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SLC7A11-associated ferroptosis in acute injury diseases: mechanisms and strategies

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Abstract. **Ferroptosis is a kind of iron-dependent renewal programmed death. Its main mechanism is to catalyze the unsaturated fatty acids highly expressed on the cell membrane under the effect of divalent iron, to produce lipid peroxidation, thus inducing cell death. SLC7A11 is a known iron death-related factor. It has been proved that iron death is involved in the occurrence and development of acute diseases, but the specific mechanism is unknown. The purpose of this review is to highlight the regulatory properties of SLC7A11 and gain a deeper understanding of its role in ferroptosis-related acute injury diseases.**

This is a narrative review. PubMed was used as the main source to randomly implement literature search strategy to index Scopus articles. No specific terms are used.

Studies have shown that SLC7A11 may affect the sensitivity of cells to iron ptosis by regulating it at the transcriptional or post-transcriptional level, which is related to the pathology of many acute injury diseases, such as acute lung injury (ALI), acute kidney injury (AKI), acute liver injury, myocardial ischemia-reperfusion injury, and acute cerebral hemorrhage. In order to clarify this point, more and more researchers turn their attention to the study of the specific mechanism between SLC7A11 and ferroptosis-related acute injury diseases.

In summary, this review summarized some specific mechanisms by which ferroptosis could be controlled by SLC7A11 and clarified the underlying mechanisms of a series of diseases caused by SLC7A11-associated ferroptosis. It also provided more scientific justification for the clinical application of targeting ferroptosis in preventing and treating various diseases.

Key Words:
Ferroptosis, SLC7A11, Transcription, Post-transcription, Acute injury diseases..

Introduction

Ferroptosis, is a new form of programmed cell death that is characterized by an accumulation of iron-dependent lipid peroxidation[1-4]. Cystine/glutamic acid reverse transporter (System Xc^-), a heterodimeric transporter for cystine/glutamate exchange, consists of a light chain subunit (XCT, also known as SLC7A11) and a heavy chain subunit (cd98hc, also known as SLC3A2) that mediates the acquisition of extracellular cysteine for intracellular glutamate in a ratio of 1:1 for the biosynthesis of glutathione[5,6], which can be utilized by GPX4 in order to convert toxic lipid hydrogen peroxide into non-toxic fatty alcohol, thereby inhibiting ferroptosis[7]. A reduction of SLC7A11 disrupts the metabolism of glutathione, however, overexpression of SLC7A11 may increase the synthesis of glutathione to alleviating the stress-induced injury caused by lipid reactive oxygen species (ROS), improving the ability of cells against ferroptosis[8]. Therefore, SLC7A11 is an essential subunit of System Xc^- involved in the protection of cells from oxidative injury and lipid peroxide-induced ferroptosis[9,10]. In this review, the regulation mechanisms and signaling pathways of ferroptosis mediated by SLC7A11 are revealed and discussed in relation to non-neoplastic disease.

Gene and Protein Structure of SLC7A11

In human and mouse, the full lengths of the System Xc^- gene are 2483 bp and 9181 bp, respectively. The amino acid sequence of the human System Xc^- is highly homologous to that of mice, but unlike mice, human System Xc^- may possess an extracellular N-linked glycosylation

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site. System Xc^- consists of two subunits, light chain subunit SLC7A11 and heavy chain subunit SLC3A2 (CD98hc or 4F2hc) connected by a disulfide bond. Humans SLC7A11 is located on chromosome 4 and contains 14 exons encoding 501 amino acids, with its N-terminal and C-terminal domains located in the cytoplasm[11,5,12], along with a transmembrane channel. This channel is a specific substrate-binding protein and mediates the transport of cystine into the cytoplasm[11]. In mice, the full length of the SLC7A11 coding region is 1509 bp, which consists of 12 exons encoding 502 amino acids[13]. SLC7A11 is a core subunit of system Xc^- in vertebrates, and no homologous genes have been found in any lower organisms[14,15]. In addition to being a chaperone subunit, SLC3A2 maintains the stability of SLC7A11[16].

Regulation of SLC7A11 at the Transcriptional Level

Nuclear Factor Erythroid 2-Related Factor2 (Nrf2)

Nuclear factor erythroid 2-related factor2 (Nrf2), a member of the Cap-n-Collar family of basic leucine zipper protein that controls cellular responses against environmental stresses[17], is crucial for regulating intracellular peroxidation[18-20]. The upregulation of Nrf2-SLC7A11 enhanced the survival of astrocytes infected with leukemia virus thyroid storm 1 (Tsl), which produced ROS accumulation[21]. In addition, Nrf2-SLC7A11 activation can help cells to resist glucose deficiency-induced damage[22]. When Nrf2 is knocked down in oxygen and glucose deprivation/reoxygenation (OGD/R) models, a decreased expression of SLC7A11 facilitates type II alveolar epithelial cell death in intestinal ischemia reperfusion-induced acute lung injury (IIR-ALI)[23]. Based on those studies, it appears that organisms mobilize their redox defenses by upregulating the antioxidant factor Nrf2 to protect cells against the harmful effects of oxidative stress.

Pharmacological or chemical activation of Nrf2 and upregulation of SLC7A11 may reduce the susceptibility of cells to oxidative damage[24,25]. However, inhibiting Nrf2 to cause SLC7A11 to be transcriptionally inactivate may promote cell death[26]. Previous studies[27-29] have shown that Chinese medicine or natural plant extracts such as pachymic acid (PA), green tea derivative (-)-epigallocatechin-3-gallate (EGCG) and Kaempferol decrease ROS and prevent ferroptosis induced by lipid peroxidation through activation of Nrf2 and its downstream target SLC7A11. Accordingly, these studies demonstrate that activated Nrf2-SLC7A11 signaling can attenuate the ferroptotic sensitivity of cells[30].

Normally, Nrf2 is degraded through ubiquitination by combining with Kelch-1 like ECH-associated protein1 (Keap1) in the cytoplasm[31]. On the one hand, Nrf2 can activate the transcription of SLC7A11 *via* binding to the antioxidant response element (ARE) at the promoter after it has been separated from keap1 and transferred to the nucleus[32,33], through which the cell proliferates and resists to ferroptosis[34]. Inhibition of the Keap1/Nrf2 by dihydroartemisinin (DHA) can cause mitochondrial damage and eventual ferroptosis[35]. On the other hand, Nrf2 can activate signal transducer and activator of transcription 3 (STAT3) phosphorylation to augment SLC7A11 protein expression, indicating that activated STAT3 may indirectly mediate SLC7A11 upregulation by Nrf2[36].

p53

The tumor suppressor p53 participates in cell survival and differentiation under various stresses by regulating specific genes at transcriptional level[37]. Iron overload and ROS-triggered ferroptosis are related to the activation of p53, which inhibits SLC7A11 expression[38,39]. Moreover, increase of the expression of p53 by drugs such as flubendazole, gambogenic acid (GNA) and pseudolaric acid B (PAB) promoted ferroptosis by suppressing the expression of SLC7A11[40-43]. Gain-of-function mutations in the p53 gene resulted in hypersensitivity to cell death owing to reduced SLC7A11 expression[44], whereas loss-of-function mutations in the p53 gene conferred cancer cells with radioresistance through suppression of ferroptosis by SLC7A11[45]. Moreover, after intracerebral hemorrhage, the antioxidant isorhynchophylline reversed ferroptosis-induced nerve damage *via* the p53/SLC7A11 pathway[46]. The above results illustrate that P53-regulated SLC7A11 expression sensitizes cells to ferroptosis. Interestingly, 1-methyl-4-phenylpyridinium (MPP^+) induced senescence in PC12 cells by activating the p53/SLC7A11 pathway[47], suggesting p53-mediated ferroptosis may contribute to senescence phenotypes through downregulation of SLC7A11[48]. As a mechanism, p53 inhibits the expression of SLC7A11 through decreased mono-ubiquitination of histone H2B on lysine 120 (H2Bub1), the region of DNA that regulates the

expression of SLC7A11, and the attenuation of gene transcriptional activation and elongation[49]. Furthermore, p53 is also capable of causing oxidative damage-induced ferroptosis in cells directly by binding to Nrf2[50].

Activating Transcription Factor 4 (ATF4)

Activating transcription factor 4 (ATF4) plays an important role in metabolic and oxidative homeostasis and cell survival by mediating the expression of adaptive genes that allow cells to resist stress[51]. Previous studies have demonstrated that the gain-of-function upregulation of ATF4 promotes resistance of cells to oxidative stress-induced injury by upregulating SLC7A11 expression[52], but also prevents cells death through the increased expression of SLC7A11 induced by histone deacetylases (HDAC)-inhibitors suberoylanilide hydroxamic acid (SAHA)[53]. In conjunction with E26 transformation-specific-1 (ETS-1), ATF4 is able to upregulate the expression of SLC7A11 by directly binding to its promoter[54]. Moreover, ATF4 protects the cells from ferroptosis through a synergistic reaction with the histone lysine demethylase 3B (KDM3B), which is kown to increase SLC7A11 expression by accelerating demethylation of Histone H3 lysine 9 (H3K9) in the SLC7A11 promoter[55,56]. Those results suggest that ATF4-modulated SLC7A11 overexpression is closely associated with resistance to ferroptosis[57-60].

Activating Transcription Factor3 (ATF3)

Activating transcription factor 3 (ATF3), a member of the ATF/cAMP response element-binding (CREB) family, which may be activated by oxidative stress, increases the sensitivity to erastin-induced ferroptosis through competitively binding to the SLC7A11 promoter and repressing SLC7A11 expression in a p53-independent manner[61,62]. Knockdown of ATF3 significantly increases SLC7A11 expression and decreases susceptibility to ferroptosis[63], suggesting ATF3 negatively regulates SLC7A11 to promote ferroptosis.

BTB Domain and CNC Homolog 1 (BACH1)

The transcription factor BTB and CNC homology 1 (BACH1), a cap'n'collar (CNC) b-Zip protein, participates in the regulation of heme and iron metabolism[64]. Studies[65] have reported that inhibition of BACH-1 induced the expression of SLC7A11, improving the ability of cells to protect themselves from oxidative damage. In a mechanism, activated BACH1 can reduce the synthesis of GSH by inhibiting the transcription of SLC7A11 to promote ferroptosis[66,67].

Breast-Cancer Susceptibility Gene 1(BRCA1)-Associated Protein 1 (BAP1)

BAP1, a ubiquitin carboxy-terminal hydrolase, is utilized to regulate programmed cell death *via* its deubiquitinating activity[68]. In experiments, BAP1 decreased the level of histone 2A ubiquitination (H2Aub) located at the promoter of SLC7A11, inhibiting its expression in a deubiquitination-dependent manner, resulting in ferroptosis[69,70], suggesting that BAP1 promotes ferroptosis by inhibiting the expression of SLC7A11[71].

Posttranscriptional Regulation of SLC7A11

Cluster of Differentiation-44 (CD44)

CD44, a non-kinase transmembrane glycoprotein, can be separated into two types according to the type of exon transcription: CD44 standard (CD44s) and specific CD44 variant (CD44v)[72]. By interacting with SLC7A11, CD44v can suppress redox status in order to improve cysteine transport by stabilizing System Xc^-[73,74]. However, the transmembrane mucin 1-C-terminal subunit (MUC1-C) can inhibit the activity of SLC7A11 and promote cell death *via* competitively binding to CD44v[75]. The results of these studies indicate that the CD44v-SLC7A11 complex contributes to the stabilization of System Xc^- and plays an anti-ferroptosis role in a ROS defense manner[76].

Ovarian Tumor Domain-Containing Ubiquitin Aldehyde-Binding Protein 1 (OTUB1)

Ovarian tumor domain-containing ubiquitin aldehyde-binding protein 1 (OTUB1) is a member of the ovarian tumor domain protease (OTU) subfamily of deubiquitinases (DUBs), which negatively regulates ubiquitination of protein and thus regulates their stability and activity[77,78]. A study[79] has shown that OTUB1-mediated deubiquitination enhances SLC7A11 stability and activates System Xc^- to prevent carbon tetrachloride (CCl_4)-triggered hepatocyte ferroptosis. Through direct interactions with SLC7A11, OTUB1 affects the sensitivity of cells to ferroptosis by deubiquitinating SLC7A11 and then stabilizing the cystine transportation[80,81]. Moreover, the over-sulfated modification in OTUB1 at cysteine residues by hydrogen sulfide increased the stability of SLC7A11[82], suggesting OTUB1 regulation is responsible for cell sensitivity to ferroptosis.

Beclin1 (BECN1)

Beclin 1 (BECN1), which is a core component of the class III phosphatidylinositol 3-kinase (PtdIns3K) complex, directly inhibits System Xc^- activity *via* binding to SLC7A11, forming the Beclin-SLC7A11 complex and promotes ferroptosis[83,84]. It is important to note that the phosphorylation of Beclin1 is essential for the formation of a of BECN1-SLC7A11 complex in BECN1-dependent ferroptosis[85].

Tripartite Motif-Containing Protein 26 (TRIM26)

Tripartite motif-containing protein 26 (TRIM26) may function as an E3 ubiquitin ligase that participates in a wide range of biological and pathological processes[86]. The finding from previous study[87] has confirmed that TRIM26 mediates the ubiquitination and degradation of SLC7A11 to promote ferroptosis in hepatic stellate cells (HSCs), inhibiting liver fibrosis.

SLC7A11-Involved Ferroptosis in Acute Injury Diseases

Acute Lung Injury (ALI)

Acute lung injury (ALI) is characterized by lung alveolar epithelial damage caused by neutrophil aggregation-induced acute inflammation[88]. According to previous study[89], excess iron accumulates in the lower respiratory tract of patients with ALI, and ferroptosis inducer ferrostatin-1 reversed lipopolysaccharide-induced ALI *via* upregulating SLC7A11[36], suggesting there may be a specific relationship between SLC7A11-mediated ferroptosis and ALI. It has proved that upregulation of SLC7A11 expression can prevent from intestinal ischemia-reperfusion (IIR)-induced ALI by inhibiting epithelial ferroptosis[23]. This process is not only associated with the direct regulation of Nrf2 to SLC7A11, but also with the activation of the Nrf2/telomerase reverse transcriptase (TERT) or Nrf2/pSTAT3 (phospho-STAT3) signaling pathways[36,90]. Even though up-regulation of SLC7A11 at the transcriptional level inhibits ferroptosis-induced ALI, it is unclear whether regulation of SLC7A11 at the post-transcriptional level and other factors related to iron metabolism are also involved.

Acute Kidney Injury

Since the emergence of our understanding of ferroptosis, it has been discovered that SLC7A11-associated ferroptosis plays a role in the pathophysiology of acute kidney injury (AKI) and renal ischemia/reperfusion (I/R) injury. Renal I/R induces ferroptosis-mediated AKI through downregulated expression of SLC7A11[91]. Further investigation reveals that downregulation of SLC7A11 responsible for ferroptosis in renal tubular epithelial cell accelerates calcium oxalate-induced AKI[92]. In addition, transforming growth factor-β1 (TGF-β1) and connexin 43 (Cx43) expressed predominantly in renal tubular epithelial cells contribute to ferroptosis-mediated AKI through modulating the expression of SLC7A11[90,93]. Nevertheless, the increased expression of SLC7A11 by natural flavonoids, such as quercetin (QCT), do indeed inhibit ferroptosis and mitigate AKI associated with I/R or FA[63]. Because the circadian clock components Rev-erb-α/β directly binds to a Ror/Rev-erb response element (RORE) cis-element and suppresses the transcription of SLC7A11, the extensive ferroptosis is responsible for folic acid (FA)-induced AKI[94]. In addition, activated NRF nuclear translocation can also promote the transcriptional expression of SLC7A11, which protects against I/R-induced AKI in mouse renal tissues[29], as well as p53 in FA-induced kidney injury[95]. These results suggest that upregulation of SLC7A11 expression may reverse ferroptosis-mediated AKI.

Acute Liver Injury

Evidence shows that SLC7A11 is closely related to acute liver injury. Activating SLC7A11 can curb the occurrence of ferroptosis, thereby alleviating liver injury in concanavalin A (ConA)-induced acute immune hepatitis (AIH)[96]. The upregulated expression of SLC7A11 played a protective role against acetaminophen (APAP)-induced liver injury (DILI) *via* inhibiting hepatocyte ferroptosis[97]. However, the enhancing zeste homolog 2 (EZH2)-mediated inhibition of SLC7A11 can promote acute liver failure (ALF) due to hepatocyte ferroptosis[98]. Moreover, the activation of hepatic stellate cells (HSC) participates in liver injury99. It is shown that SLC7A11 is positively regulated by hypoxia-inducible factor-1α (HIF-1α), and substantiating inactivation of HIF-1α/SLC7A11 pathway is required for sorafenib-induced HSC ferroptosis[100]. More intriguingly, OTUB1-mediated deubiquitination can enhance the stability of SLC7A11 by inhibiting the abnormal ubiquitination of SLC7A11, and thus ameliorate HSC ferroptosis of induced by CCl_4[79]. All these results confirm that regulating the activity or expression of SLC7A11 can attenuate liver injury by antagonizing ferroptosis.

Myocardial Injury

It is reported that SLC7A11 exerts strong antagonistic effects on angiotensin II (Ang II)-mediated

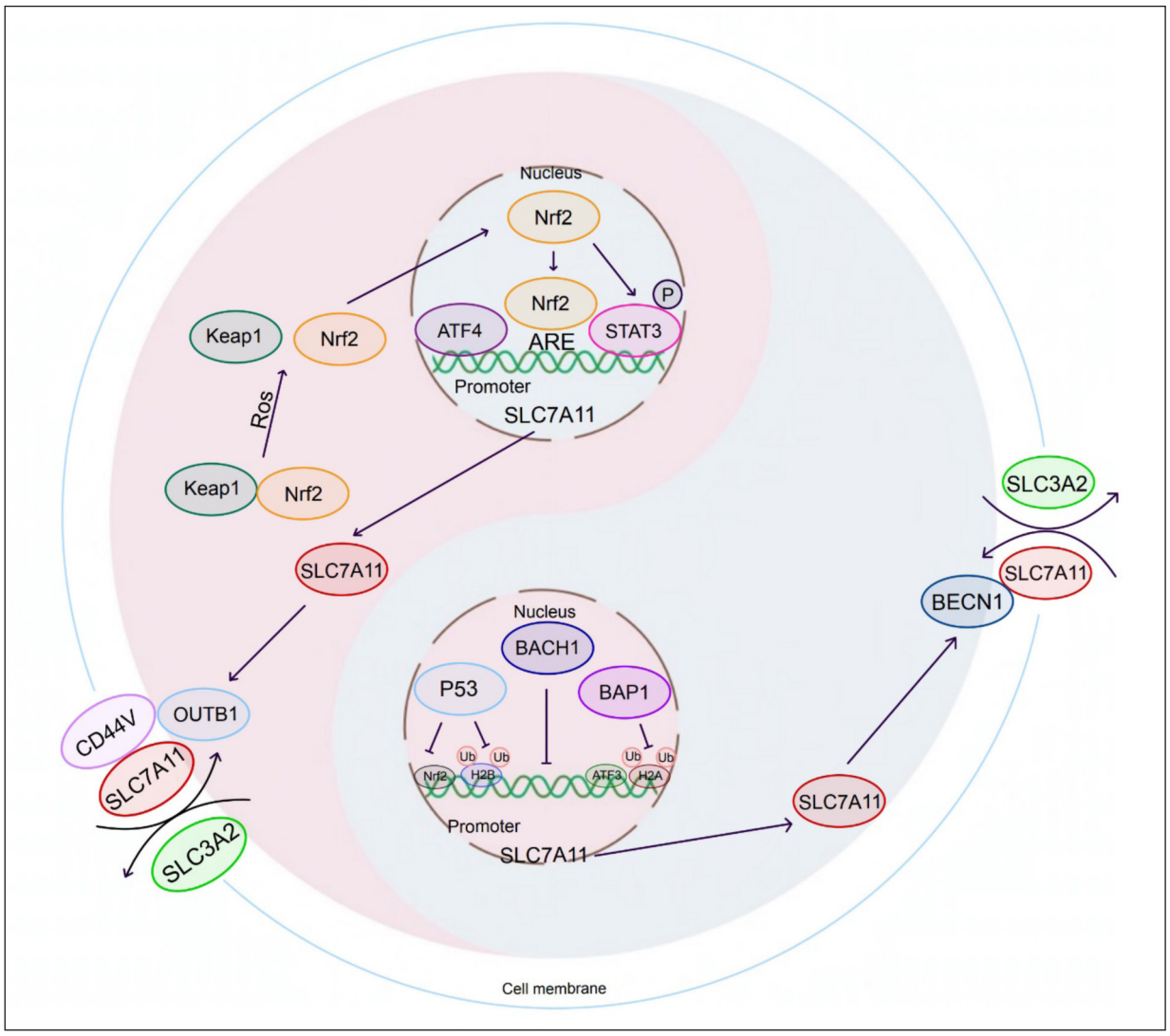

Figure 1. Molecular regulation of SLC74A11-mediated ferroptosis.

cardiac hypertrophy through suppressing ferroptosis[101]. Deficiency of SLC7A11 causes ferroptosis-induced cardiomyopathy[9]. Moreover, the involvement of Nrf2-SLC7A11/GPX4 pathway in atorvastatin-induced ferroptosis is an innovative potential pathophysiological mechanism of atorvastatin-induced cardiomyopathy[102]. Additionally, bach1, a regulator of heme and iron metabolism, promotes ferroptosis and induces cardiomyopathy by inhibiting the transcription of SLC7A11[67]. All these suggest that SLC7A11-mediated ferroptosis is related to the pathogenesis of myocardial injury. The overexpression of SLC7A11 not only protects the overall function of the myocardiumon[103], but also prevents organic cardiac injury[104] on account of ischemia/reperfusion (IR)-mediated ferroptosis. The overexpression of ubiquitin specific peptidase 22 (USP22), a member of the deubiquitinase family, protects cardiomyocytes from ferroptosis through the sirtuin1 (SIRT1)/p53/SLC7A11 signal, thereby preventing myocardial I/R injury[105]. Resveratrol improves myocardial infarction injury by inducing lysine acetyltransferase 5 (KAT5)/SLC7A11 and inhibiting ferroptosis[106]. As a result, more information about the possible mechanisms of SLC7A11 in ferroptosis-related myocardial injury will open new opportunities for developing new therapeutic approaches, as well as potential prevention measures.

Table I. The regulatory mechanism of SLC7A11.

Factors	Effects	Reglation	Specific mechanism	References
Nrf2	promote	transcription	1. Nrf2 binds to ARE and activates transcription of SLC7A11	32
			2. Nrf2 phosphorylates STAT3 and promotes transcription of SLC7A11	36 49
p53	inhibit	transcription	1. p53 reduces the occupancy of monoubiquitination of histone H2B on lysine 120 (H2Bub1) in the regulatory region of the SLC7A11 gene	
			2. p53 binds to Nrf2	50
ATF3	inhibit	transcription	ATF3 binds to the SLC7A11 promoter and represses SLC7A11 expression in a p53-independent manner	62
ATF4	promote	transcription	ATF4 directly binds to the promoter on SLC7A11 to upregulate the expression of SLC7A11	54
BACH1	inhibit	transcription	BACH1 inhibits the transcription of SLC7A11	67
BAP1	inhibit	transcription	BAP1 decreases histone 2A ubiquitination (H2Aub) occupancy on the SLC7A11 promoter and inhibits SLC7A11 expression in a deubiquitin-dependent manner	71
CD44v	stabilize	posttranscription	CD44v interacts with SLC7A11 and stabilizes XC^-	111
OTUB1	stabilize	posttranscription	OTUB1 interacts directly with SLC7A11 and stabilizes SLC7A11	81
BECN1	inhibit	posttranscription	BECN1 binds to SLC7A11 to form BECNI-SLC7A11 complex	83

Table II. Drugs and targets in abnormal physiological conditions are involved in the regulation of SLC7A11 signaling pathway.

Drugs or abnormal physiological conditions	Effects	References
ROS accumulation	Activating Nrf2/SLC7A11	21
Glucose starvation		22
Oxidative stress	ARF inhibits Nrf2/SLC7A11	26
Triptolide	Inhibition of Nrf2/SLC7A11	112
TCBQ	Activating Nrf2/SLC7A11	24, 25
EGCG		27
Kaempferol		28
PA		29
Iron overload	Upregulation of p53 inhibits SLC7A11	38
ROS accumulation		39
Flubendazole		40
GNA		41
PAB		42
Isorhynchophy	Inhibition of p53 upregulation of SLC7A11	46
MPP^+		47
SAHA	Inhibition of ATF4/SLC7A11	53
miR-K12-11	Inhibition of BACH-1-induced SLC7A11 expression	65
MUC1-C	Forms compounds with SLC7A11, CD44	75
H_2S	Stability of SLC7A11 by over sulfating OTUB1	82

Acute Cerebral I/R

During cerebral I/R, upregulated mir-27a may induce ferroptosis by inhibiting SLC7A11, thus leading to brain tissue damage[107], and has confirmed that altered level of SLC7A11 is linked to the development of cerebral ischemia or I/R injury[108,109]. Dexmedetomidine inhibits ferroptosis by increasing the expression of SLC7A11 and has a protective effect on cerebral I/R injury in mice[110]. Activation of the SCL7A11/GPX4 pathway by traditional Chinese herbal compound Naotaifang extract (NTE) and flavonoid galangin ameliorates neuronal ferroptosis induced by acute cerebral I/R[111,112]. Moreover, saffron and kaempferol (KF) promotes the expression of SLC7A11 and alleviates neuronal ferroptosis dependent on Nrf2 nuclear translocation[113], confirming the classic Nrf2/SLC7A11/GPX4 signaling pathway in I/R-induced neuronal ferroptosis is a therapeutic target for cerebral I/R injury[28]. Moreover, further studies[114] reported that PI3K/

Table III. The relationship between SLC7A11-mediated ferroptosis and diseases.

Diseases	Mechanisms and signaling pathways of ferroptosis	References
Acute lung injury (ALI)	Nrf2/SLC7A11	23
	Nrf2/pSTAT3/SLC7A11	36
	Nrf2/TERT/SLC7A11	90
Acute kidney injury(AKI)	Nrf2/SLC7A11	29
	SLC7A11/RORE	94
Renal ischemia-reperfusion injury	miR-378a-3p/SLC7A11	91
Liver Fibrosis	HIF-1α/SLC7A11	113
Acute liver failure (ALF)	EZH2-mediated inhibition of SLC7A11	98
Cardiomyopathy	SLC7A11	9
Cardiac hypertrophy	SLC7A11	99
Myocardial ischemia-reperfusion injury (MI/R)	P53/SLC7A11	100
Sarcopenia	P53/SLC7A11	38
Cerebral ischemia-induced neuronal death	P53/SLC7A11	106
Acute cerebral ischemia	SCL7A11/GPX4	102
Age-related macular degeneration (AMD)	STAT1/SLC7A11	109

AKT/NRF2 participated in SLC7A11/GPX4-mediated neuroprotective effect in cerebral ischemia model by inhibiting neuronal ferroptosis.

Conclusions

Ferroptosis is primarily caused by an abundance of polyunsaturated fatty acid phospholipids in the cell membrane, where they undergo peroxidation as a consequence of high concentrations of iron and reactive oxygen species[115]. The accumulation of lipid peroxides in the cell membrane may eventually lead to membrane collapse. As a consequence, the balance between the formation and removal of ROS-induced lipid peroxides is a key pivot in avoiding ferroptosis, among which the Xc^-/GSH/GPX4 axis plays a crucial role in preventing the accumulation of lipid peroxides[116]. The functional modulator of system Xc^-, SLC7A11, is able to inhibit ferroptosis to alleviate cellular injury[112], suggesting that activation or overexpression of SLC7A11 is an important element in the prevention of ferroptosis. Therefore, it is necessary to research SLC7A11-associated ferroptosis in order to elucidate the relationship between various ferroptosis-related diseases and specific regulatory mechanism of SLC7A11.

SLC7A11 is regulated by multiple factors at the transcriptional or posttranscriptional level (see Figure 1). At the transcriptional level, in addition to ATF3 and ATF4, which are able to facilitate transcription of SLC7A11 by binding directly to its promoter, Nrf2 is also capable of promoting SLC7A11 transcription by binding both antioxidant response element (ARE) within the promoter and by phosphorylating STAT3[32,54]. However, the transcription inhibitors p53 and BAP1 suppress the transcription of SLC7A11 by deubiquitinating histone H2B (H2B) and histone 2A (H2A)[49,71]. At the posttranscriptional level, although CD44, OUTB1 and BECN1 can directly bind to SLC7A11, CD44V and OUTB1 stabilize SLC7A11 to facilitate transport of cystine, while BECN1 combines with SLC7A11 and inhibits its activity[81,116] (see Table I). It is expected that epigenetic modifications regulating the expression or activity of SLC7A11 will be an effective defense against ferroptosis. In-depth studies of the molecular structure of channel protein SLC7A11, especially the spatial configuration of regulatory site and active residues, will provide more accurate targets for molecular research. According to detailed research into ferroptosis, there have been studies demonstrating that ferroptosis results in acute injury in lung, kidney, and liver damage[23,91,117], as well as heart disease[9], nervous system disease[118] and retinal diseases[119,120] (see Table II, III). There is no doubt that these factors and drugs (Table II) can influence ferroptosis by regulating SLC7A11, however, the exact mechanism and the most effective methods of treatment for non-neoplastic diseases remain unknown.

In summary, this review summarized some specific mechanisms by which ferroptosis could be controlled by SLC7A11 and clarified the underlying mechanisms of a series of diseases caused by SLC7A11-associated ferroptosis. It also provided more scientific justification for the clinical application of targeting ferroptosis in preventing and treating various diseases. However, there is still considerable work to be done on determining

whether ferroptosis is dominant in these diseases, as well as and the implication of SLC7A11-associated ferroptosis in future prospective cohort studies and clinical studies.

Conflict of Interest

The authors declared that they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Authors' Contribution

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Ethics Approval

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