces intracellular reactive oxygen species (ROS) accumulation by maintaining GSH levels, thereby lowering the cytotoxicity of temozolomide (TMZ). Knockout of SLC7A11 can reverse TMZ resistance and enhance TMZ-induced apoptosis.

3.3.2. Ferroptosis Resistance and Metabolic Reprogramming

SLC7A11-mediated cystine uptake supports GPX4 activity and inhibits lipid peroxidation. In GBM, high SLC7A11 expression is strongly associated with resistance to ferroptosis, while inhibition of System Xc⁻ by erastin induces ferroptosis and suppresses tumor growth. Elevated SLC7A11 causes NADPH depletion, triggering disulfidptosis under glucose starvation, which depends on abnormal crosslinking of the actin cytoskeleton. This presents a novel therapeutic opportunity for targeting metabolically aberrant gliomas [4].

3.4. SLC7A11 and Breast Cancer

SLC7A11 exhibits significant subtype-specific expression

patterns in breast cancer. Its expression levels are markedly higher in triple-negative breast cancer (TNBC) and estrogen receptor-positive (ER+) breast cancer compared to normal breast tissue, correlating with poor patient prognosis. High SLC7A11 expression promotes breast cancer progression through the following mechanisms:

3.4.1. Ferroptosis Resistance:

SLC7A11-mediated cystine uptake supports glutathione (GSH) synthesis, inhibiting lipid peroxidation and protecting cancer cells from ferroptosis. In ER+ breast cancer, estrogen upregulates SLC7A11 to enhance antioxidant capacity, and SLC7A11 expression is further elevated in endocrine therapy-resistant patients, suggesting its potential as a marker of resistance. Data from Wenzhou Medical University indicate that targeting estrogen-regulated SLC7A11 and SLC3A2 can enhance ferroptosis in ER+ breast cancer, offering new therapeutic options especially for endocrine-resistant patients [7].

3.4.2. Metabolic Reprogramming:

High SLC7A11 expression leads to NADPH depletion, triggering glucose- and glutamine-dependent metabolic pathways that support cancer cell survival under nutrient-deficient conditions. This feature is particularly pronounced in TNBC, providing a therapeutic window to target metabolic abnormalities [8].

3.4.3. Multidimensional Regulation of SLC7A11 Expression:

1) Estrogen Signaling Regulation: ER α directly activates SLC7A11 transcription by binding to its promoter, promoting ferroptosis resistance in ER+ breast cancer. Preclinical studies show that targeting the estrogen-SLC7A11 axis can restore endocrine therapy sensitivity.

2) UFMylation Modification: Metformin induces ferroptosis by inhibiting the UFMylation (a ubiquitin-like modification) of SLC7A11, reducing its protein stability. This mechanism shows significant antitumor activity in TNBC models.

3) ceRNA Network Regulation: SLC7A11 mRNA acts as a competing endogenous RNA (ceRNA) binding miRNAs such as miR-375, indirectly regulating autophagy-related genes (e.g., STX17, UVRAG), thereby influencing chemotherapy resistance [9].

4. SLC7A11 and Its Relationship with Other Diseases

4.1. Liver Diseases

The role of SLC7A11 in liver diseases is bidirectional and varies depending on the disease type and stage.

4.1.1. Acute Liver Injury (ALI):

In drug-induced liver injury, such as acetaminophen overdose, SLC7A11 regulates cystine uptake to maintain glutathione (GSH) levels and inhibit lipid peroxidation-driven ferroptosis. Mesenchymal stem cell (MSC)-derived exosomes (MSC-Exo) stabilize SLC7A11 protein expression, reducing ferroptosis in hepatocytes induced by CCl₄ and improving pathological damage [10]. Both in vivo and in vitro studies support that MSCs and their exosomes exert pathological remission and inhibit lipid peroxidation [11]. Ferroptosis inhibitors like Fer-1 may protect hepatocytes via the SLC7A11/GPX4 axis.

4.1.2. Metabolic Dysfunction-associated Steatotic Liver Disease (MASLD):

High SLC7A11 expression leads to serine metabolism imbalance. Specifically, reducing cysteine synthesis through the transsulfuration pathway can cause serine metabolism disruption, triggering lipid peroxidation and ferroptosis, thus accelerating fatty liver progression. Supplementation with serine or ferroptosis inhibitors alleviates hepatic lipid accumulation and inflammation. In SLC7A11-overexpressing mouse models, the serum serine/glutamate ratio decreases, indicating its potential as a biomarker for MASLD.

4.1.3. Alcoholic Liver Disease (ALD):

Chronic alcohol intake suppresses intestinal SIRT1 signaling, downregulating SLC7A11 expression, resulting in GSH depletion and ferroptosis. Activating SLC7A11 or supplementing antioxidants like N-acetylcysteine can alleviate alcohol-induced liver fibrosis and oxidative stress.

4.2. Neurodegenerative Diseases

SLC7A11 functions in the nervous system exhibit duality, requiring a balance between its antioxidant role and glutamate excitotoxicity.

4.2.1. Alzheimer's Disease (AD) and Parkinson's Disease (PD):

A β deposition and α -synuclein aggregation suppress SLC7A11 expression, leading to decreased neuronal GSH levels and ferroptosis. Overexpression of IGFBP-2 increases concomitantly with neuronal ferritin deposition. In AD models, specific miRNAs are significantly downregulated, negatively correlating with IGFBP-2 and neuronal ferritin expression. Functional experiments with miRNA mimics and inhibitors confirm their regulatory effects. Further studies show these miRNAs influence antioxidant enzyme activity and oxidative stress by targeting key genes in the Nrf2/SLC7A11/GPX4 pathway, thereby regulating neuronal ferritin accumulation [12].

4.2.2. Cerebral Ischemia and Hemorrhage:

Local iron overload after brain injury activates ferroptosis pathways; inhibition of SLC7A11 exacerbates neuronal death. Exosomal delivery of miR-25-3p activates the SLC7A11/GPX4 axis, significantly improving motor function and reducing infarct size in mice. Eupatilin (EUP) rescues increased cell death and the downregulation of GPX4, FTH1, SLC7A11, and SOX2 in intracerebral hemorrhage (ICH) mouse models. In SH-SY5Y cells stimulated with hemin, EUP treatment restores ROS and MDA levels, SOD activity, and iron levels by reversing the downregulation of GPX4, FTH1, SLC7A11, and SOX2. SOX2 silencing abolishes EUP's protective effects on oxidative stress and ferroptosis, suggesting EUP alleviates ICH-induced secondary brain injury by inhibiting the SOX2/SLC7A11 axis-mediated ferroptosis [13].

4.3. Metabolic Diseases

4.3.1. SLC7A11 in Oxidative Stress and Insulin Resistance in Diabetes

SLC7A11 promotes glutathione (GSH) synthesis by mediating cystine uptake; GSH is a critical intracellular antioxidant essential for maintaining pancreatic β -cell function and insulin sensitivity. In type 2 diabetes (T2D), oxidative stress induced by hyperglycemia suppresses SLC7A11 expression, resulting in GSH depletion and

aggravated lipid peroxidation, which accelerates β -cell apoptosis and insulin resistance.[14].Metabolomic studies reveal significantly elevated succinate levels in bone marrow cells of diabetic mice, suggesting oxidative metabolic imbalance related to SLC7A11 dysfunction. Moreover, high SLC7A11 expression may activate the mTORC1 signaling pathway, inhibiting phosphorylation of insulin receptor substrate (IRS) and disrupting insulin signaling. Other studies highlight SLC7A11's role in regulating immune response and oxidative stress in diabetic wound healing by affecting insulin secretion and mTOR signaling, both associated with delayed wound repair. This underscores current progress in targeting SLC7A11 for treating related complications [15].

4.3.2. SLC7A11 in Metabolic Regulation of Obesity and Fatty Liver

SLC7A11 expression is increased in adipose tissue of obese patients, exacerbating chronic inflammation by modulating macrophage polarization. SLC7A11-mediated glutamate export depletes intracellular glutamate pools, driving glutamine-dependent metabolism that increases lipid synthesis and oxidative stress accumulation in adipocytes. In non-alcoholic fatty liver disease (NAFLD), high SLC7A11 expression correlates with serine metabolism imbalance, reducing cysteine synthesis via the transsulfuration pathway, triggering ferroptosis and accelerating hepatic lipid accumulation. Animal experiments show that inhibiting SLC7A11 or supplementing serine significantly alleviates hepatic steatosis and inflammation. Research also identifies the nonessential amino acid transporter SLC7A11 as critical in MASLD: patient samples show elevated SLC7A11 expression. Genetic models demonstrate that *Slc7a11* accelerates MASLD progression by blocking ferroptosis induced by classical cystine/cysteine deficiency. Serine deficiency and subsequent impaired de novo cysteine synthesis contribute to MASLD progression in liver-specific *Slc7a11*-overexpressing mice, suggesting its potential as a prognostic biomarker for MASLD patients [16].

4.4. Immune-related Diseases (Example: Multiple Sclerosis)

4.4.1. Metabolic Regulation of Treg Cells

SLC7A11 regulates regulatory T cell (Treg) proliferation via the NRF2 signaling pathway. In relapsing-remitting multiple sclerosis (RRMS) patients, Treg cells show impaired SLC7A11 expression, leading to reduced proliferation and defective immunosuppressive function. Reports indicate that pseudo-starvation signals reverse human Treg cell anergy in vitro. At the molecular level, Treg cell proliferative response depends on induction of the cystine/glutamate antiporter SLC7A11, whose expression is controlled by nuclear factor erythroid 2-related factor 2 (NRF2). In RRMS patients, impaired SLC7A11 induction in Treg cells correlates with decreased proliferative capacity. Treatment with dimethyl fumarate (DMF) rescues SLC7A11 induction and fully restores Treg expansion [17].

4.4.2. Redox and Immune Balance

SLC7A11-mediated glutamate export may activate NMDA receptors on macrophages, inducing pro-inflammatory cytokines such as IL-6 and TNF- α , thereby exacerbating neuroinflammation. This suggests a dual role for SLC7A11 in the neuroimmune microenvironment [18].

4.5. Chronic Kidney Disease (CKD)

Ferroptosis of renal tubular cells contributes to fibrosis progression. Inhibiting SLC7A11 reduces oxidative stress but must be balanced to avoid exacerbating renal function damage. In CKD mouse models, increased malondialdehyde (MDA), iron content, and lipid peroxidation levels are observed alongside decreased expression of glutathione peroxidase 4 (GPX4) and SLC7A11, confirming the involvement of SLC7A11-mediated ferroptosis in CKD progression [19].

5. Potential Intervention Strategies Targeting SLC7A11

SLC7A11 (also known as xCT), the core subunit of the cystine/glutamate antiporter, plays a critical role in maintaining redox homeostasis, regulating ferroptosis, and metabolic reprogramming across various diseases. Targeting its function has become a research hotspot in recent years. The following summarizes five major intervention approaches and their mechanisms based on the latest studies.

5.1. Exosome-Mediated Regulation of SLC7A11

Exosomes, as natural carriers, enable precise regulation of SLC7A11 by delivering functional molecules.

1) Mechanisms and Applications

Mesenchymal stem cell-derived exosomes (MSC-Exo) can deliver SLC7A11 protein or regulatory miRNAs to stabilize SLC7A11 expression in hepatocytes or neurons, thereby inhibiting ferroptosis. For instance, in acute liver injury models, MSC-Exo delivering SLC7A11 reduce CCl₄-induced lipid peroxidation and markedly improve liver function.

2) Targeted Delivery Optimization

Nanoparticle-modified exosomes enhance targeting efficiency. Adipose-derived stem cell (ADSC) exosomes delivering miR-138-5p to bladder cancer tissues inhibit downstream pathways of SLC7A11, increasing chemosensitivity [20].

5.2. Small Molecule Inhibitors Blocking SLC7A11 Function

Inhibiting SLC7A11 transport activity depletes cystine and induces ferroptosis, thereby killing tumor cells.

1) Classical Drugs

Sulfasalazine, a competitive inhibitor of SLC7A11, blocks cystine uptake, lowers glutathione (GSH) levels, and triggers ferroptosis. It significantly inhibits tumor growth and enhances radiosensitivity in esophageal and liver cancer models [3].

2) Novel Inhibitor Development

Allosteric inhibitors targeting specific domains of SLC7A11 (e.g., Erastin derivatives) improve inhibitory efficiency and reduce off-target effects. Combined treatment with Erastin and sorafenib shows synergistic suppression of hepatocellular carcinoma proliferation.

5.3. RNA Modification Regulates SLC7A11 Expression

Epigenetic modifications, such as m6A methylation, affect SLC7A11 mRNA stability and expression.

1) m6A Methylation Regulation

METTL3-mediated m6A modification stabilizes SLC7A11 mRNA. In hepatoblastoma, the METTL3/IGF2BP1 complex inhibits mRNA deadenylation, upregulating SLC7A11 and enhancing ferroptosis resistance. Blocking this axis restores tumor cell sensitivity to ferroptosis.

2) siRNA and Antisense Oligonucleotides
SLC7A11-targeting siRNAs silence its expression, reducing GSH synthesis capacity. For example, in laryngeal cancer models, silencing HIF-1 α indirectly suppresses SLC7A11 expression and enhances radiosensitivity.

5.4. Ubiquitin-Mediated Degradation Induces SLC7A11 Inactivation

The ubiquitin-proteasome system degrades SLC7A11 protein, rapidly inhibiting its function.

1. E3 Ubiquitin Ligase Regulation

SOCS2, an E3 ubiquitin ligase, mediates K48-linked ubiquitination of SLC7A11, promoting its proteasomal degradation. Overexpression of SOCS2 in liver cancer significantly reduces SLC7A11 protein levels, induces ferroptosis, and enhances radiotherapy efficacy.

2. Combination Therapy

Combining ubiquitination activators (e.g., MLN4924) with ferroptosis inducers (e.g., RSL3) synergistically inhibits SLC7A11. This approach shows promising effects in lung and colorectal cancer models.

5.5. Metabolic Compensation Therapies Bypassing SLC7A11 Dependency

Supplementing alternative metabolites or activating bypass pathways can mitigate toxicity caused by SLC7A11 inhibition.

1. Cysteine Precursors Supplementation

N-acetylcysteine (NAC), a cysteine precursor, bypasses SLC7A11-mediated cystine uptake via the transsulfuration pathway, maintaining GSH levels. NAC treatment reduces oxidative stress and kidney damage in diabetic nephropathy.

2. Serine Metabolism Intervention

In non-alcoholic fatty liver disease (NAFLD), serine supplementation restores transsulfuration pathway activity, reducing cysteine demand dependent on SLC7A11, thus inhibiting ferroptosis and lipid accumulation.

6. Summary and Outlook

As the core subunit of the cystine/glutamate antiporter, SLC7A11 plays a dual role by regulating redox homeostasis, ferroptosis, and metabolic reprogramming across tumors, metabolic diseases, and immune-related disorders. Dysfunction of SLC7A11 can drive disease progression, such as tumor drug resistance and exacerbation of fatty liver, while also serving as a critical target for therapeutic intervention. Currently, intervention strategies targeting SLC7A11 have evolved from single-drug inhibition to multimodal precise regulation, including exosome-mediated delivery, RNA modification, ubiquitin-mediated degradation, and metabolic compensation therapies, showing significant preclinical potential. For example, exosome-based targeted delivery can specifically modulate SLC7A11 expression in diseased tissues, minimizing systemic toxicity; epigenetic interventions based on m6A methylation or ubiquitination pathways offer new avenues to overcome resistance.

However, clinical translation of SLC7A11-targeted therapies still faces multiple challenges. First, SLC7A11 function exhibits marked tissue specificity: while inhibition

induces ferroptosis in liver cancer, excessive suppression in neurons may cause glutamate excitotoxicity. Second, metabolic compensation mechanisms (e.g., activation of the methionine cycle) may weaken therapeutic efficacy, necessitating combined multi-pathway targeting to overcome these barriers. Third, most current research is based on animal models, and pharmacokinetics and long-term safety in humans require systematic evaluation. Future studies should integrate multi-omics technologies—such as spatial metabolomics and single-cell sequencing—to elucidate the dynamic regulatory network of SLC7A11, and develop intelligent delivery systems (e.g., stimuli-responsive nanoparticles) to achieve spatiotemporal precision in therapy.

Notably, strategies targeting SLC7A11 are driving the development of personalized medicine. For instance, liquid biopsy monitoring of SLC7A11-related metabolites in patient blood (such as cystine/glutamate ratios) can dynamically assess treatment response and guide therapy adjustment. Moreover, the interplay between SLC7A11 and immune checkpoint molecules (e.g., PD-L1) provides a theoretical basis for combined “ferroptosis-immune” therapies. In summary, with deeper mechanistic insights and technological innovation, SLC7A11 is poised to become a central therapeutic target across diseases. Yet, its comprehensive clinical application will require interdisciplinary collaboration and ongoing efforts in translational medicine.

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