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REVIEW

The Role of SLC7A11 in Tumor Progression and the Regulation Mechanisms Involved in Ferroptosis

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Abstract: SLC7A11 (xCT) is a key subunit of the cysteine/glutamate transporter (system xc $^{-}$), which is crucial for maintaining cellular redox homeostasis (especially glutathione synthesis) and regulating Ferroptosis. It is highly expressed in various malignant tumors and is a key factor leading to treatment resistance, making it an important anti-cancer target. This review systematically summarizes the complex multi-level regulatory network of SLC7A11: at the transcriptional level, key factors form precise regulatory hubs: the KEAP1/NRF2 pathway directly activates SLC7A11 transcription, endowing cancer cells with antioxidant and anti ferroptotic abilities; P53 acts as a core inhibitory factor, and its activity state (activated by STEAP3 iron overload or regulated by Gankyrin/DM2 degradation) directly determines the intensity of inhibition of SLC7A11; ATF4 integrates endoplasmic reticulum stress, oxidative damage, and epigenetic signals (such as SIRT3/KDM3B/KDM4A), and bidirectionally regulates SLC7A11 transcription. Epigenetic regulation involves RNA m6A modification (ALKBH5/FTO reduces stability, METTL3/IGF2BP3 enhances stability) and histone modification (BAP1/PRC1 inhibits through H2Aub). After translation, the stability of SLC7A11 protein is strictly regulated by ubiquitination (SOCS2/HECTD3 promotes degradation, OTUB1/TCF12 inhibits degradation) and palmitoylation (ZDHHC8/DUXAP8 antagonizes degradation). Of particular importance is that non coding RNAs indirectly release their inhibition of SLC7A11 mRNA by acting as "molecular sponges" to adsorb specific miRNAs, profoundly affecting tumor progression and resistance to ferroptosis. This study reveals how cancer cells abnormally upregulate SLC7A11 by hijacking multi-level mechanisms, gaining strong antioxidant/anti ferroptotic abilities, which are the core basis for their survival, proliferation, and resistance to treatment. This study also identified SLC7A11 as a convergence point for multiple key pathways, making it an ideal hub target for intervening in cancer and overcoming drug resistance.

Keywords: SLC7A11, ferroptosis, non-coding RNA, TP53, epigenetic regulation

Introduction

The solute carrier family 7 member 11 (SLC7A11), also known as xCT, is a member of the solute carrier family 7 and mainly serves as a key subunit of the cystine/glutamic acid transporter, participating in the transport of amino acids on the plasma membrane.[1] The cystine/glutamic acid transport system is composed of two subunits, the light chain subunit SLC7A11 and the heavy chain subunit SLC3A2, among which SLC7A11 plays the main transport function activity.[2] Research has shown that SLC7A11 is highly expressed in various solid tumors, including breast, pancreatic, ovarian cancers, and gliomas, and is closely associated with treatment resistance in malignant tumors.[3] Thus, SLC7A11 has become a key target in cancer therapy.

The main physiological function of SLC7A11 is to act as a cystine/glutamic acid reverse transporter, simultaneously transporting glutamic acid within the cell to the outside.[4] Then it will be reduced to cysteine, which is a key rate-limiting step in the synthesis of glutathione (GSH). Glutathione is one of the most important antioxidant substances in cells and an important cofactor of glutathione peroxidase 4 (GPX4).[5] Ferroptosis is a novel type of programmed cell death driven

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by iron-dependent lipid peroxidation. Its core feature is the accumulation of lipid peroxides within cells. Glutathione peroxidase 4 (GPX4) is a key molecule within cells that combates this lipid peroxidation and thereby inhibits the occurrence of ferroptosis.[6] SLC7A11 has complex regulatory relationships with various non-coding RNA such as LncRNA, CircRNA and miRNA. For instance, in terms of the diversity of regulatory directions, different non-coding RNA have different regulatory effects on SLC7A11.[7] The complexity of the regulatory hierarchy enables non-coding RNA to regulate SLC7A11 at multiple levels after transcription.[8] Pathologically speaking, non-coding RNA participate in tumor progression by regulating SLC7A11 to affect ferroptosis sensitivity.[9] Overall, non-coding profoundly influences the biological behavior of tumors and the sensitivity of cells to ferroptosis.

As a critical subunit of the cystine/glutamate reverse transporter (system xc^-), SLC7A11 is mainly responsible for the uptake of extracellular cystine and the release of intracellular glutamate.[10] SLC7A11 plays various roles in regulating numerous pathophysiological processes related to several diseases, such as maintaining cellular redox homeostasis, ferroptosis, and neurodegenerative diseases.[11] Due to the complex regulation of SLC7A11 in tumors, it has multiple clinical significations. It is not only a potential target for various cancers, but its expression level also provides directions for prognosis and the development strategies of new drugs. In addition, non-coding RNA related to SLC7A11 may serve as prognostic markers and also have the potential to be used in gene therapy or immunotherapy. For instance, high expression of circSLC7A11 in liver cancer cells indicates a poor prognosis.[9] The midfloor expression of LncRNA SLC7A11-AS1 in gastric cancer is associated with a poor prognosis.[12] Multiple data indicate that non-coding RNA associated with SLC7A11 have potential value as targets for various cancer.

Results

Direct Regulation by Transcription Factors

The KEAP1/NRF2/SLC7A11/GPX4 pathway, as a classical oxidative stress pathway, maintains REDOX homeostasis through transcriptional activation. Under normal conditions without oxidative stress or other stimuli, NRF2 binds to KEAP1 in the cytoplasm, controlling NRF2 stability through the proteasome pathway.[13] Upon exposure to reactive oxygen species (ROS) and other stressors, modifications to KEAP1's amino acid residues lead to a conformational change in the KEAP1/NRF2 complex. NRF2 dissociates from KEAP1 and translocates into the nucleus, where it interacts with small MAF proteins to form heterodimers.[14] These heterodimers then associate with antioxidant response elements (AREs) located in the promoters of NRF2 target genes, including SLC7A11.[15] Several molecules activate the KEAP1/NRF2/SLC7A11/GPX4 axis to confer ferroptosis resistance by competing for binding with KEAP1, such as Mangiferin and hydrogen sulfide.[16,17] The KEAP1-NRF2 pathway plays a dual role in oxidative stress adaptation and malignant tumor progression by upregulating SLC7A11 (Figure 1). Understanding this mechanism provides a theoretical basis for developing targeted antioxidant defenses and novel therapeutic strategies against ferroptosis.

The P53 gene, a crucial tumor suppressor gene, is reported to be mutated in over 50% of malignant tumors. P53 encodes a transcription factor that regulates the cell cycle.[18] Notably, P53 directly modulates SLC7A11 expression, where STEAP3, serving as a ferrireductase, facilitates the transfer of ferric ions (Fe^{3+}) into the cells, leading to iron overload and ROS accumulation, which subsequently activates P53. P53 then directly inhibits SLC7A11, reducing glutathione (GSH) synthesis, amplifying oxidative stress, and inducing ferroptosis. The STEAP3-P53 axis plays a critical role in iron metabolism-related cancers, such as liver cancer.[19] Gankyrin can enhance the interaction between MDM2 and P53 by forming a complex with both, promoting the ubiquitination and degradation of P53. This releases the repression on the SLC7A11 promoter, increasing SLC7A11 expression and allowing cancer cells to tolerate ferroptosis.[20] miR-26a-1-3p, a typical epigenetic regulator of P53, indirectly enhances P53 function by inhibiting MDM2. By targeting the 3' UTR of MDM2 mRNA, it reduces MDM2-mediated P53 degradation.[21] In OCCC cells, MEX3A promotes P53 degradation to enhance sensitivity to ferroptosis similarly.[22] ERO1alpha is an endoplasmic reticulum-resident thiol oxido-reductase that has been proven to be highly upregulated in various cancer types.[23] REO1alpha can also serve as a functional downstream target of mTORC1 at the transcriptional activation level, activating the IL-6/STAT3 pathway to stimulate the transcription of SLC7A11.[24]

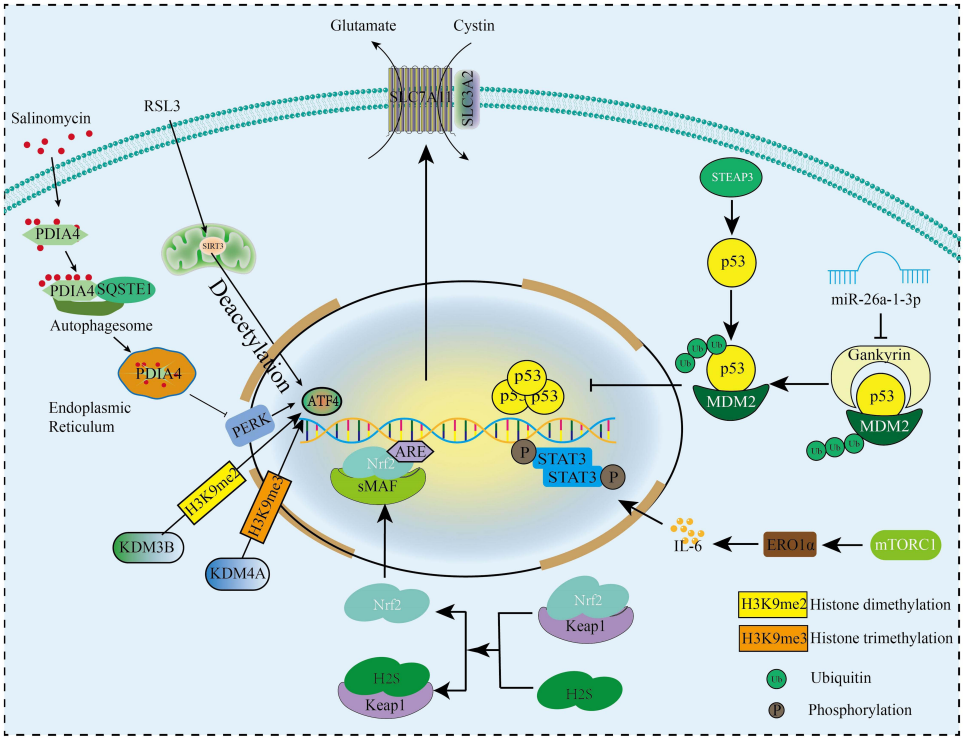

Figure 1 Regulation of SLC7A11 Transcription and Stability via Keap1, P53, and Various Epigenetic Factors. Hydrogen sulfide and Mangiferin compete with Keap1, causing Nrf2 to enter the nucleus and form a dimer with sMAF, and bind to ARE to induce transcription of SLC7A11. STEAP3 activating P53 can directly inhibit the expression of SLC7A11. Gankyrin promotes the ubiquitination and degradation of P53 by facilitating the binding of P53 to MDM2. Among them, miR-26a-1-3p reduces the degradation of P53 mediated by MDM2 by inhibiting the 3'UTR terminal of MDM2 mRNA. PDIA4 is degraded by lysosomes after stimulation with Salinomycin, and then inhibits the PERK/ATF4 pathway, thereby directly suppressing the activity of SLC7A11. SIRT3 reduces the inhibition of SLC7A11 transcription by deacetylating ATF4. KDM3B and KDM4A control the modification of histones on the promoter of SLC7A11 to regulate its expression.

Overall, these cytokines regulate SLC7A11 directly by enhancing or inhibiting P53's function or modifications. Examples include USP22 and SHARPIN, while others, such as STEAP3 and ALOX15B, regulate it indirectly via P53 activation. These key factors elucidate the core pathway centered on P53, which finely controls SLC7A11 expression through multi-layer regulation (direct/indirect action, degradation/stabilization) and affects ferroptosis, laying an important foundation for the development of precise cancer intervention strategies targeting this pathway (Figure 1).

Transcription activator 4(ATF4) is a multifunctional transcriptional regulatory protein in the basic leucine zipper superfamily. It can participate in REDOX homeostasis through transcription, thereby affecting cancer cells.[25] In liver cancer cells, ATF4 ablation prevents liver steatosis; however, it increases sensitivity to ferroptosis by decreasing SLC7A11 expression, thus inhibiting liver cancer progression.[26] PDIA4, an endoplasmic reticulum chaperone protein, degrades upon external stimuli and enhances ATF4's transcriptional activity through the PERK/ATF4 pathway, directly inhibiting the SLC7A11 promoter activity. The reduced SLC7A11 expression subsequently affects cellular antioxidant capacity and promotes susceptibility to ferroptosis.[27]

SIRT3, a deacetylase, plays a vital role in the epigenetic regulation of ATF4. In contrast to PDIA4, SIRT3 enhances ATF4's ability to bind to the SLC7A11 promoter by deacetylation, positively regulating SLC7A11 transcription.[28] Histone deacetylase KDM3B removes the repressive marks of H3K9me2, forming a transcription complex with ATF4 to cooperatively upregulate SLC7A11 expression.[29] KDM4A, a member of the JmjC domain demethylase family, specifically demethylates histone H3 at lysine 9 (H3K9me3), which is primarily associated with chromatin and gene silencing.[30] By controlling H3K9me3 demethylation in the SLC7A11 promoter region, it regulates SLC7A11 transcription and ferroptosis in OS cells.[31] providing new insights into understanding epigenetics in disease and developing targeted therapies.

ATF4 serves as a molecular hub, integrating signals from endoplasmic reticulum stress, epigenetics, and oxidative damage to dynamically adjust SLC7A11 levels. This dual role in initiating or inhibiting ferroptosis presents potential therapeutic targets for cancers or neurodegenerative diseases (Figure 1).

Epigenetic Regulation of SLC7A11

In addition to direct transcription factor regulation, SLC7A11 is subject to epigenetic regulation. For instance, ALKBH5 can remove m6A modifications on SLC7A11 mRNA in colorectal cancer cells, reducing its stability and consequently lowering SLC7A11 expression.[32] Fat mass and obesity-associated protein (FTO) may regulate m6A modifications in the SLC7A11 gene, leading to reduced m6A levels and consequent downregulation of SLC7A11.[33] Inversely, IGF2BP3, recruited by LINC00942, enhances SLC7A11 RNA stability via m6A modifications, promoting HCC cells' sensitivity to ferroptosis.[34] The RNA methyltransferase METTL3 can also promote m6A methylation of SLC7A11 mRNA, enhancing ferroptosis resistance[35] (Figure 2A). BAP1 and PRC1[36] coordinate to suppress the expression of SLC7A11 by erasing and writing H2Aub on the promoter of SLC7A11 (Figure 2B). These results highlight the multi-layered epigenetic control of SLC7A11 expression, revealing how diverse regulators (RNA modifications, histone marks) converge to critically modulate cellular sensitivity to ferroptosis.

Post-Translational Modifications (PTMs)

SOCs2, an E3 ubiquitin ligase, induces the ubiquitination and degradation of SLC7A11 protein. It can also bind to the N-terminal domain of SLC7A11 through its SH2 domain, transferring ubiquitin molecules.[37] Similarly, HECTD3 interacts with SLC7A11 to promote its polyubiquitination[38] (Figure 3A). Mechanistically, AMER1 recruits β-TrCP1/2 via binding SLC7A11 and ferritin light chain (FTL), leading to phosphorylation-dependent degradation of SLC7A11.[39] Conversely, OTUB1 lowers SLC7A11's ubiquitination levels by directly interacting with it; TCF12 indirectly suppresses SLC7A11 degradation by repressing OTUB1 transcription[40] (Figure 3B). Moreover, SLC7A11 ubiquitination is regulated by multiple cytokines, and protein palmitoyltransferase ZDHHC8 can reduce SLC7A11 ubiquitination by

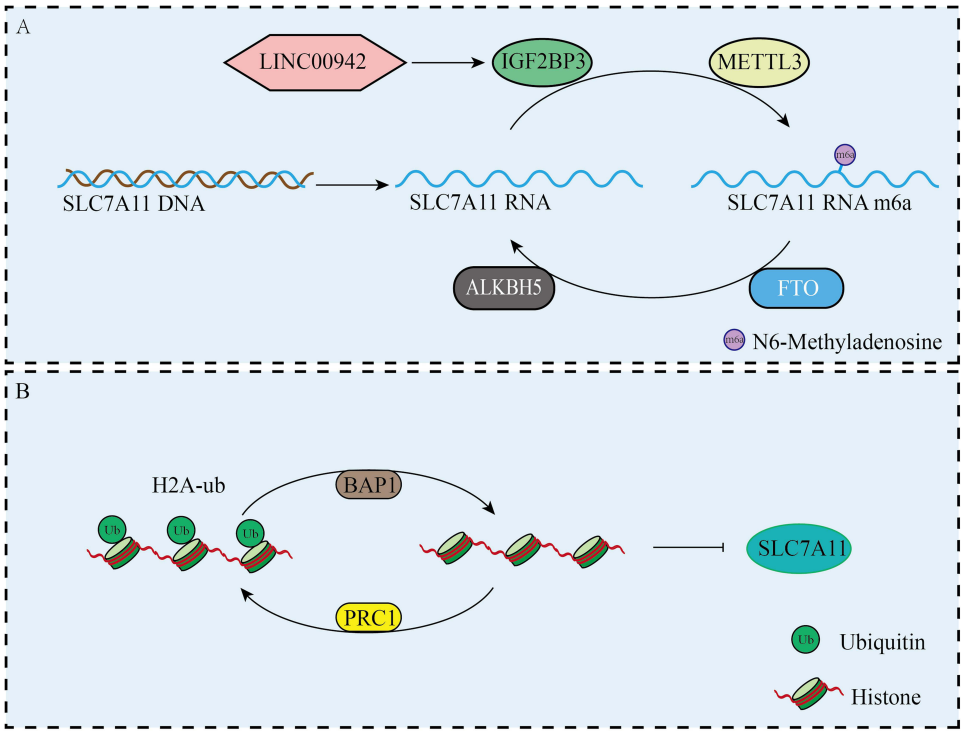

Figure 2 Modifications of SLC7A11 mRNA: The Role of m6A Methylation and Its Regulatory Elements. (**A**) ALBKH5 and FTO clear the m6A modification on SLC7A11mRNA, leading to the down-regulation of SLC7A11 expression. The IGF2BP1 and METTL3 recruited by LINC00924 can enhance the m6A modification. (**B**) BAP1 and PRC1 can regulate the expression of SLC7A11 by adjusting the monoubiquitination modification of H2A.

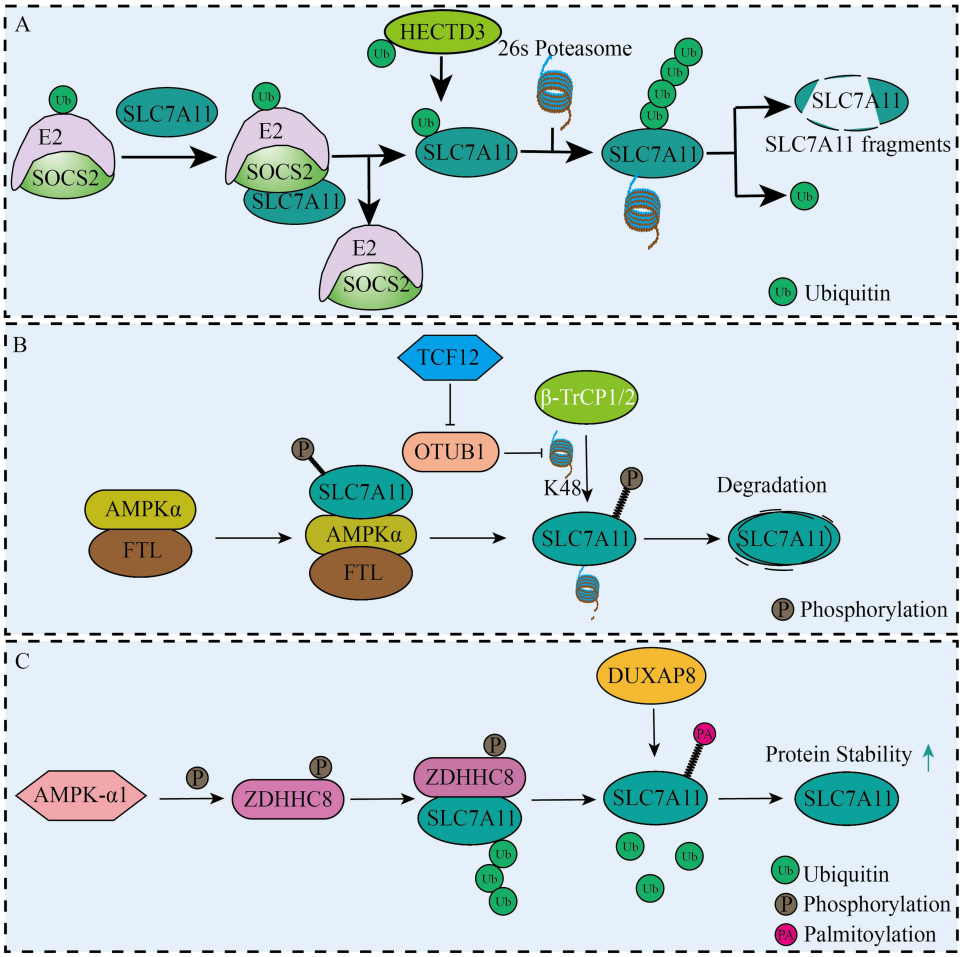

Figure 3 Ubiquitination and Degradation Pathways of SLC7A11: Integrating Multiple Regulatory Factors. (**A**) SOCS2 and HECTD3 transferred ubiquitin molecules to the SLC7A11 protein, inducing polyubiquitination degradation of the K48 chain. (**B**) After AMPKα binds to SLC7A11, it recruits β-trcp1/2 to promote its phosphorylation-dependent ubiquitination degradation. TCF12 can inhibit the ubiquitination and degradation of SLC7A11 by suppressing OTUB1. (**C**) ZDHHC8 reduces the ubiquitination level of SLC7A11 by promoting the palmitoylation of SLC7A11. DUXAP8 can acylate SLC7A11 palmitoides, preventing it from being degraded by lysosomes.

promoting palmitoylation.[41] DUXAP8 can prevent the degradation of SLC7A11 by lysosomes by promoting the palmitoylation of SLC7A11[42] (Figure 3C). Taken together, these research reveals that the stability of SLC7A11 protein is finely regulated by a complex network, in which multiple factors (such as Ubiquitin ligases, Deubiquitinases, Palmitoylation modifying factors, etc) promote or inhibit its ubiquitination and degradation pathways, collectively determining its intracellular abundance.[43]

Non-Coding RNAs and SLC7A11 Regulation

Non-coding RNAs significantly influence gene expression and play different roles in tumorigenesis.[44] Recently, non-coding circular RNAs (circRNAs) have garnered attention for their roles in modulating SLC7A11 in tumorigenesis, progression, and treatment resistance. For example, miR-27a-3p can directly bind to SLC7A11's 3'-UTR in NSCLC cells, suppressing SLC7A11 expression.[45] EZH2 inhibits ferroptosis in TSCC cells by decreasing miR-125b targeting SLC7A11[46] (Figure 4A). CrcPDSS1 knockdown in NSCLC cells downregulates miR-137, targeting SLC7A11 and GPX4, which leads to increased sensitivity to ferroptosis.[47] circFNDC3B also regulates SLC7A11 by modulating miR-520d-5p, thereby affecting the progression of OSCC[48] (Figure 4B). Long non-coding RNA OIP5-AS1 can resist cellular oxidative stress in prostate cancer by reducing the expression of nuclear factor erythrocyte 2 (NRF2) and stabilizing miR-365.[49] It was also found that OIP5-AS1 promotes cell growth and inhibits cadmium expoor-mediated ferroptosis by targeting miR-128-3p/SLC7A11 signal transduction[50] (Figure 4C). Circular RNABCAR3 regulates ferroptosis and peroxidation of B lymphocytic leukemia cells by targeting the miR-27a-3p/SLC7A11

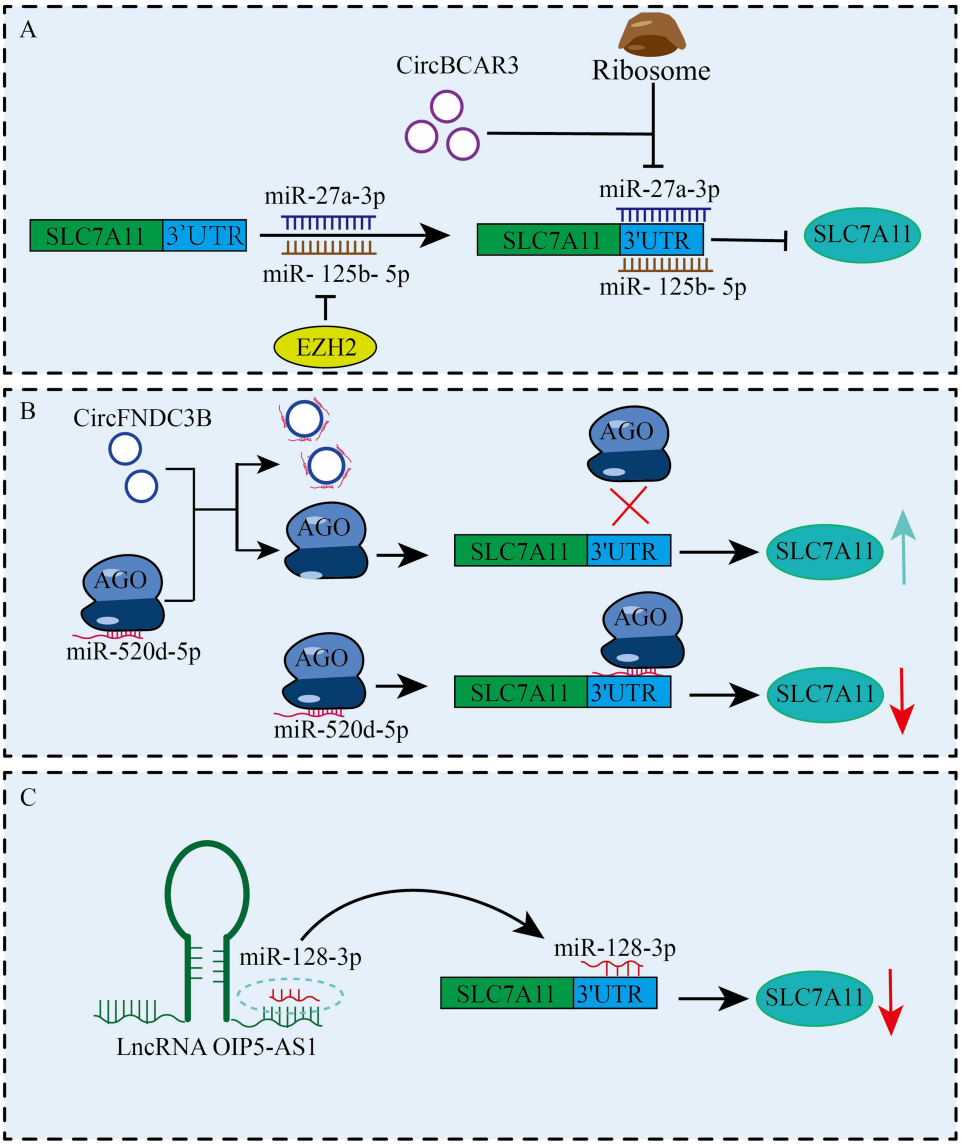

Figure 4 The Role of Non-Coding RNAs and Cytokines in Modulating SLC7A11 Expression. (**A**) Most non-coding RNAs function by directly binding to the 3'UTR of the target fragment, such as miR-27a-3p and miR-128-3p, etc. Some cytokines play the role of "molecular sponges" in the mechanism. EZH2 can inhibit the binding of miR-125b-5p. (**B**) And circFNDC3B also absorbs miR-520d-5p so that it cannot bind to the 3'-UTR of the target fragment, thereby affecting the expression of SLC7A11. (**C**) LncRNA OIP5-AS1 inhibits SLC7A11 by targeting miR-128-3p/SLC7A11 signal transduction.

axis.[51] In addition, most other non-coding Rnas affect tumor growth by indirectly or directly regulating SLC7A11. For example, circ-007044 inhibits miR-485-5p, upregulates SLC7A11, and promotes LUAD.[52] Hsa-circ-0018139 upregulates SLC7A11 through miR-656-3p and promotes the growth of NSCLC.[53] Overall, multiple non-coding circular RNAs (circRNA) achieve the progression of malignant tumors or the inhibition of ferroptosis by adsorbing specific miRNAs. Furthermore, the high stability and tissue specificity of circRNA make it a potential diagnostic marker.[54] The regulation of SLC7A11 by non-coding RNA deepens the understanding of the remodeling of tumor metabolism and the mechanism of ferroptosis resistance, and also lays a theoretical foundation for the development of innovative therapies for non-coding RNA (Figure 4).

Beyond specific circRNAs, the stable and tissue-specific nature of circRNAs highlights their potential as diagnostic markers in cancer. Moreover, non-coding RNAs deepen the understanding of metabolic remodeling and ferroptosis resistance mechanisms, laying a theoretical foundation for developing innovative therapies.

CircRNA, as a stable and tissue-specific biomarker in the human body, has great potential in the field of body fluid biopsy. The expression of specific circRNA in body fluids may represent the relevant characteristics of cancer and can be

used for the early diagnosis, molecular typing, therapeutic effect monitoring and prognosis assessment of cancer.[55] Future research can further clarify the generation, function and degradation mechanisms of circRNA, develop more efficient targeting strategies, and promote the clinical transformation of these findings. We are expected to enter a new era of precision medicine for cancer, ultimately improving the quality of life and treatment outcomes of cancer patients.[56]

Conclusion and Outlook

Cancer cells increase SLC7A11 expression through various mechanisms to enhance oxidative stress and resistance to ferroptosis, ensuring normal growth. Recent studies highlight the roles of circRNAs in modulating the cystine/glutamate transporter SLC7A11 in tumorigenesis, progression, and treatment resistance. circRNAs, as stable closed-loop non-coding RNAs, can regulate SLC7A11 expression at the post-transcriptional level through a "molecular sponge" effect on specific miRNAs.

This discovery of the circRNA-miRNA-SLC7A11 regulatory pathway offers new directions for cancer treatment. Targeting circ/SLC7A11 may provide strategies against ferroptosis resistance and chemotherapy resistance.[57] Furthermore, the high stability and tissue specificity of circRNAs suggest their potential as diagnostic markers, as exemplified by abnormal circP4HD expression in LUAD serving as a target for liquid biopsy technologies.

From a translational medicine perspective, interventions targeting circRNAs are currently in exploration. For instance, siRNA targeting hsa_circ_0136666 not only adjusts cancer cell development through the miR-375/PRKDC axis but also enhances the efficacy of PD-L1 antibodies and suppresses gastric cancer immune evasion when combined with nano-lipid particles.[58] While several degradation pathways of circRNAs have been identified, elucidating their degradation mechanisms remains crucial for future research, potentially integrating techniques like single-cell sequencing to explore cellular factor changes within the tumor microenvironment related to circRNA/SLC7A11 mechanisms.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the paper.

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