European Review for Medical and Pharmacological Sciences 2021; 25: 1650-1662

Insights into the novel function of system Xc^- in regulated cell death

H. TU[1], L.-J. TANG[1], X.-J. LUO[2], K.-L. AI[1,3], J. PENG[1,3]

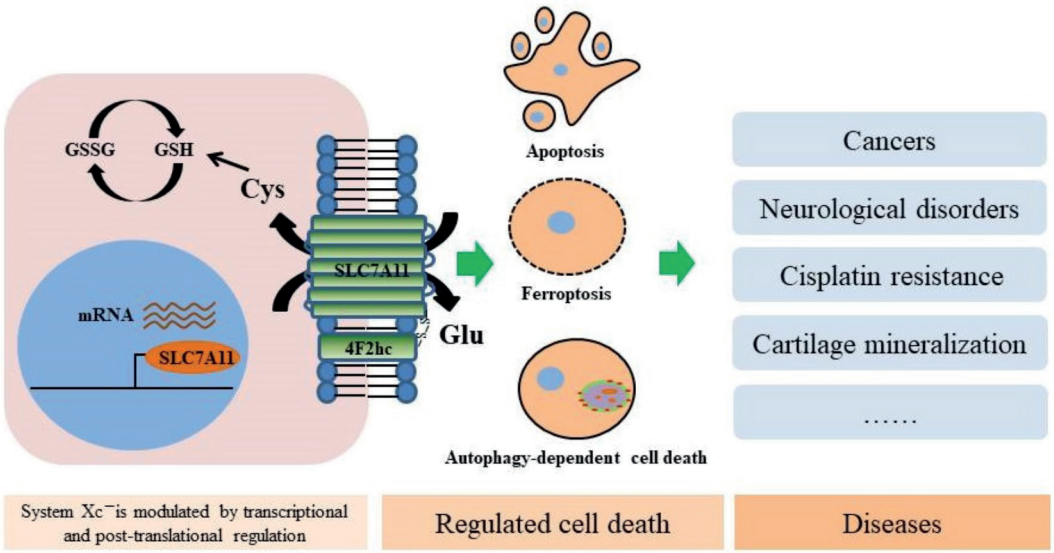
[1]Department of Pharmacology, Xiangya School of Pharmaceutical Sciences, Central South University, Changsha, China
[2]Department of Laboratory Medicine, Xiangya Third Hospital, Central South University, Changsha, China
[3]Hunan Provincial Key Laboratory of Cardiovascular Research, School of Pharmaceutical Sciences, Central South University, Changsha, China

Abstract. – System Xc^-, also named cystine/glutamate antiporter, is an important intracellular antioxidant element. It is composed of the light chain SLC7A11 (xCT) and the heavy chain SLC3A2 (4F2hc) and functions as raw materials for the synthesis of glutathione (GSH). Recent studies have demonstrated that system Xc^- plays an important role in different types of regulated cell death, which is referred to cell death controlled by dedicated molecular machinery. It has been shown that system Xc^- involves in ferroptosis, apoptosis, and autophagy-dependent cell death, contributing to different diseases and drug resistance, such as cancer, neurological disorders, and cisplatin resistance to cancers. To date, the intervention of system Xc^- by its inhibitors or activators displays a beneficial effect on the treatment of certain diseases. In this review, we summarize recent findings on the role of system Xc^- in regulated cell death, including molecular mechanisms and potential therapeutic applications.

Key Words:
System Xc^-, Cystine/glutamate antiporter, Ferroptosis, Apoptosis, Autophagy-dependent cell death.

Introduction

Types of cell death are mainly divided into apoptosis, necrosis, and autophagy-dependent cell death with the following morphological or biochemical features: (1) apoptosis forms apoptotic bodies taken up by neighboring cells with phagocytic activity and degraded in lysosomes, showing cytoplasmic shrinkage, nuclear frag-



Graphical abstract.

Corresponding Author: Jun Peng, MD, Ph.D; e-mail: Junpeng@csu.edu.cn

mentation and plasma membrane blebbing; (2) autophagy-dependent cell death, is triggered by autophagy-inducing peptides, starvation, ischemia or hypoxia manifesting with extensive cytoplasmic vacuolization and similarly culminating with phagocytic uptake and consequent lysosomal degradation; and (3) necrosis deals with the cell corpses in phagocytic and lysosomal-independent manner, showing irreversible plasma membrane permeabilization or complete cellular fragmentation. Traditionally, classic necrosis is thought a passive and unregulated cell death. Some necrosis also occurs in a programmed fashion, such as necroptosis, pyroptosis, and ferroptosis[1,2]. Based on morphological, biochemical and functional perspectives, cell death relying on dedicated molecular machinery is defined as regulated cell death (RCD), including apoptosis, ferroptosis, necroptosis, MPTP-dependent necrosis, pyroptosis, autophagy-dependent cell death, entotic cell death, and NETotic cell death. These RCD modes are initiated and propagated by molecular mechanisms that exhibit a considerable degree of interconnectivity.

There is growing evidence that system Xc⁻ modulates a number of RCDs under pathophysiological conditions. To date, ferroptosis, apoptosis, and autophagy-dependent cell death are the most well-studied RCD relevant to system Xc⁻. Among them, apoptosis is a classical form of caspase-dependent cell death, dividing into intrinsic or extrinsic pathways; ferroptosis is a form of RCD initiated by oxidative perturbations of the intracellular microenvironment that is under constitutive control by glutathione peroxidase 4 (GPX4); while autophagy-dependent cell death is a form of RCD that mechanistically depends on the autophagic machinery (or components thereof). Numerous studies have demonstrated that system Xc⁻ plays an important role in ferroptosis[3-7], apoptosis[8-11], as well as autophagy-dependent cell death[12,13]. This review will focus on recent progress in the role of system Xc⁻ in ferroptosis and apoptosis.

System Xc⁻

Structure and Localization of System Xc⁻

System Xc⁻, also referred to cystine/glutamate antiporter, was first reported in human fetal lung fibroblasts in 1980[14], and then a similar transport system was identified in a rat hepatoma cell line[15]. System Xc⁻ consists of the light chain SLC7A11 (xCT) and the 4F2 heavy chain (4F2hc), and they are linked by a disulfide bond. The 4F2hc heavy subunit is common to several amino acid transport systems and can interact with other homologous light chains, for instance, with LAT1 to form a system l neutral amino acid transporter. However, the transport-specific light chain xCT is unique in that and it only interacts with 4F2hc to mediate the cysteine-glutamate exchange. In mouse, system Xc⁻ is widely distributed in the thymus and spleen but it is lowly expressed in lung, heart, liver, and kidney; while in human, system Xc⁻ is highly expressed in the brain and spinal cord, but it is not detected in peripheral leukocytes, spleen, thymus and lymph nodes.

The Physiological Functions of System Xc⁻

The primary function of system Xc⁻ is to import cystine and export glutamate simultaneously with a ratio of 1:1. Usually, system Xc⁻ transfers cystine into the cells, where it is reduced to cysteine immediately. In cells, cysteine and glutamate are utilized to synthetize γ-glutamyl cysteine (γGC) *via* glutamate cysteine ligase (GCL), and to produce glutathione (GSH) by adding glycine under glutathione synthase catalysis. Of note, cysteine is a rate-limiting substrate for generating GSH, an important antioxidant and a vital element of a redox couple maintaining oxidation-reduction balance.

System Xc⁻ possesses dual functions, including control of extracellular glutamate and defense against oxidative stress. On one hand, system Xc⁻plays a key role in preserving glutamate homeostasis in the nervous system. Glutamate exported by system Xc⁻ is largely responsible for the extracellular glutamate concentration in the brain. Disruptions in glutamate homeostasis have been linked to numerous diseased states of the brain and can lead to widespread changes in synaptic activity, called central nervous (CNS) toxicity. On the other hand, the imported cystine *via* system Xc⁻ is important for the endogenous defense system against oxidative stress. Disturbances in the function of system Xc⁻ have been shown to decrease the intracellular cysteine and subsequent glutathione, which results in antioxidant dysfunction concomitant with reactive oxygen species (ROS) overload and lipid peroxidation, leading to cell death and disease ultimately. More information regarding the role of system Xc⁻ in the modulation of glutamate homeostasis can be found in several comprehensive reviews[16-18].

Transcriptional Regulation of System Xc-Light Chain: SLC7A11

Transcriptional regulation of SLC7A11 is one of the most important determinants for system Xc^- activity. Thereby, the physiological function of system Xc^- mainly relies on the SLC7A11 subunit. The transcriptional level of SLC7A11 in cancer cells is significantly higher than that in normal cells. It has been demonstrated that the NRF2-Keap1 pathway is critical for glioma cell growth, which involves in SLC7A11 transcription. Nuclear factor erythroid 2-related factor 2 (Nrf2) dissociates from Kelch-like ECH-associated protein 1 (Keap1), translocates into nucleus, and interacts with antioxidant response element (ARE) in the SLC7A11 promotor, leading to the upregulation of SLC7A11 transcription against oxidative stress[19]. When amino acid starvation leads to phosphorylation of eIF2, activating transcription factor 4 (ATF4) interacts with ARE, leading to tumor proliferation *via* increase of the transcription of SLC7A11. The activating transcription factor 3 (ATF3) enhances erastin-induced ferroptosis through forming ATF3 dimer retaining SLC7A11's transcription. However, ferroptosis promoted by ATF3 is not related to response to oxidative stress[3,20].

There are reports showing that p53 could suppress SLC7A11 mRNA expression *via* modulating certain protein deubiquitination. It has been shown that p53 promotes the nuclear translocation of the deubiquitinase ubiquitin special peptidase 7 (USP7), leading to negatively regulating monoubiquitination of histone H2B on lysine 120 (H2Bub1). Deubiquitinated H2Bub1 occupies the SLC7A11 gene regulatory region and represses the expression of SLC7A11 in the presence of erastin[21]. Similarly, another tumor suppressor, BRCA1-associated protein 1 (BAP1), can also decrease histone 2A ubiquitination (H2Aub). The interaction between H2Aub and BAP1 can retain the transcription of SLC7A11, which represses tumor growth[22]. In addition, PRC1, a major H2Aub ubiquitin ligase, increases the binding of H2Aub to the SLC7A11 promoter. Both BAP1 and PRC1 suppress SLC7A11 expression, revealing that dynamic regulation of H2Aub is important for SLC7A11 repression.

Of note, BAP1 promotes ferroptosis induced by erastin but not by GPX4 inhibitor (RSL3), and BAP1-mediated SLC7A11 repression does not require NRF2 and ATF4 transcription factors[23]. Furthermore, it has been shown that p53 increases the sensibility of ALOX12-dependent ferroptosis by indirectly repressing the transcription of SLC7A11[5]. As a tumor suppressor, ARF inhibits NRF2 or promotes p53 to suppress SLC7A11 transcriptional activation, causing cancer cell demise *via* ferroptosis[24]. The bromodomain 4 protein (BRD4) level in multiple cancer is elevated, accompanied by upregulation of GPX4, SLC7A11, and SLC3A2 and downregulation of ferritin heavy light (FHT), leading to poor prognosis of cancer patients[25]. POU2F1, an octamer transcription factor-1, is associated with anti-cytotoxicity, stem cell function, and cancer tumor deterioration. A recent study illustrated that POU2F1 binding to the SLC7A11 promotor inhibited its transcription in skin pigmentation[4]. The scheme for the transcriptional regulation of SLC7A11 is summarized in Figure 1.

Post-Translational Regulation of SLC7A11

The function of SLC7A11 in ferroptosis is tightly controlled by post-translational regulation. On one hand, AMP-activated protein kinase phosphorylates BECN1 at Ser90/93/96, which accelerates BECN1 binding to SLC7A11 in erastin-treated cells. The formation of BECN1-SLC7A11 complex leads to SLC7A11 dysfunction, accompanied by intracellular lipid peroxidation and ferroptosis in the end[26]. On the other hand, ferroptosis can be triggered due to the change in SLC7A11 stability. CD44 or CD44 variant (CD44v) is stem cell marker in cancer cells. It has been shown that CD44-positive cells promote tumor growth and metastasis through forming CD44-SLC7A11 complex[27], and its stability is affected by certain pathways. Firstly, OTUB1 (ovarian tumor family member deubiquitinase) directly interacts with SLC7A11 and increases the connection between CD44 and SLC7A11, which enhances the stability of CD44-SLC7A11 complex[6,28]. Secondly, the transmembrane protein mucin 1 (MUC1-C) also binds directly to CD44v, which increases the stability of SLC7A11 and maintains the redox balance in triple-negative breast cancer[29]. Finally, an increase of intracellular iron concentration elevates the expression of lipocalin 2 (LCN2), an iron transporter, and antioxidant element, which enhances the interaction between CD44 and SLC7A11 *via* upregulation of both of them, resulting in malignant transformation of tumors[30]. Therefore, increasing the phosphorylation of BECN1 or targeting the MUC1-C/SLC7A11 or SLC7A11/OTUB1 pathway or LCN2 can induce ferroptosis and decrease tumors' survival effec-

tively. The scheme for the post-translational regulation of SLC7A11 is summarized in Figure 2.

The Pathological Roles of System Xc⁻

Relations Among System Xc⁻, Ferroptosis and Cancer

The occurrence of ferroptosis is controlled by multiple signaling pathways, including iron homeostasis pathway, system Xc⁻ pathway, and voltage-dependent anion channel (VDAC) pathway. It is well recognized that the suppression of system Xc⁻ leads to ferroptosis. Erastin, a commonly-used ferroptosis inducer, not only inhibits system Xc⁻ but also blocks VDAC. In the presence of erastin, mitochondria become smaller, and the membrane density is increased due to the inhibition of VDAC2 and VDAC3, concomitant with loss of structural integrity, collapse of the mitochondrial transmembrane potential and overproduction of ROS, resulting in mitochondrial dysfunction and ferroptosis ultimately[31]. Although erastin-induced ferroptosis involves in inhibition of system Xc⁻ as well as VDACs, it is believed that targeting system Xc⁻ plays a major role in this process[32].

The system Xc⁻ expression is upregulated in many tumors, such as glioma[33-35], hand and neck cancers (HNC)[36,37], triple-negative breast cancers (TNBC)[29,38], colorectal carcinoma cancer (CCC)[39], ovarian clear cell carcinoma[30], liver carcinoma[40], oral squamous cell carcinoma[41], and non-small cell lung cancer[42]. There are reports

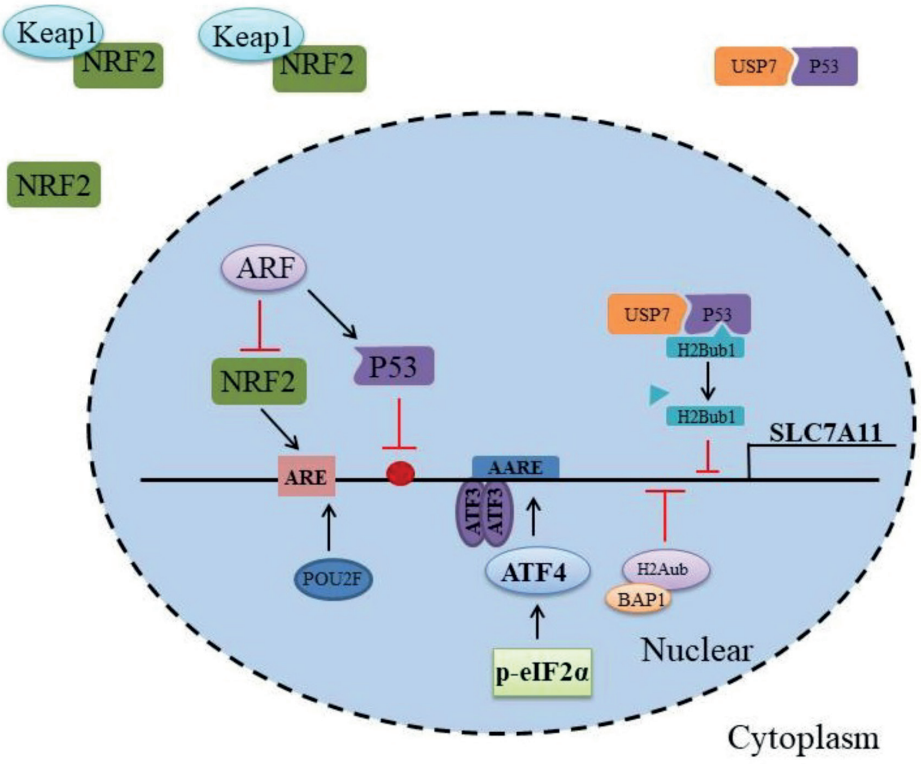


Figure 1. A schematic diagram for transcriptional regulation of SLC7A11. In tumors, NRF2-keap1 and POU2F pathway is activated *via* interacting with antioxidant response element (ARE) while the ATF4 pathway is activated by interacting with amino-acid response element (AARE), leading to the upregulation of SLC7A11 transcription. p53 can block these pathways by binding a cis-regulatory element proximal to ARE; p53 also can promote the nuclear translocation of USP7, leading to H2Bub1 deubiquitination and negatively regulating the transcription of SLC7A11; meanwhile, BAP1 can also remove H2Aub ubiquitination to retain the transcription of SLC7A11; ARF inhibits NRF2 or promotes p53 to suppress SLC7A11 transcriptionally activation simultaneously; and ATF3 dimer enhances the retaining SLC7A11's transcription in erastin-induced ferroptosis. System Xc⁻, cystine/glutamate antiporter; SLC7A11, solute carrier family 7 member 11; NRF2, nuclear factor erythroid 2-related factor 2; keap1, Kelch-like ECH-associated protein 1; POUF2, octamer transcription factor-1; ATF4, activating transcription factor 4; USP7, ubiquitin special peptidase 7; H2Bub1, histone H2B on lysine 120; BAP1, BRCA1-associated protein 1; H2Aub, histone 2A ubiquitination; ARF, p14 alterative reading frame; ATF3, activating transcription factor 3.

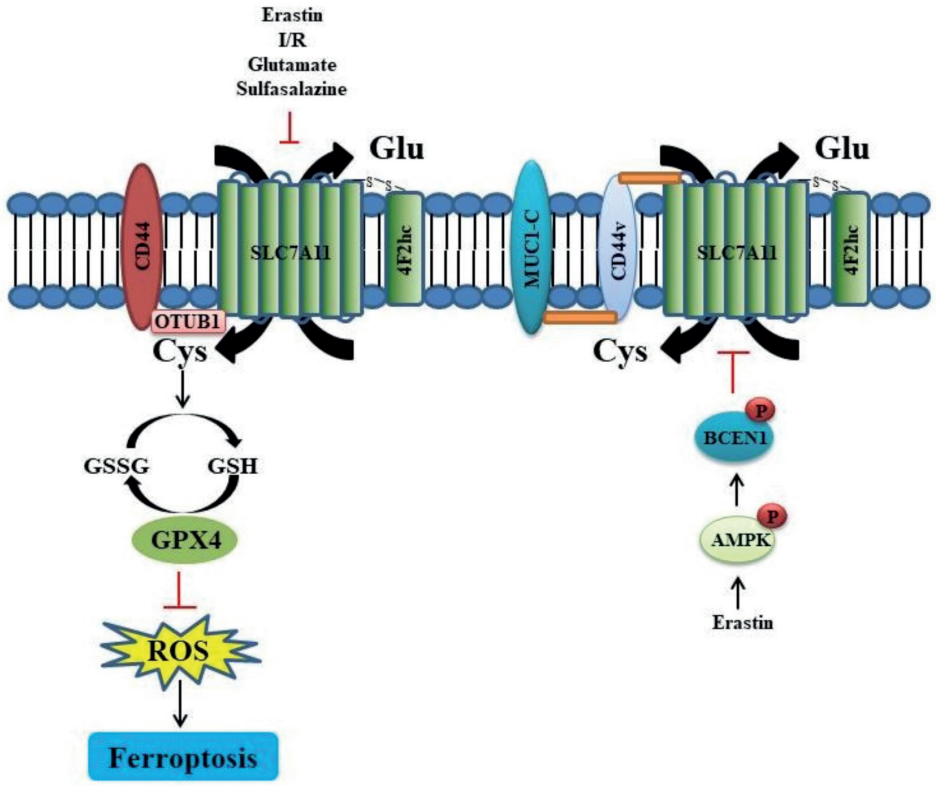


Figure 2. A schematic diagram for post-translational regulation of SLC7A11. Under the conditions of erastin, sulfasalazine, glutamate or ischemia/reperfusion treatment, the function of SLC7A11 is restricted, which decreases the production of GSH and compromise the GPX4 ability to counteract ROS production, leading to ferroptosis. When erastin induces the activation of AMPK, BECN1 is phosphorylated and forms a complex with SLC7A11, causing SLC7A11 dysfunction. However, it will be changed in CD44-positive tumor cells. CD44 (or CD44v)-SLC7A11 complex promotes tumor growth and metastasis, and its stability is affected by OTUB1 and MUC-1, respectively. GSH: glutathione; GPX4: glutathione peroxidase 4; ROS: reactive oxygen species; AMPK: AMP-activated protein kinase; BECN1: beclin 1; OTUB1: OTU deubiquitinase ubiquitin aldehyde-binding 1; MUC-1: mucin 1.

that specific inhibition of the system Xc^- against cystine uptake by erastin can decrease GSH production, which compromises the GPX4 ability to counteract iron-dependent ROS generation and in turn leads to ferroptosis. Thus, suppression of the system Xc^- can promote cancer cell death *via* initialing ferroptosis. As a key component of the system Xc^-, SLC7A11 might be a potential target for the treatment of cancer in clinic[43].

SLC7A11's expression is involved in promoting anti-cancer drug resistance (such as cisplatin resistance) and ferroptosis-inducer can overcome this phenomenon. It had been shown that a very short pre-treatment of erastin can synergize with cisplatin to induce cancer cell death[44]. Sulfasalazine has been reported to decrease the generation of GSH by suppressing SLC7A11. GSH interacts with cisplatin to form a conjugate, which is transferred outside of the cells *via* multidrug resistance-associated protein (MRPs) in tumors. Therefore, repressing the function of SLC7A11 effectively enhanced the intracellular platinum level and cytotoxicity of cisplatin in colorectal cancer (CRC)[45]. In addition, the silence of the SLC7A11 gene in cisplatin-resistant head and neck cancer (HNC) cells led to a significant inhibition of glutamate release and cancer cell viability[36]. Based on these reports, it is likely that a combination of SLC7A11 inhibitor with cisplatin can raise the therapeutic effect on cisplatin-resistant tumors.

Sorafenib is the only ferroptosis inducer approved for the treatment of liver cancer, thyroid cancer, and kidney cancer. There was a report that sorafenib increased the anti-tumor activity of cisplatin in drug resistant HNC cells[46]. In this study, sorafenib or aspirin alone enhanced the toxicity of cisplatin in HNC cells *via* inhibition of SLC7A11

(mRNA and protein) expression, deletion of GSH, accumulation of ROS and damage of DNA *in vitro* and in a tumor xenograft mouse model, and these effects were further enhanced by a combination of sorafenib and aspirin. The mechanisms for the inhibitory effect of sorafinib on SLC7A11 expression remain unclear. Previously, Drayton et al[47] reported that miRNA-27a was able to target SLC7A11 and contributed to cisplatin resistance *via* modulation of GSH biosynthesis. It is not known, however, whether the inhibitory effect of sorafenib on SLC7A11 expression also involves miRNA-27a or not. It is worth mentioning that the application of sorafenib plus aspirin in cancer treatment is reported to overcome resistance to chemotherapy. However, this is based on a limited number of studies, and the efficacy is poor to non-existent. Therefore, research for better strategies is warranted.

Contribution of System Xc⁻ to Ferroptosis in Neurological Disorders

Besides its involvement in ferroptosis of tumors, system Xc⁻ also contributes to ferroptosis in neurological disorders. It has been shown that BECN1-SLC7A11 complex not only plays a pivotal role in tumors but also involves in subarachnoid hemorrhage (SAH) in rats. Inhibition of BECN1-SLC7A11 by siRNA enhanced its antioxidative capacity and ameliorated neurological deficits and brain edema, suggesting that BECN1 modulates ferroptosis through interacting with the system Xc⁻[7]. Actually, ferroptosis also exists in other neurological disorders, such as Alzheimer's disease, ischemic and/or hemorrhagic stroke[48,49]. A number of hydroxylated chalcones have been reported to inhibit amyloid-beta peptide aggregation as well as ferroptosis simultaneously, indicating that chalcones compounds were good inhibitors of erastin-induced ferroptosis and could prevent or slow down Alzheimer's disease[48]. In the ischemic stroke of rodents and humans, SLC7A11 and its function are upregulated, and these effects could last several days. Genetic deletion of SLC7A11 in cortical cells of mice inhibited either oxygen-glucose deprivation/reoxygenation (OGDR) or cerebral ischemia/reperfusion-induced glutamate excitotoxicity-related cell death *in vitro* and *in vivo*[49]; using a mouse model of hemorrhagic stroke, Karuppagounder et al[49] have found that N-acetylcysteine, a cysteine prodrug, prevented hemin-induced ferroptosis *via* neutralizing toxic lipids generated by arachidonate-dependent arachidonate 5-lipoxygenase (ALOX5) activity, and the efficacy of N-acetylcysteine required the increase of glutathione and was correlated with suppression of reactive lipids by glutathione-dependent enzymes such as glutathione S-transferase. These reports confirmed that system Xc⁻ exerts an important role in ferroptosis in cerebral ischemia and/or hemorrhagic stroke.

Actually, system Xc⁻ also plays an important role in the mediation of central nervous system (CNS) toxicity. Oxidative stress, inflammation, mitochondrial dysfunction, and excitotoxicity are key players in the pathogenesis of many neurological diseases/disorders. Two important neurological disorder players are GSH and glutamate. Increased extracellular glutamate levels, which induce excitotoxic damage, can also compromise the proper functioning of system Xc⁻, resulting in GSH depletion and cell death. Piani and Fontana's study[50] demonstrated that neuronal killing by macrophage-mediated glutamate release was dependent on system Xc⁻ activity *in vitro*, firstly showing the neurotoxic potential for this transporter. In addition, the export of glutamate *via* system Xc⁻ from glioma cells produces an excitotoxic necrosis that aids in tumor growth, migration, and invasion both *in vitro* and *in vivo*[51]. These reports support the key role of system Xc⁻ in mediating the CNS excitotoxicity, which might be involved in ferroptosis.

System Xc⁻ and Apoptosis

Apoptosis is a caspase-dependent regulated cell death with the intrinsic and extrinsic pathways. Caspase-3 is the common executioner caspase for both intrinsic and extrinsic pathways of apoptosis[52]. Since system Xc⁻ itself possesses the anti-apoptotic function, the suppression of system Xc⁻ has been repeatedly reported to accelerate the activation of apoptosis pathway. Here are the reports to support the involvement of system Xc⁻ in apoptosis: (1) GSH levels were decreased rapidly while the caspase 3-dependent apoptosis was elevated in the SLC7A11$^{-/-}$ neutrophils cells compared with the wild-type cells[53]; (2) in case of oxidative stress, SLC7A11-deficient cells triggered apoptosis *via* the c-Jun N-terminal kinase (JNK) pathway and the latter induced the caspase-dependent (caspase-9-caspase-3) apoptosis as well as the endoplasmic reticulum (ER) apoptotic signaling pathway (eIF2-CHOP)[54]. Under such condition, TNF receptor-associated protein 1(TRAP1), the member of heat shock protein 90 (HSP90) family located in mitochondria, favors the phosphorylation of eIF2a and attenuates

caspase-dependent translation, which enhances the synthesis of stress-responsive proteins including ATF4 and SLC7A11, attenuating the ER stress, oxidative damage, and nutrient deprivation[8]; (3) in addition to endogenous factors, the change of amino acid content also affects the activity of SLC7A11. On one hand, lysine starvation causes the downregulation of SLC7A11, leading to cell-cycle arrest and apoptosis. On the other hand, excess glutamate regulates chondrogenic differentiation toward mineralization via apoptosis mechanism-mediated the depletion of intracellular GSH after the retrogradation of system Xc^{-}[9,55]; (4) SLC7A11 is highly expressed in Kaposi's sarcoma-associated herpesvirus (KSHV)-infected primary effusion lymphoma (PEL) cell lines, which induce KSHV-infected PEL apoptosis[10]; and (5) the upregulation of miR-375 can inhibit the proliferation and invasion of oral squamous cell carcinoma *via* inhibiting the expression of SLC7A11. The miR-375 directly targeted SLC7A11 3' UTR and suppressed its expression, contributing to the cell cycle arrest in the G0/G1 phase and induced cell apoptosis compared with negative controls[41].

Besides ferroptosis and apoptosis, there is evidence that system Xc^{-} also involves in autophagy-dependent cell death. In hepatocellular carcinoma cells, knockdown of SLC7A11 results in the aggregation of PE-conjugated microtubule-associated protein LC3-II signals with an increase of intracellular ROS levels, following by autophagy-dependent cell death[12,56]; while in sut melanocytes, SLC7A11 deficiency leads to autophagy-dependent cell death *via* activation of p38 MAPK and NF-κB pathways and subsequently inhibiting the functions of Akt/mTOR/p70S6K survival pathways. However, phenyl butyric acid, function as facilitating protein folding and ameliorating endoplasmic reticulum stress, prevents the conversion of LC3 I to LC3 II in SLC7A11-deficient sut melanocytes, further confirming the involvement of system $XcXc^{-}$ in autophagy-dependent cell death[13].

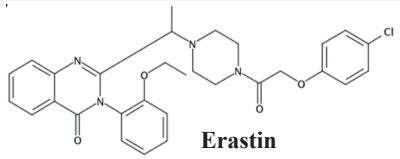
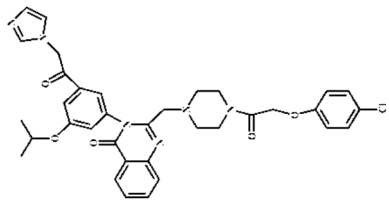
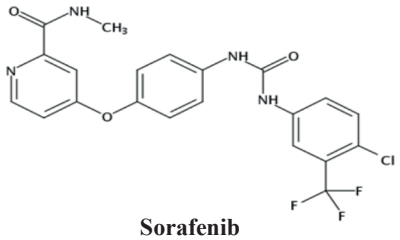
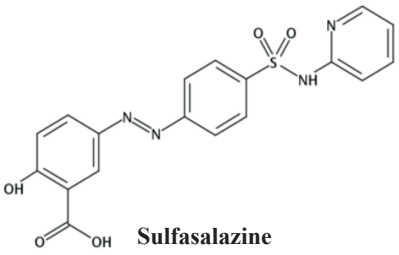
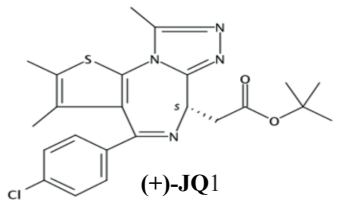
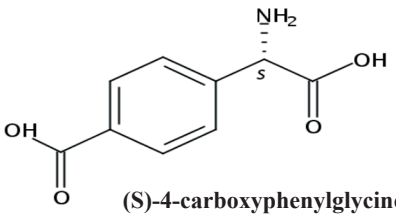
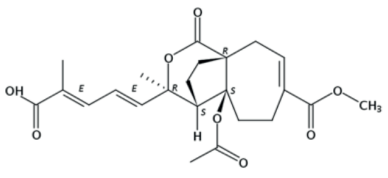
Inhibitors or Activators of System Xc^{-}: the Potential Drugs for Treating Cancer or Neurological Disorders

Due to its involvement in ferroptosis, apoptosis, and autophagy-dependent cell death, system Xc^{-} might be a potential therapeutic target for multiple diseases, particularly for cancer and neurological disorders. To date, a number of potential inhibitors for system Xc^{-} are identified as follows: (1) Erastin, the firstly identified system $XcXc^{-}$ nhibitor, is frequently used to induce ferroptosis[20,21,26,28,44]. Imidazole ketone erastin, an erastin analogue, also exerts anti-tumor effect *via* inhibition of system Xc^{-}, leading to GSH depletion and lipid peroxidation in a diffuse large B cell lymphoma[57]; (2) Sorafenib, a new type of oral anti-cancer drug, dramatically reduces plasmodium liver stage parasite infection *via* downregulation of SLC7A11[58]; (3) Sulfasalazine, an FDA approved anti-inflammatory drug, retains the activity of SLC7A11 and prevents KSHV plus PEL cells progression[10]. Meanwhile, sulfasalazine selectively kill the CD44v-expressing cells, enhancing the cytotoxicity of cisplatin[27]; (4) (+)-JQ1, an inhibitor of BRD4, can downregulate the GPX4, SLC7A11 and SLC3A2, and increase the anti-cancer function of erastin- or RSL3-induced ferroptosis[25]; (5) (S)-4-carboxyphenylglycine is able to inhibit cysteine uptake by inhibiting system Xc^{-} [59]; and (6) Pseudolaric acid B, a natural compound, can deplete intracellular GSH *via* p53-mediated SLC7A11 pathway, which further exacerbates accumulation of H_2O_2 and lipid peroxides in glioma cells[60].

Although the above-mentioned system Xc^{-} inhibitors all possess anti-tumor activity on certain cancer cells, their clinical potentials are varied. As the most commonly used system Xc^{-} inhibitor, erastin's clinical prospect is dim due to the poor water solubility and renal toxicity[61]. Compare to erastin, imidazole ketone erastin, a derivative of erastin, shows an increased potency (about 100-fold over erastin), solubility, and stability, making it an attractive molecule for *in vivo* preclinical study[57]. As a selective BET bromodomain inhibitor, (+)-JQ1 shows effects on tumor growth and survival, cell cycle arrest, and differentiation[62,63]. Some BET inhibitors structurally similar to (+)-JQ1 are being tested in clinical trials for a variety of cancers[64]. More information regarding the possible system Xc^{-} inhibitors and therapeutic potentials are summarized in Table I.

In addition to the inhibitors of system Xc^{-} inhibitor, several potential activators of system Xc^{-} have also been reported. SRS 16-86 can recover spinal cord injury from ferroptosis through the upregulation of SLC7A11 and GPX4, accompanied by downregulation of 4-HNE production and lipid peroxidation[65,66]; lactacystin, a proteasome inhibitor, elevates the mRNA and protein levels of SLC7A11, resulting in the proliferation of colorectal cancer cells[39]; pituitary adenylate cyclase-activating polypeptide activates system Xc^{-}, which can convey signals to astrocytes at

Table I. System Xc^- inhibitors and therapeutic potentials.

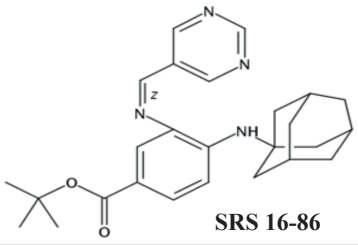
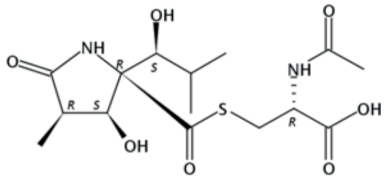
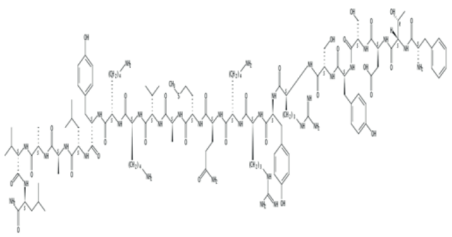
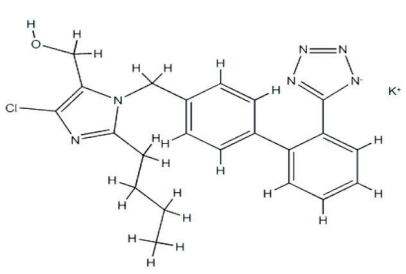
Chemical structure	Molecular formula	Pharmacological actions	Ref
 **Erastin**	$C_{30}H_{31}ClN_4O4$	Irreversible inhibitor of system Xc^-, exert anti-tumor effect via inducing ferroptosis.	[23,25,27,30,41]
 **Imidazole Ketone Erastin**	$C_{35}H_{35}ClN_6O_5$	Erastin analogue, slowing tumor growth in a diffuse large B cell lymphoma.	[57]
 **Sorafenib**	$C_{21}H_{16}ClF_3N_4O_3$	Oral anti-cancer drug, reducing plasmodium liver stage parasite infection and cisplatin resistance in head and neck cancer cells.	[44,58]
 **Sulfasalazine**	$C_{18}H_{14}N_4O_5S$	Anti-inflammatory drug, retain KSHV plus PEL cells and CD44v- positive cancer cell progression as well as cisplatin resistance in colorectal cancer.	[3,6,7,11,58]
 **(+)-JQ1**	$C_{23}H_{25}ClN_4O_2S$	Increasing the anti-cancer function of erastin- or RSL3-induced ferroptosis.	[21]
 **(S)-4-carboxyphenylglycine**	$C_9H_9NO_4$	Decreasing cystine uptake in primary neurons cells and intestinal epithelial cells.	[59,67]
 **Pseudolaric acid B**	$C_{23}H_{28}O_8$	Exacerbating accumulation of H_2O_2 and lipid peroxides in glioma cells.	[60]

the synapse by PACAP/ vasoactive intestinal polypeptide (VIP) signal[59]; and erythropoietin plays a role in red blood production, which mediates cytoprotection in intestinal epithelial cells *via* activation of system Xc^{-}[67,68]. The possible system Xc^{-} activators and therapeutic potentials are summarized in Table II.

Conclusions

Cell death is the most common biological phenomenon under physiological or pathological conditions. Thus, promotion of cell death (such as anti-cancer therapy) or prevention of cell death (such as anti-infarction therapy) is an important strategy for disease treatment. Identification of the signaling pathways that involve in the regulation of cell death is the first step to provide the targets for drug development. Here, we provide evidence to support the role of system Xc^{-} in regulated cell death, including ferroptosis, apoptosis, and autophagy-dependent cell death. As an antiporter for cysteine and glutamate, system Xc^{-} plays a key role in maintaining intracellular GSH homeostasis directly and ROS homeostasis indirectly. Its role in

Table II. Possible system Xc^{-} activators and therapeutic potentials.

Chemical structure	Molecular formula	Pharmacological actions	Ref
 SRS 16-86	$C_{26}H_{32}N_4O_2$	Promoting functional recovery in contusion spinal cord injury.	65
 Lactacystin	$C_{15}H_{24}N_2O_7S$	Defending colorectal cancer cells against oxidative stress	34
 Pituitary adenylate cyclase-activating polypeptide	$C_{121}H_{193}N_{33}O_{31}S$	Enhancing cystine uptake in astrocytic for treatment of neurological disorders.	59
 Erythropoietin	$C_{22}H_{22}ClKN_6O$	Mediating cytoprotection in intestinal epithelial cells as well as neuroprotective effect in B104 cell line.	67,68

the regulation of ferroptosis was immerging with Dixon et al[32] report in 2012 because system Xc^- specific inhibitor (erastin)-induced cell death could be attenuated by iron chelator (deferoxamine). In addition to its key role in ferroptosis, system Xc^- was also reported to be involved in apoptosis and autophagy-dependent cell death. To date, system Xc^--relevant regulated cell death has been found to play an important role in cancer, neurodegenerative diseases, myocardial infarction, and stroke. While the intervention of system Xc^- by inhibitor or activator has achieved a beneficial effect on anti-cancer or anti-infarction therapy, there is still a long way to go before translating these findings into clinical applications.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 81872873 to Jun Peng; No. 82073849 to Xiu-Ju Luo).

References

1) Tian J, Guo S, Chen H, Peng JJ, Jia MM, Li NS, Zhang XJ, Yang J, Luo XJ, Peng J. Combination of emricasan with ponatinib synergistically reduces ischemia/reperfusion injury in rat brain through simultaneous prevention of apoptosis and necroptosis. Transl Stroke Res 2018; 9: 382-392.
2) She L, Tu H, Zhang YZ, Tang LJ, Li NS, Ma QL, Liu B, Li Q, Luo XJ, Peng J. Inhibition of phosphoglycerate mutase 5 reduces necroptosis in rat hearts following ischemia/reperfusion through suppression of dynamin-related protein 1. Cardiovasc Drugs Ther 2019; 33: 13-23.
3) Chen D, Fan Z, Rauh M, Buchfelder M, Eyupoglu IY, Savaskan N. ATF4 promotes angiogenesis and neuronal cell death and confers ferroptosis in a xCT-dependent manner. Oncogene 2017; 36: 5593-5608.
4) Chen Y, Hu S, Mu L, Zhao B, Wang M, Yang N, Bao G, Zhu C, Wu X. Slc7a11 modulated by POU2F1 is involved in pigmentation in rabbit. Int J Mol Sci 2019; 20.
5) Chu B, Kon N, Chen D, Li T, Liu T, Jiang L, Song S, Tavana O, Gu W. ALOX12 is required for p53-mediated tumour suppression through a distinct ferroptosis pathway. Nat Cell Biol 2019; 21: 579-591.
6) Gan B. DUBbing ferroptosis in cancer cells. Cancer Res 2019; 79: 1749-1750.
7) Guo Y, Liu X, Liu D, Li K, Wang C, Liu Y, He B, Shi P. Inhibition of BECN1 suppresses lipid peroxidation by increasing System Xc(-) activity in early brain injury after subarachnoid hemorrhage. J Mol Neurosci 2019; 67: 622-631.
8) Matassa DS, Amoroso MR, Agliarulo I, Maddalena F, Sisinni L, Paladino S, Romano S, Romano MF, Sagar V, Loreni F, Landriscina M, Esposito F. Translational control in the stress adaptive response of cancer cells: a novel role for the heat shock protein TRAP1. Cell Death Dis 2013; 4: e851.
9) Yin J, Li Y, Han H, Zheng J, Wang L, Ren W, Chen S, Wu F, Fang R, Huang X, Li C, Tan B, Xiong X, Zhang Y, Liu G, Yao J, Li T, Yin Y. Effects of lysine deficiency and Lys-Lys dipeptide on cellular apoptosis and amino acids metabolism. Mol Nutr Food Res 2017; 61(9).
10) Dai L, Cao Y, Chen Y, Parsons C, Qin Z. Targeting xCT, a cystine-glutamate transporter induces apoptosis and tumor regression for KSHV/HIV-associated lymphoma. J Hematol Oncol 2014; 7: 30.
11) Hu K, Li K, Lv J, Feng J, Chen J, Wu H, Cheng F, Jiang W, Wang J, Pei H, Chiao PJ, Cai Z, Chen Y, Liu M, Pang X. Suppression of the SLC7A11/glutathione axis causes synthetic lethality in KRAS-mutant lung adenocarcinoma. J Clin Invest 2020; 130: 1752-1766.
12) Guo W, Zhao Y, Zhang Z, Tan N, Zhao F, Ge C, Liang L, Jia D, Chen T, Yao M, Li J, He X. Disruption of xCT inhibits cell growth via the ROS/autophagy pathway in hepatocellular carcinoma. Cancer Lett 2011; 312: 55-61.
13) Zheng X, Li Y, Zhao R, Yan F, Ma Y, Zhao L, Qiao H. xCT deficiency induces autophagy via endoplasmic reticulum stress activated p38-mitogen-activated protein kinase and mTOR in sut melanocytes. Eur J Cell Biol 2016; 95: 175-181.
14) Bannai S, Kitamura E. Transport interaction of L-cystine and L-glutamate in human diploid fibroblasts in culture. J Biol Chem 1980; 255: 2372-2376.
15) Makowske M, Christensen HN. Contrasts in transport systems for anionic amino acids in hepatocytes and a hepatoma cell line HTC. J Biol Chem 1982; 257: 5663-5670.
16) Reissner KJ, Kalivas PW. Using glutamate homeostasis as a target for treating addictive disorders. Behav Pharmacol 2010; 21: 514-522.
17) Massie A, Boillee S, Hewett S, Knackstedt L, Lewerenz J. Main path and byways: non-vesicular glutamate release by system xc(-) as an important modifier of glutamatergic neurotransmission. J Neurochem 2015; 135: 1062-1079.
18) Bridges R, Lutgen V, Lobner D, Baker DA. Thinking outside the cleft to understand synaptic activity: contribution of the cystine-glutamate antiporter (System xc-) to normal and pathological glutamatergic signaling. Pharmacol Rev 2012; 64: 780-802.
19) Qaisiya M, Coda ZCD, Bellarosa C, Tiribelli C. Bilirubin mediated oxidative stress involves antioxidant response activation via Nrf2 pathway. Cell Signal 2014; 26: 512-520.
20) Wang L, Liu Y, Du T, Yang H, Lei L, Guo M, Ding HF, Zhang J, Wang H, Chen X, Yan C. ATF3 pro-

motes erastin-induced ferroptosis by suppressing system Xc. Cell Death Differ 2020; 27: 662-675.

21) Wang Y, Yang L, Zhang X, Cui W, Liu Y, Sun QR, He Q, Zhao S, Zhang GA, Wang Y, Chen S. Epigenetic regulation of ferroptosis by H2B monoubiquitination and p53. EMBO Rep 2019; 20: e47563.

22) Zhang Y, Zhuang L, Gan B. BAP1 suppresses tumor development by inducing ferroptosis upon SLC7A11 repression. Mol Cell Oncol 2019; 6: 1536845.

23) Zhang Y, Koppula P, Gan B. Regulation of H2A ubiquitination and SLC7A11 expression by BAP1 and PRC1. Cell Cycle 2019; 18: 773-783.

24) Chen D, Tavana O, Chu B, Erber L, Chen Y, Baer R, Gu W. NRF2 is a major target of ARF in p53-independent tumor suppression. Mol Cell 2017; 68: 224-232.e224.

25) Sui S, Zhang J, Xu S, Wang Q, Wang P, Pang D. Ferritinophagy is required for the induction of ferroptosis by the bromodomain protein BRD4 inhibitor (+)-JQ1 in cancer cells. Cell Death Dis 2019; 10: 331.

26) Song X, Zhu S, Chen P, Hou W, Wen Q, Liu J, Xie Y, Liu J, Klionsky DJ, Kroemer G, Lotze MT, Zeh HJ, Kang R, Tang D. AMPK-mediated BECN1 phosphorylation promotes ferroptosis by directly blocking System Xc(-) activity. Curr Biol 2018; 28: 2388-2399.

27) Yoshikawa M, Tsuchihashi K, Ishimoto T, Yae T, Motohara T, Sugihara E, Onishi N, Masuko T, Yoshizawa K, Kawashiri S, Mukai M, Asoda S, Kawana H, Nakagawa T, Saya H, Nagano O. xCT inhibition depletes CD44v-expressing tumor cells that are resistant to EGFR-targeted therapy in head and neck squamous cell carcinoma. Cancer Res 2013; 73: 1855-1866.

28) Liu T, Jiang L, Tavana O, Gu W. The deubiquitylase OTUB1 mediates ferroptosis via stabilization of SLC7A11. Cancer Res 2019; 79: 1913-1924.

29) Hasegawa M, Takahashi H, Rajabi H, Alam M, Suzuki Y, Yin L, Tagde A, Maeda T, Hiraki M, Sukhatme VP, Kufe D. Functional interactions of the cystine/glutamate antiporter, CD44v and MUC1-C oncoprotein in triple-negative breast cancer cells. Oncotarget 2016; 7: 11756-11769.

30) Yamada Y, Miyamoto T, Kashima H, Kobara H, Asaka R, Ando H, Higuchi S, Ida K, Shiozawa T. Lipocalin 2 attenuates iron-related oxidative stress and prolongs the survival of ovarian clear cell carcinoma cells by up-regulating the CD44 variant. Free Radic Res 2016; 50: 414-425.

31) Yagoda N, von Rechenberg M, Zaganjor E, Bauer AJ, Yang WS, Fridman DJ, Wolpaw AJ, Smukste I, Peltier JM, Boniface JJ, Smith R, Lessnick SL, Sahasrabudhe S, Stockwell BR. RAS-RAF-MEK-dependent oxidative cell death involving voltage-dependent anion channels. Nature 2007; 447: 864-868.

32) Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, Patel DN, Bauer AJ, Cantley AM, Yang WS, Morrison BR, Stockwell BR. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell 2012; 149: 1060-1072.

33) Haryu S, Saito R, Jia W, Shoji T, Mano Y, Sato A, Kanamori M, Sonoda Y, Sampetrean O, Saya H, Tominaga T. Convection-enhanced delivery of sulfasalazine prolongs survival in a glioma stem cell brain tumor model. J Neurooncol 2018; 136: 23-31.

34) Wang XY, Li YL, Wang HY, Zhu M, Guo D, Wang GL, Gao YT, Yang Z, Li T, Yang CY, Chen YM. Propofol inhibits invasion and proliferation of C6 glioma cells by regulating the Ca(2+) permeable AMPA receptor-system xc(-) pathway. Toxicol In Vitro 2017; 44: 57-65.

35) Arensman MD, Yang XS, Leahy DM, Toral-Barza L, Mileski M, Rosfjord EC, Wang F, Deng S, Myers JS, Abraham RT, Eng CH. Cystine-glutamate antiporter xCT deficiency suppresses tumor growth while preserving antitumor immunity. Proc Natl Acad Sci U S A 2019; 116: 9533-9542.

36) Roh JL, Kim EH, Jang HJ, Park JY, Shin D. Induction of ferroptotic cell death for overcoming cisplatin resistance of head and neck cancer. Cancer Lett 2016; 381: 96-103.

37) Kim EH, Shin D, Lee J, Jung AR, Roh JL. CISD2 inhibition overcomes resistance to sulfasalazine-induced ferroptotic cell death in head and neck cancer. Cancer Lett 2018; 432: 180-190.

38) Timmerman LA, Holton T, Yuneva M, Louie RJ, Padro M, Daemen A, Hu M, Chan DA, Ethier SP, van T VLJ, Polyak K, McCormick F, Gray JW. Glutamine sensitivity analysis identifies the xCT antiporter as a common triple-negative breast tumor therapeutic target. Cancer Cell 2013; 24: 450-465.

39) Huseby NE, Ravuri C, Moens U. The proteasome inhibitor lactacystin enhances GSH synthesis capacity by increased expression of antioxidant components in an Nrf2-independent, but p38 MAPK-dependent manner in rat colorectal carcinoma cells. Free Radic Res 2016; 50: 1-13.

40) Zhang L, Huang Y, Ling J, Zhuo W, Yu Z, Luo Y, Zhu Y. Overexpression of SLC7A11: a novel oncogene and an indicator of unfavorable prognosis for liver carcinoma. Future Oncol 2018; 14: 927-936.

41) Wu Y, Sun X, Song B, Qiu X, Zhao J. MiR-375/SLC7A11 axis regulates oral squamous cell carcinoma proliferation and invasion. Cancer Med 2017; 6: 1686-1697.

42) Ji X, Qian J, Rahman SMJ, Siska PJ, Zou Y, Harris BK, Hoeksema MD, Trenary IA, Heidi C, Eisenberg R, Rathmell JC, Young JD, Massion PP. xCT (SLC7A11)-mediated metabolic reprogramming promotes non-small cell lung cancer progression. Oncogene 2018; 37: 5007-5019.

43) Lewerenz J, Hewett SJ, Huang Y, Lambros M, Gout PW, Kalivas PW, Massie A, Smolders I,

Methner A, Pergande M, Smith SB, Ganapathy V, Maher P. The cystine/glutamate antiporter system x(c)(-) in health and disease: from molecular mechanisms to novel therapeutic opportunities. Antioxid Redox Signal 2013; 18: 522-555.

44) Sato M, Kusumi R, Hamashima S, Kobayashi S, Sasaki S, Komiyama Y, Izumikawa T, Conrad M, Bannai S, Sato H. The ferroptosis inducer erastin irreversibly inhibits system xc- and synergizes with cisplatin to increase cisplatin's cytotoxicity in cancer cells. Sci Rep 2018; 8: 968.

45) Ma MZ, Chen G, Wang P, Lu WH, Zhu CF, Song M, Yang J, Wen S, Xu RH, Hu Y, Huang P. Xc- inhibitor sulfasalazine sensitizes colorectal cancer to cisplatin by a GSH-dependent mechanism. Cancer Lett 2015; 368: 88-96.

46) Roh JL, Kim EH, Jang H, Shin D. Aspirin plus sorafenib potentiates cisplatin cytotoxicity in resistant head and neck cancer cells through xCT inhibition. Free Radic Biol Med 2017; 104: 1-9.

47) Drayton RM, Dudziec E, Peter S, Bertz S, Hartmann A, Bryant HE, Catto JW. Reduced expression of miRNA-27a modulates cisplatin resistance in bladder cancer by targeting the cystine/glutamate exchanger SLC7A11. Clin Cancer Res 2014; 20: 1990-2000.

48) Cong L, Dong X, Wang Y, Deng Y, Li B, Dai R. On the role of synthesized hydroxylated chalcones as dual functional amyloid-beta aggregation and ferroptosis inhibitors for potential treatment of Alzheimer's disease. Eur J Med Chem 2019; 166: 11-21.

49) Karuppagounder SS, Alin L, Chen Y, Brand D, Bourassa MW, Dietrich K, Wilkinson CM, Nadeau CA, Kumar A, Perry S, Pinto JT, Darley-Usmar V, Sanchez S, Milne GL, Pratico D, Holman TR, Carmichael ST, Coppola G, Colbourne F, Ratan RR. N-acetylcysteine targets 5 lipoxygenase-derived, toxic lipids and can synergize with prostaglandin E2 to inhibit ferroptosis and improve outcomes following hemorrhagic stroke in mice. Ann Neurol 2018; 84: 854-872.

50) Piani D, Fontana A. Involvement of the cystine transport system xc- in the macrophage-induced glutamate-dependent cytotoxicity to neurons. J Immunol 1994; 152: 3578-3585.

51) Lyons SA, Chung WJ, Weaver AK, Ogunrinu T, Sontheimer H. Autocrine glutamate signaling promotes glioma cell invasion. Cancer Res 2007; 67: 9463-9471.

52) Hua L, Wang FQ, Du HW, Fan J, Wang YF, Wang LQ, Shi XW. Upregulation of caspase-3 by high glucose in chondrocyte involves the cytoskeleton aggregation. Eur Rev Med Pharmacol Sci 2020; 24: 5925-5932.

53) Sakakura Y, Sato H, Shiiya A, Tamba M, Sagara J, Matsuda M, Okamura N, Makino N, Bannai S. Expression and function of cystine/glutamate transporter in neutrophils. J Leukoc Biol 2007; 81: 974-982.

54) Qiao HX, Hao CJ, Li Y, He X, Chen RS, Cui J, Xu ZH, Li W. JNK activation mediates the apoptosis of xCT-deficient cells. Biochem Biophys Res Commun 2008; 370: 584-588.

55) Wang L, Hinoi E, Takemori A, Nakamichi N, Yoneda Y. Glutamate inhibits chondral mineralization through apoptotic cell death mediated by retrograde operation of the cystine/glutamate antiporter. J Biol Chem 2006; 281: 24553-24565.

56) Sun B, Xu Y, Liu ZY, Meng WX, Yang H. Autophagy assuages myocardial infarction through Nrf2 signaling activation-mediated reactive oxygen species clear. Eur Rev Med Pharmacol Sci 2020; 24: 7381-7390.

57) Zhang Y, Tan H, Daniels JD, Zandkarimi F, Liu H, Brown LM, Uchida K, O'Connor OA, Stockwell BR. Imidazole ketone erastin induces ferroptosis and slows tumor growth in a mouse lymphoma model. Cell Chem Biol 2019; 26: 623-633.

58) Kain HS, Glennon EKK, Vijayan K, Arang N, Douglass AN, Fortin CL, Zuck M, Lewis AJ, Whiteside SL, Dudgeon DR, Johnson JS, Aderem A, Stevens KR, Kaushansky A. Liver stage malaria infection is controlled by host regulators of lipid peroxidation. Cell Death Differ 2020; 27: 44-54.

59) Resch JM, Albano R, Liu X, Hjelmhaug J, Lobner D, Baker DA, Choi S. Augmented cystine-glutamate exchange by pituitary adenylate cyclase-activating polypeptide signaling via the VPAC1 receptor. Synapse 2014; 68: 604-612.

60) Wang Z, Ding Y, Wang X, Lu S, Wang C, He C, Wang L, Piao M, Chi G, Luo Y, Ge P. Pseudolaric acid B triggers ferroptosis in glioma cells via activation of Nox4 and inhibition of xCT. Cancer Lett 2018; 428: 21-33.

61) Yu M, Gai C, Li Z, Ding D, Zheng J, Zhang W, Lv S, Li W. Targeted exosome-encapsulated erastin induced ferroptosis in triple negative breast cancer cells. Cancer Sci 2019; 110: 3173-3182.

62) Jostes S, Nettersheim D, Fellermeyer M, Schneider S, Hafezi F, Honecker F, Schumacher V, Geyer M, Kristiansen G, Schorle H. The bromodomain inhibitor JQ1 triggers growth arrest and apoptosis in testicular germ cell tumours in vitro and in vivo. J Cell Mol Med 2017; 21: 1300-1314.

63) Lee S, Rellinger EJ, Kim KW, Craig BT, Romain CV, Qiao J, Chung DH. Bromodomain and extraterminal inhibition blocks tumor progression and promotes differentiation in neuroblastoma. Surgery 2015; 158: 819-826.

64) Alqahtani A, Choucair K, Ashraf M, Hammouda DM, Alloghbi A, Khan T, Senzer N, Nemunaitis J. Bromodomain and extra-terminal motif inhibitors: a review of preclinical and clinical advances in cancer therapy. Future Sci OA 2019; 5: FSO372.

65) Zhang Y, Sun C, Zhao C, Hao J, Zhang Y, Fan B, Li B, Duan H, Liu C, Kong X, Wu P, Yao X, Feng S. Ferroptosis inhibitor SRS 16-86 attenuates ferroptosis and promotes functional recov-

ery in contusion spinal cord injury. Brain Res 2019; 1706: 48-57.

66) Yao X, Zhang Y, Hao J, Duan HQ, Zhao CX, Sun C, Li B, Fan BY, Wang X, Li WX, Fu XH, Hu Y, Liu C, Kong XH, Feng SQ. Deferoxamine promotes recovery of traumatic spinal cord injury by inhibiting ferroptosis. Neural Regen Res 2019; 14: 532-541.

67) Martin C, Patel M, Melendez-Ferro M, Sims B. Erythropoietin-induced cytoprotection in intestinal epithelial cells is linked to system Xc. Exp Cell Res 2017; 352: 202-206.

68) Sims B, Clarke M, Njah W, Hopkins ES, Sontheimer H. Erythropoietin-induced neuroprotection requires cystine glutamate exchanger activity. Brain Res 2010; 1321: 88-95.