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REVIEW

The Dual Role of SLC7A11 in Colorectal Cancer Ferroptosis: From Molecular Mechanisms to Therapeutic Opportunities

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Abstract: Colorectal cancer (CRC) ranks as the third most prevalent malignancy globally based on recent epidemiological studies. In China, the rising incidence and mortality rates of CRC have underscored the importance of elucidating its pathogenic mechanisms, which remain major focus in current biomedical research. Ferroptosis, a regulated cell death process driven by iron-dependent lipid peroxidation, is closely associated with disruptions in iron homeostasis, lipid metabolism, and amino acid metabolism. This unique iron-catalysed death process plays a crucial role in both tumor initiation and malignant progression by disturbing cellular redox imbalance. The cystine/glutamate antiporter SLC7A11 (also known as xCT) has been identified as a central regulator of ferroptosis susceptibility. The tumor suppressor p53 and its associated microRNAs modulate ferroptotic responses through regulation of SLC7A11 expression, forming a critical axis in oncogenic transformation and metastasis. However, the precise role of SLC7A11 in CRC—particularly its context-dependent dual functions as both a tumor promoter and a therapeutic vulnerability—remains a critical unanswered question. This review aims to systematically summarize current advances in understanding the multiple roles of SLC7A11 in CRC-related ferroptosis pathways and to evaluate emerging therapeutic strategies targeting this axis. Importantly, we also underscore the existing knowledge gaps and outline future research directions essential for leveraging this unique molecular pathway to improve patient outcomes.

Keywords: SLC7A11, ferroptosis, colorectal cancer

Introduction

Colorectal cancer (CRC) is the third most prevalent malignancy worldwide, accounting for approximately 10% of all diagnosed cancers and ranking as the second leading cause of cancer-related mortality globally.[1] In China, from 2000 to 2019, the age-standardized incidence rate (ASIR) of CRC increased by 42.3%, while mortality rose by 15.7%. These upward trends impose a substantial burden on healthcare systems and hinder socioeconomic development.[2] Current therapeutic strategies for CRC are stratified based on tumor-node-metastasis (TNM) staging and molecular profiling. Treatment modalities include surgical resection, neoadjuvant radiotherapy, platinum-based chemotherapy, epidermal growth factor receptor (EGFR)-targeted biologics, and programmed death-1 (PD-1)/programmed death ligand-1 (PD-L1) immune checkpoint inhibitors. Alarmingly, 83% of CRC cases in developing countries are diagnosed at stage III or IV, and 78% of these patients are ineligible for curative surgery, leaving chemotherapy as the primary treatment option.[3] The development of multidrug resistance (MDR) in CRC, largely driven by the upregulation of ATP-binding cassette (ABC) transporters, which markedly worsens patient outcomes. Five-year survival rates decline from approximately 65% in treatment-responsive cases to less than 12% in non-responsive cases.[4] As a result, elucidating the mechanisms of drug resistance, metabolism, and apoptosis in CRC has become the central focus of current research.

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Ferroptosis is a distinct form of regulated cell death, differing from apoptosis, necrosis, and autophagy. It is characterized by the iron-mediated peroxidation of phosphatidylethanolamine-containing polyunsaturated fatty acids (PE-PUFAs) within cell membranes. This process is driven by dysregulated iron metabolism, depletion of glutathione, and compromised lipid peroxide repair mechanisms.[5] SLC7A11 (Gene ID: 23657), the light chain subunit (xCT) of the Xc system, mediates the sodium-independent 1:1 exchange of extracellular cystine for intracellular glutamate, thereby sustaining redox homeostasis through glutathione biosynthesis.[6,7] This transmembrane transporter protects cells from ferroptosis by preserving intracellular cysteine pools for glutathione synthesis. Notably, oncogenic overexpression of SLC7A11 is observed in 53% of CRC samples (TCGA dataset) and is associated with advanced TNM staging and chemoresistance.[8] Recent studies have demonstrated that knocking down SLC7A11 increases lipid reactive oxygen species (ROS) levels in HCT116 cells, confirming its regulatory role in CRC ferroptosis.[9] Given its central function in ferroptosis, investigating SLC7A11 is critical for the development of novel therapeutic strategies for CRC. This review will explore how SLC7A11 mediates ferroptosis and outline recent progress in related research in CRC.

New Mechanistic Insights into Ferroptosis Defense Systems

Three primary defence mechanisms against ferroptosis have been systematically characterized, as summarized in Figure 1.

The Glutathione-GPX4 Axis

The main defense mechanism is mediated by the glutathione peroxidase 4 (GPX4), which reduces lipid hydroperoxides. This process relies on glutathione (GSH) biosynthesis, which in turn depends on the cystine/glutamate antiporter xCT. The xCT transporter, a heterodimer of SLC7A11 and SLC3A2 (Gene IDs: 23657/6520), facilitates cystine/glutamate exchange at a 1:1 stoichiometry, as revealed by cryo-EM structural analysis (PDB ID: 6RMJ).[8] This antiporter mediates the import of extracellular cystine (Cys) in exchange for intracellular glutamate (Glu), maintaining intracellular cysteine concentrations at 100–300 μM under physiological conditions. Once inside the cell, cystine is reduced to cysteine in an NADPH-dependent manner. Cysteine then serves as the rate-limiting precursor for GSH synthesis, catalyzed by γ-glutamylcysteine ligase.[10] GPX4 catalyzes the GSH-dependent reduction of phospholipid hydroperoxides, maintaining membrane integrity by preventing the propagation of the peroxidation cascade.[11]

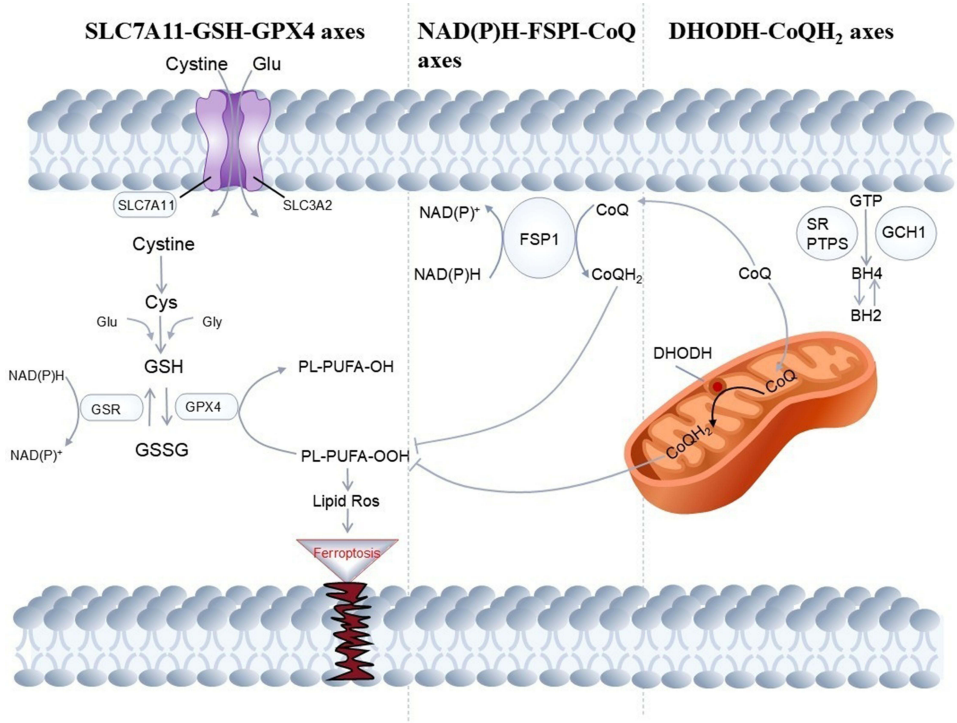

Figure 1 Ferroptosis defense mechanism.

FSP1-CoQ Redox Cycle

The ferroptosis suppressor protein 1 (FSP1, formerly known as AIFM2) constitutes a secondary defense system that generates ubiquinol through NAD(P)H-dependent reduction at plasma membrane-localized FSP1.[12] FSP1 (AIFM2, Gene ID: 83451) exhibits dose-dependent protection against ferroptosis, with a 50% effective concentration of 15 nM in HT29 cells, mediated by its oxidoreductase domain. Membrane-anchored FSP1, which has been confirmed through immunofluorescence showing 85% colocalization with plasma membrane markers, effectively reduces CoQ to CoQH, consuming NAD(P)H to terminate lipid radical chain reactions.[13] While FSP1 mRNA expression correlates with the CRC stage, pharmacological FSP1 inhibition (50 nM iFSP1) induces only 22% ferroptosis in organoid models unless combined with GPX4 inhibition, indicating redundancy in ferroptosis defense pathways.[14]

Mitochondrial DHODH Pathway

The tertiary defense mechanism involves mitochondrial dihydroorotate dehydrogenase (DHODH, EC 1.3.5.2), which becomes critical when GPX4 is inactivated. This inner mitochondrial membrane protein couples orotate synthesis with CoQ reduction, thereby maintaining mitochondrial membrane potential, which is essential to prevent cristae dysfunction-induced ferroptosis.[15]

GCH1-BH4 Metabolic Axis

GTP cyclohydrolase 1 (GCH1, EC 3.5.4.16) is a key enzyme in the biosynthesis of tetrahydrobiopterin (BH4), which exhibits dual antioxidant functions: directly scavenging free radicals and selectively protecting bis-allylic phospholipids through stereospecific interactions. GCH1 is a key enzyme in the synthesis of BH4 as well as its oxidation product, dihydrobiopterin (BH2). These compounds contribute to remodelling the cellular lipid structure and effectively inhibited ferroptosis by scavenging free radicals and selectively protecting phospholipids. Additionally, BH4 promotes the conversion of phenylalanine to tyrosine, which increasing the precursors for CoQ synthesis, which can be integrated into the FSP1-CoQ-NAD(P)H and DHODH-CoQH2 pathways to further inhibit ferroptosis.[16]

Functional Paradigms of SLC7A11

The functional complexity of SLC7A11 and its regulatory networks are illustrated in Figures 2 and 3.

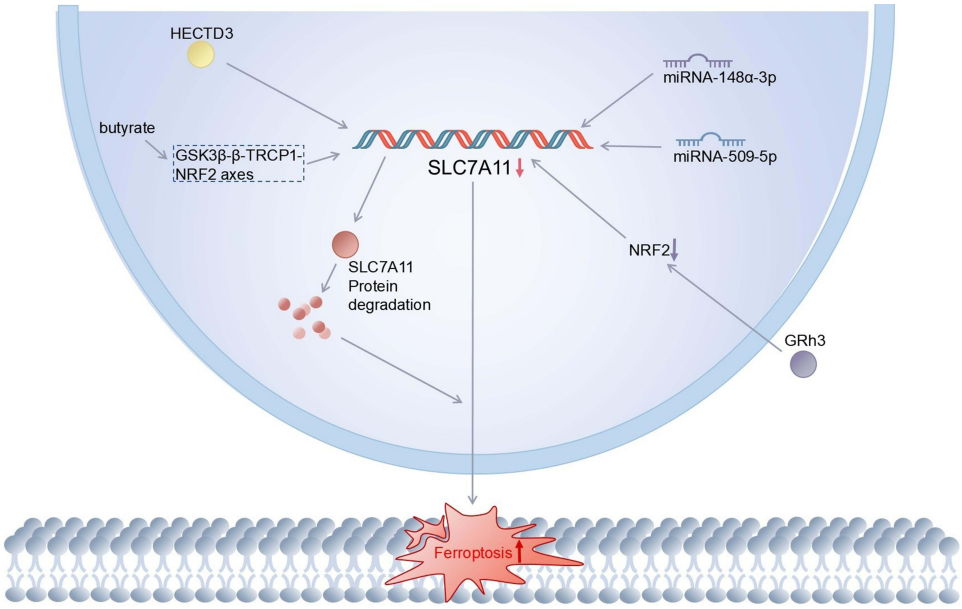

Figure 2 Regulatory Pathways Promoting Ferroptosis via SLC7A11 Downregulation in Colorectal Cancer.
Notes: Schematic diagram illustrating the HECTD3-mediated regulatory network involving butyrate, GSK3β-β-TRCP1, and NRF2 axes. Key mechanisms include SLC7A11 protein degradation, modulation by miRNA-148α-3p and miRNA-509-5p, and GRh3-dependent pathways.

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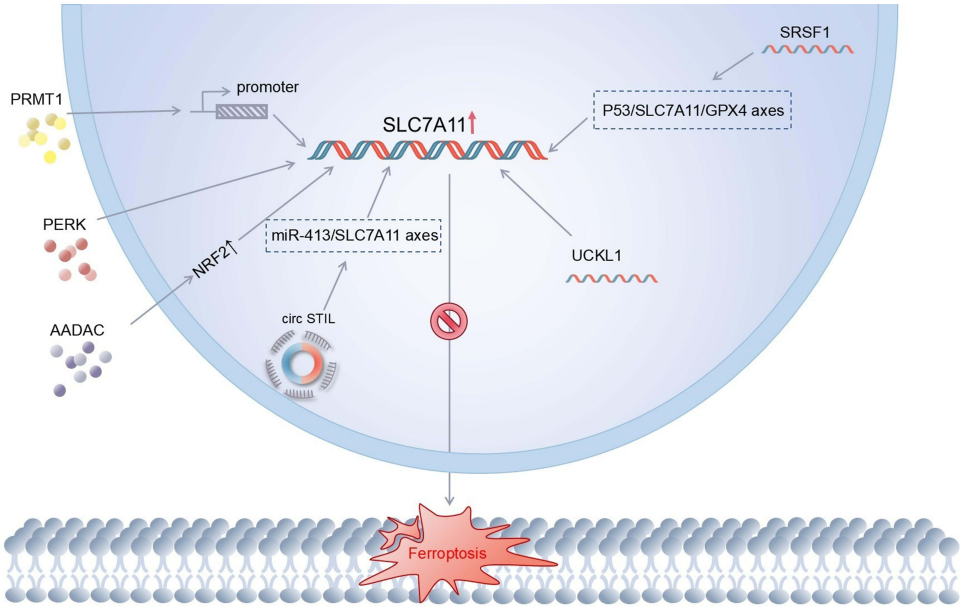

Figure 3 Regulatory Pathways Inhibiting Ferroptosis via SLC7A11 Upregulation in Colorectal Cancer.
Notes: Molecular interplay among PRMT1, PERK, and AADAC pathways. Highlights include PRMT1-driven *SLC7A11* promoter activity, PERK-regulated miR-413/SLC7A11 interactions, UCKL1, and AADAC-associated circ STIL, converging on ferroptosis regulation.

The Antioxidant Regulatory Network of SLC7A11

ROS, including superoxide anion ($O_2\bullet^-$), hydroxyl radical (•OH), hydrogen peroxide (H_2O_2), and singlet oxygen ($^1O_2$), are oxygen-derived chemical entities produced during normal metabolic processes. Disturbance of ROS homeostasis can lead to lipid peroxidation chain reactions that propagate through biomembranes, resulting in macromolecular damage to nucleic acids, structural proteins, and organelles, ultimately impairing cellular viability. Pharmacological inhibition of SLC7A11 impairs cystine uptake via the Xc^- antiporter system, thereby disrupting the glutathione biosynthesis. This cascade leads to GPX4 dysfunction and progressive depletion of antioxidant defenses, creating a permissive environment for ROS-induced oxidative stress, which can trigger necroptotic cell death in malignant cells. Therefore, SLC7A11 serves as a critical regulatory node in the oxidative stress management through its role by controlling intracellular redox homeostasis, thereby establishing its central role in the regulation of ferroptosis.[17,18] As a key functional component of the Xc^- system, SLC7A11 expression is dynamically regulated by multiple oncogenic signaling cascades in different cancer types. The molecular interplay among key regulators such as PRMT1, PERK, and AADAC pathways, which converge on SLC7A11 to mediate ferroptosis, is depicted in Figures 2 and 3 Mechanistically, the NRF2/KEAP1 signaling axis transcriptionally upregulates SLC7A11 expression under oxidative stress conditions, illustrating its regulatory complexity.[19] Notably, the stemness factor SOX2 promotes SLC7A11 transcription in lung adenocarcinoma, conferring ferroptosis resistance through enhanced antioxidant buffering capacity.[20]

Role of SLC7A11 in Drug Resistance During Tumor Therapy

The effectors of the Hippo pathway, YAP/TAZ, drive the overexpression of SLC7A11 in hepatocellular carcinoma (HCC), promoting therapeutic resistance by modulating redox homeostasis.[21] Post-translational stabilization of SLC7A11 by ABCC5 maintains redox balance through two mechanisms: suppression of lipid peroxidation cascades and preservation of GPX4 protein levels in sorafenib-refractory HCC models.[22] SLC7A11-mediated chemoresistance primarily stems from enhanced glutathione biosynthesis and suppression of ferroptosis, a mechanism conserved across various malignancies. This paradigm underlies resistance to multiple chemotherapeutic agents, including cisplatin resistance in gastric adenocarcinoma,[23] mithramycin resistance in lung cancer,[24] temozolomide resistance in glioma[25] and gemcitabine resistance in pancreatic cancer.[26] Targeting SLC7A11 disrupts redox balance, resulting in lethal ROS accumulation that overcomes drug resistance by inducing ferroptosis. Paradoxically, certain interventions, such as cold plasma therapy,

transiently upregulate SLC7A11 expression as an adaptive stress response in resistant phenotypes. However, sustained glutathione buffering capacity enables compensatory survival mechanisms to develop under these conditions, ultimately limiting therapeutic efficacy.[27]

Role of SLC7A11 in P53 Regulation

The tumor suppressor p53 orchestrates critical cellular processes, including genome maintenance, oncogene surveillance, and metabolic homeostasis. As a master regulator, it coordinates tumor-suppressive programs by activating cell cycle checkpoints, inducing replicative senescence, and regulation of intrinsic apoptotic pathways.[28] Emerging evidence reveals the multifaceted regulatory network involving p53 in ferroptosis, with context-dependent modulation patterns.[29] The p53-SLC7A11 axis constitutes a core regulatory circuit where p53 transcriptionally represses SLC7A11 expression to enhance ferroptosis-driven tumor suppression.[30] Using isogenic HCT116 $p53^{-/-}$ cells, Wang et al demonstrated that the p53 mutation suppressed xenograft growth by 62%, an effect that was fully reversed by overexpressing SLC7A11.[31] Structural analysis showed that the p53 mutation results in a loss of DNA-binding capacity at the SLC7A11 promoter region, thereby abolishing both transcriptional repression and subsequent ferroptosis induction. The p53 pathway can inhibit SLC7A11 to induce ferroptosis not only in tumor cells but also in cardiac, hepatic, and cartilage cells.[32–34] Therefore, p53-dependent suppression of SLC7A11 establishes a permissive environment for glutathione depletion-driven ferroptosis. Paradoxically, under certain pathophysiological conditions, such as atherosclerotic plaque formation, p53 upregulates SLC7A11 to maintain vascular wall integrity by preventing ferroptosis of smooth muscle cells.[35]

Modulation of the Tumor Microenvironment and Anti-Tumor Immunity

Beyond its intrinsic role in cancer cells, SLC7A11 is a pivotal regulator of the tumor microenvironment (TME) by mediating metabolic crosstalk.[36] Its high expression creates a metabolically hostile microenvironment, primarily by strongly competing for extracellular cystine.[37] This competition effectively "deprives" tumor-infiltrating lymphocytes, particularly $CD8^+$ T cells, of a crucial resource for glutathione (GSH) synthesis.[36,37] Consequently, these T cells experience severe oxidative stress and lipid peroxide accumulation, which ultimately drives them toward ferroptotic cell death.[37] This cystine deprivation-induced T-cell dysfunction is further characterized by exhaustion phenotypes, including diminished cytokine secretion and elevated expression of checkpoint proteins such as PD-1 and TIM-3.[37] This metabolic warfare illustrates how tumor-specific SLC7A11 activity directly neutralizes anti-tumor immunity.[37] Moreover, SLC7A11's influence on the TME contributes to the establishment of a broader immunosuppressive landscape.[38–40] Mechanistically, SLC7A11 upregulation, sometimes driven by oncogenic pathways like MerTK-ERK/SP1, has been directly implicated in resistance to anti-PD-1/PD-L1 blockade. This resistance operates through a dual mechanism: SLC7A11 not only suppresses ferroptosis in tumor cells but also promotes the recruitment of myeloid-derived suppressor cells (MDSCs), thereby further dampening the immune response.[38] High SLC7A11 expression frequently correlates with elevated PD-L1 expression in tumors and serves as an independent prognostic marker for poor survival and immune evasion in cancers such as HCC and LUAD.[39,40] Furthermore, SLC7A11 has been identified as a key gene associated with disulfidptosis. Prognostic models based on such disulfidptosis-related genes (DRGs) specifically predict alterations in the TME and distinct immune infiltration patterns.[39,41] By integrating ferroptosis, disulfidptosis, and immune regulation, SLC7A11 emerges as a pivotal therapeutic target capable of remodeling the TME from immunologically "cold" to "hot".[36,38,39]

SLC7A11-Mediated Ferroptosis in Colorectal Carcinogenesis

Ferroptosis is characterized by iron-catalyzed peroxidation of polyunsaturated fatty acid (PUFA)-containing phospholipids and represents a distinct form of regulated cell death.[5] Epidemiological studies show that obesity contributes to approximately 20% of cancer-related mortality, with CRC incidence being 33% higher in obese populations than in those of normal weight.[42] Given the central role of lipid metabolism reprogramming in regulating ferroptosis, targeting this pathway appears to be a promising strategy for managing obesity-associated CRC. The lipid chaperone MTTP mediates the transport of intravesicular triglycerides through its lipid-binding domain and is predominantly expressed in adipocytes, where it regulates systemic lipid homeostasis. Zhang et al[43] demonstrated that adipocyte-derived exosomes transport MTTP-PRAP1 complexes to CRC cells and activate ZEB1-mediated transcriptional upregulation of GPX4 and xCT (2.3-fold increase), thereby suppressing lipid

peroxidation through dual mechanisms. Environmental obesogens, such as bisphenol A (100 nM), induce MTTP overexpression in mature adipocytes. This establishes paracrine suppression of ferroptosis, conferring chemoresistance to neighboring CRC cells. Paradoxically, oncogenic KRAS mutations (G12D/V) paradoxically modulate ferroptosis susceptibility through metabolic rewiring, demonstrating context-dependent regulatory effects. KRAS-driven de novo lipogenesis (ACLY activation, 2.5-fold) coordinates with enhanced antioxidant capacity (GSH elevation 1.8-fold) to establish ferroptosis resistance. Therapeutic agents, including cetuximab and β-element overcome KRAS-mediated resistance by inhibiting the NRF2 pathway (HO-1 downregulation by 65%) and suppression EMT (E-cadherin upregulation by 2.1-fold).[44,45] Despite these new findings, the spatiotemporal regulation of SLC7A11 in CRC ferroptosis requires further investigation, particularly in relation to the influence of the TME.

Endoplasmic Reticulum Stress Modulates SLC7A11 Activity

The unfolded protein response (UPR) is an evolutionarily conserved quality control system activated when the accumulation of misfolded polypeptides in the endoplasmic reticulum (ER) exceeds its capacity for proper folding. Although drug-resistant malignancies exhibit increased basal susceptibility to cell death pathways, they may paradoxically exploit UPR activation to develop adaptive survival mechanisms against therapeutic insults.[46] Emerging evidence implicates UPR signaling in the regulation of ferroptosis. Saini et al[47] identified PERK (EIF2AK3) as a critical mediator of SLC7A11 transcriptional control during ER stress adaptation. PERK-mediated phosphorylation of eIF2α (Ser51) increases SLC7A11 transcription by 2.3-fold, providing malignant cells with an anti-ferroptotic shield. Genetic ablation of PERK increases the accumulation of lipid ROS by 3.1-fold in CRC organoids, confirming its role as a gatekeeper in preventing ferroptosis.

Post-Translational Regulation of SLC7A11 in CRC

The functional repertoire of SLC7A11 is dynamically regulated through post-translational modifications that modulate its subcellular localization, protein-protein interactions, and turnover rates. Huang et al[48] demonstrated that HECTD3 catalyzes K48-linked polyubiquitination of SLC7A11 at residues Lys236/281, targeting it for proteasomal degradation (half-life reduced from 18 h to 6 h) and consequently triggering ferroptosis-mediated tumor suppression. This ubiquitination event simultaneously impairs cystine transport capacity, synergistically increasing cellular sensitivity to ferroptotic stimuli. Paradoxically, HECTD3 mRNA levels are downregulated 4.2-fold in CRC samples (TCGA dataset), with patients in the highest tertile of HECTD3 expression demonstrating 38% longer overall survival (HR = 0.62, P = 0.017). PRMT1-mediated symmetric dimethylation of histone H4R3 (H4R3me2s) activates SLC7A11 transcription, whereas LPCAT2-controlled PEMT K145 acetylation (Ac-K145) dictates its nuclear-cytoplasmic shuttling, forming competing regulatory circuits. This subcellular redistribution sequesters PRMT1 in cytoplasmic compartments (63% vs 22% nuclear localization), attenuating its transcriptional activation of SLC7A11 by 2.8-fold.[49]

Metabolic Regulation of SLC7A11 in CRC

Aromatic acetamide deacetylase (AADAC, EC 3.5.1.13) confers resistance to ferroptosis in CRC by reducing lipid peroxidation cascades through its metabolic activity. Mechanistically, AADAC-generated aromatic amines (eg, 4-aminobiphenyl) activate downstream signaling pathways that provide an anti-ferroptotic shield. Sun et al[50] showed that AADAC-mediated SLC7A11 upregulation (2.8-fold) maintains intracellular GSH pools, creating a permissive environment for the formation of hepatic metastasis. In addition, AADAC stabilizes NRF2 by dissociating from KEAP1, which enhances SLC7A11 transcription (3.1-fold) and establishes redox homeostasis in metastatic niches.

Genomic Regulation of SLC7A11 in CRC

MITD1 acts as a tumor suppressor by disrupting the TAZ-SLC7A11 axis, increasing lipid ROS accumulation by 2.5-fold and reducing xenograft growth by 62%.[51] Hu et al[52] demonstrated that the overexpression of SRSF1 can rescue MITD1-deficient cells from ferroptosis. This finding establishes an antagonistic regulatory relationship. Mechanistic studies have revealed that SRSF1 modulates the p53-SLC7A11-GPX4 axis through alternative splicing of MITD1 transcripts, creating a feedback loop that influences CRC progression. UCKL1 (EC 2.7.1.48), a key pyrimidine salvage enzyme, is

overexpressed by 3.2-fold in CRC specimens. In this context, it stabilizes NRF2, increasing its half-life from 15 to 42 minutes, thereby suppressing ferroptosis. This post-translational stabilization boosts SLC7A11 transcription (2.1-fold), increases GSH levels (1.8-fold), and establishes redox homeostasis, conferring ferroptosis resistance.[53] Similarly, LGR4 activates the Wnt/β-catenin signaling pathway, leading to the transcriptional upregulation of SLC7A11. This consequently confers cellular insensitivity to ferroptosis. Zheng et al established the LGR4–Wnt–SLC7A11 axis as a key mechanism driving acquired chemoresistance in CRC.[54] Beyond transcriptional regulation, SLC7A11 is also modulated at the protein level through direct interactions; for instance, the serine protease HTRA1 binds to SLC7A11 via its Kazal domain, enhancing SLC7A11 and GPX4 expression to inhibit ferroptosis and promote chemoresistance.[55] Furthermore, the secretory glycoprotein CHI3L1 promotes radiation resistance by binding to and facilitating the ubiquitin-mediated degradation of p53, which in turn alleviates the transcriptional repression of SLC7A11 and inhibits ferroptosis through the p53/SLC7A11 axis.[56] Ferroptosis is an evolutionarily conserved tumor-suppressive mechanism, and its dysregulation contributes to malignant progression. SLC7A11 acts as a molecular rheostat for tumor suppressor networks, with its overexpression enhancing p53-mediated tumor suppression (2.3-fold increase in apoptosis) through ferroptosis modulation.[57] The tumor suppressor BAP1 exhibits a ferroptosis-inducing capacity comparable to p53 (lipid ROS increased by 2.8-fold), potentially exceeding conventional tumor-suppressive mechanisms in therapeutic efficacy.[30] Lei et al[58] identified AMER1 as a scaffold protein that recruits β-TrCP E3 ligase to SLC7A11, catalyzes its K48-linked ubiquitination (half-life reduced from 18 to 6 hours) and promotes ferroptosis. AMER1 orchestrates the assembly of a multi-protein degradation complex that includes β-TrCP1/2, targeting both SLC7A11 and ferritin light chain (FTL) for proteasomal degradation, thereby establishing a coordinated regulation of ferroptosis.

Non-Coding RNA Regulation of SLC7A11 in CRC

Dysregulated non-coding RNA networks contribute to colorectal carcinogenesis through multiple molecular mechanisms, including epigenetic regulation and post-transcriptional control. Specific non-coding RNAs have emerged as promising diagnostic biomarkers and therapeutic targets due to their regulatory roles in CRC progression. Martino et al[59] identified miR-148a-3p as a direct regulator of SLC7A11 through 3'UTR binding. Overexpression of this microRNA reduced SLC7A11 protein levels by 65% and increased ferroptosis susceptibility 2.3-fold in CRC organoids. Similarly, miR-509-5p also targets SLC7A11, its overexpression suppresses both SLC7A11 protein and mRNA expression, promoting ferroptosis by elevating levels of malondialdehyde (MDA) and iron content in CRC cells.[60] Furthermore, circSTIL acts as a molecular sponge for miR-413, releasing its repression of SLC7A11 (2.1-fold increase) and forming an oncogenic circuit that enhances proliferation while inhibiting ferroptosis.[53] Beyond microRNAs and circRNAs, long non-coding RNAs (lncRNAs) also critically regulate SLC7A11 expression. A recent study by Xin et al demonstrated that LncRNA-HMG promotes chemoresistance by binding to and facilitating the MDM2-mediated degradation of the p53 tumor suppressor, which consequently leads to the transcriptional upregulation of SLC7A11 and inhibition of ferroptosis.[61]

Metabolic Regulation of SLC7A11 in CRC

The initiation of ferroptosis primarily involves iron-catalyzed peroxidation of membrane phospholipids containing polyunsaturated fatty acids (PUFAs), which is regulated by multiple overlapping pathways.[11] Apart from genetic and enzymatic regulation, metabolic intermediates and dietary factors influence ferroptosis susceptibility through SLC7A11-dependent mechanisms. The microbial metabolite butyrate (C4:0) modulates SLC7A11 expression through epigenetic modifications, linking gut microbiota composition to ferroptosis regulation in CRC. Wang et al[62,] showed that butyrate (5 mM) induces SLC7A11 degradation (half-life reduced from 18 to 6 hours) through GSK3β-mediated phosphorylation and subsequent β-TRCP1-dependent ubiquitination. Vitamin D modulates systemic iron homeostasis by controlling the transcription of hepcidin and ferroportin, thereby establishing a connection between nutrient signaling and metal metabolism.[63] Guo et al[64] demonstrated that vitamin D (100 nM) depletes cysteine (45% reduction) and GSH (38% reduction) pools in CCSCs, effects that are reversed by SLC7A11 overexpression (1.8-fold). While SLC7A11 knock-down enhances the vitamin D-mediated reduction of cysteine (62% reduction) and GSH (55% reduction), it fails to synergize with vitamin D in inducing ferroptosis, suggesting redundancy within this pathway. These data implicate

SLC7A11 as a key mediator of the metabolic effects of vitamin D in CCSCs, although the precise molecular determinants of this regulation remain unclear.

Advances in SLC7A11 in the Treatment of Ferroptosis in CRC

As a key regulator of redox homeostasis, SLC7A11 is a promising therapeutic target for modulating ferroptosis sensitivity in CRC. Inhibiting SLC7A11 could help to overcome therapeutic resistance. While pharmacological targeting of SLC7A11 remains underexplored, natural compounds from traditional medicine have shown promising therapeutic potential by modulating SLC7A11.

Ginsenoside Rh3 (GRh3): Modulation of the STAT3/p53/NRF2 Axis

Ginsenoside Rh3 (GRh3), a tetracyclic triterpenoid saponin derived from Panax species, exhibits dose-dependent antitumor activity through multiple molecular mechanisms.[65] Wu et al[66] demonstrated that GRh3 suppressed NRF2 nuclear translocation through STAT3-mediated p53 activation, establishing a novel regulatory axis. As a master regulator of the antioxidant response, NRF2 activates the expression of SLC7A11 by binding to antioxidant response elements (AREs) in its promoter region. When NRF2 is inhibited, SLC7A11 transcription (2.3-fold reduction) depletes intracellular GSH pools (45% reduction) and compromises cellular antioxidant defenses. This GSH depletion (from 15 to 8 nmol/mg protein) creates a permissive environment for lipid peroxidation, ultimately triggering ferroptotic cell death.

Curcumin: Dual Regulation of Redox Homeostasis

Chen et al[67] demonstrated that curcumin (25 μM) downregulated SLC7A11 (65% reduction), GPX4 (58% reduction), and GSH levels (42% reduction) in HCT-8 cells. This created a pro-ferroptotic environment characterized by an accumulation of iron (1.8-fold) and an elevation of ROS (2.3-fold). These findings position curcumin as a promising therapeutic candidate for CRC, particularly in overcoming therapeutic resistance by inducing ferroptosis.

Resveratrol: Nanotechnology-Enhanced Delivery

Zhang et al[68] identified resveratrol as a potent inducer of ferroptosis through downregulation of SLC7A11 (2.5-fold reduction). Nanoparticle-encapsulated formulations of RSV demonstrated enhanced bioavailability and improved tumor targeting efficiency. RSV treatment (72 h) reduced SLC7A11 (65% reduction) and GPX4 (58% reduction) protein levels and established a pro-ferroptotic state in CRC cells. Ferroptosis inhibitors (ferrostatin-1, 1 μM) partially reversed the RSV-mediated effects (viability increased from 35% to 62%), confirming the specificity of this ferroptotic pathway. Nanoformulation of RSV (encapsulation efficiency >85%) improves pharmacokinetic properties, reduces systemic toxicity, and enhances tumor accumulation (3.2-fold increase), representing a promising strategy for CRC therapy.

Triptolide: PI3K/AKT/NRF2 Axis Inhibition

Triptolide, a diterpenoid trioxide isolated from Tripterygium wilfordii, exhibits potent antitumor activity through multiple molecular mechanisms.[69] Preclinical studies have shown its broad-spectrum antitumor effects across various cancer types, including breast and thyroid malignancies.[70] Wang et al[71] demonstrated that triptonide suppresses the PI3K/AKT/NRF2 axis, leading to the downregulation of SLC7A11 and depletion of GPX4, ultimately inducing ferroptosis in CRC cells.

Cetuximab: Combination Therapy for RAS-Mutant CRC

The combination of β-element and cetuximab synergistically induces ferroptosis in CRC by targeting of the SLC7A11 and EGFR pathways simultaneously. This combination reduces SLC7A11 expression in KRAS-mutant CRC cells and suppresses proliferation and migration through ferroptosis induction. Mechanistic studies revealed that this combination therapy also inhibits EMT markers, providing a potential strategy for the treatment of RAS-mutant CRC, particularly in overcoming therapeutic resistance. These fundings establish the β-element/cetuximab combination as a promising therapeutic approach for RAS-mutant CRC.[44]

Table 1 Therapeutic Strategies Targeting the SLC7A11 Axis in CRC

Compound/ Strategy	Type/Source	Key Mechanism of Action	Primary Downstream Effects	Final Cellular Outcome	Ref
Ginsenoside Rh3 (GRh3)	Natural product (Panax sp.)	Modulates the STAT3/p53/NRF2 axis; suppresses NRF2 nuclear translocation.	↓ SLC7A11 (transcription)	Depletes GSH, induces ferroptosis	[65,66]
Curcumin	Natural product (Polyphenol)	Downregulates SLC7A11 and GPX4.	↓ SLC7A11, ↓ GPX4	Increases iron and ROS, induces ferroptosis	[67]
Resveratrol (RSV)	Natural product (Polyphenol)	Downregulates SLC7A11. (Nanoparticle delivery 2+0enhances efficacy).	↓ SLC7A11 (protein), ↓ GPX4 (protein)	Induces ferroptosis	[68]
Triptolide	Natural product (Diterpenoid trioxide from *T. wilfordii*)	Suppresses the PI3K/AKT/NRF2 axis.	↓SLC7A11 ↓GPX4	Induces ferroptosis	[65,70,71]
Cetuximab + β-element	Combination therapy (Monoclonal antibody + Natural product)	Synergistically targets EGFR and downregulates SLC7A11.	↓SLC7A11 expression	Induces ferroptosis; Inhibits EMT (in RAS-mutant CRC)	[44]

Notes: The downward arrow (↓) indicates downregulation at the protein level unless otherwise specified (eg, transcription). Key outcomes such as ferroptosis induction are summarized based on evidence from the referenced studies.

Abbreviations: AKT, AKT serine/threonine kinase 1; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; GPX4, glutathione peroxidase 4; GSH, glutathione; NRF2, nuclear factor erythroid 2-related factor 2; p53, tumor protein p53; PI3K, phosphoinositide 3-kinase; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3; EMT, epithelial-mesenchymal transition.

Conclusions and Future Perspectives

This synthesis establishes SLC7A11 as a central regulator of iron-redox balance in colorectal carcinogenesis and is indispensable in mediating therapeutic recalcitrance by modulating ferroptosis. Clinical analyses demonstrate significant correlations between SLC7A11 overexpression and both chemoresistance and early recurrence, firmly establishing its potential as a therapeutic target. However, several critical knowledge gaps and translational barriers still need to be addressed. First, the context-dependent dual role of SLC7A11 must be fully resolved. Although it supports survival in malignant cells, its metabolic competition for cystine in the TME triggers ferroptosis in infiltrating $CD8^+$ T cells, thereby establishing an immunosuppressive barrier. Future studies must therefore focus on exploiting this vulnerability—selectively inhibiting tumor SLC7A11 to induce ferroptosis while preserving or restoring immune function. Second, validating these complex interactions within the TME requires advanced preclinical models. Current systems inadequately recapitulate human pathophysiology, highlighting the need for patient-derived organoid (PDO) platforms co-cultured with immune cells, and genetically engineered mouse models (GEMMs) with tissue-specific modulation of SLC7A11. Third, the therapeutic index of agents targeting SLC7A11, particularly in combination with checkpoint inhibitors, needs rigorous evaluation. Early Phase 0/I clinical trials are essential to balance on-target toxicity (especially potential systemic effects) with antitumor efficacy. Fourth, while the natural products and strategies summarized in this review (see Table 1) show preclinical promise, their clinical application is constrained by pharmacokinetic challenges and often unclear mechanisms of action. Finally, a key mechanistic gap lies in understanding the interplay between SLC7A11-mediated ferroptosis and the recently identified process of disulfidptosis. Elucidating whether these pathways are compensatory or synergistic will be critical for designing rational combination therapies in CRC.

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.

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Disclosure

The authors report no conflicts of interest in this work.

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