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Transcriptional Regulation of SLC7A11 /xCT in Ferroptosis: A Brief Commentary

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1. Abstract

Solute carrier family 7 member 11 (SLC7A11, also known as xCT), which is the substrate-specific subunit of cystine/glutamate antiporter protects cancer cells from oxidative stress and ferroptosis through upregulating cystine uptake and glutathione biosynthesis. The expression and activity of SLC7A11 is governed by diverse mechanisms, such as transcriptional regulation and posttranslational modification. In this commentary, we mainly summarize transcriptional regulation of SLC7A11 in both cancer cells and cancer stem cells and highlight ferroptosis-dependent functions of SLC7A11 in promoting tumor development.

2. Introduction

Ferroptosis is an iron-dependent form of regulated cell death [1]. Differing from other types of cell death, such as apoptosis [2], necroptosis [3], pyroptosis [4], and autophagy [5], ferroptosis is characterized by aberrant accumulation of lipid hydroperoxides and membrane damage [6, 7]. Emerging evidences reveal that this unique cell death modality is implicated in various pathological diseases, including neurodegenerative disorders [8], ischemia reperfusion injury [9] and tumorigenesis [6]. Therefore, targeting ferroptosis may yield significantly clinical benefit for certain disease.

Over the decades, numerous studies have elucidated the mechanisms governing ferroptosis [6, 10]. Among them, homeostasis of intracellular cysteine plays vital roles in protecting cells from ferroptosis [11]. Solute carrier family 7 member 11 (SLC7A11), a key component of the system X_c^- (cystine/glutamate antiporter), is critical to maintain redox homeostasis [12]. A wealth of studies has shed light on the mechanisms by which cysteine-glutathione-GPX4 axis regulates ferroptosis [13]. Hereby, we will focus on recent advances in the understanding of how transcriptional regulation of SLC7A11 affect ferroptosis.

Human *SLC7A11* gene is located on chromosome 4 and is conserved across vertebrates. SLC7A11 is a 12-

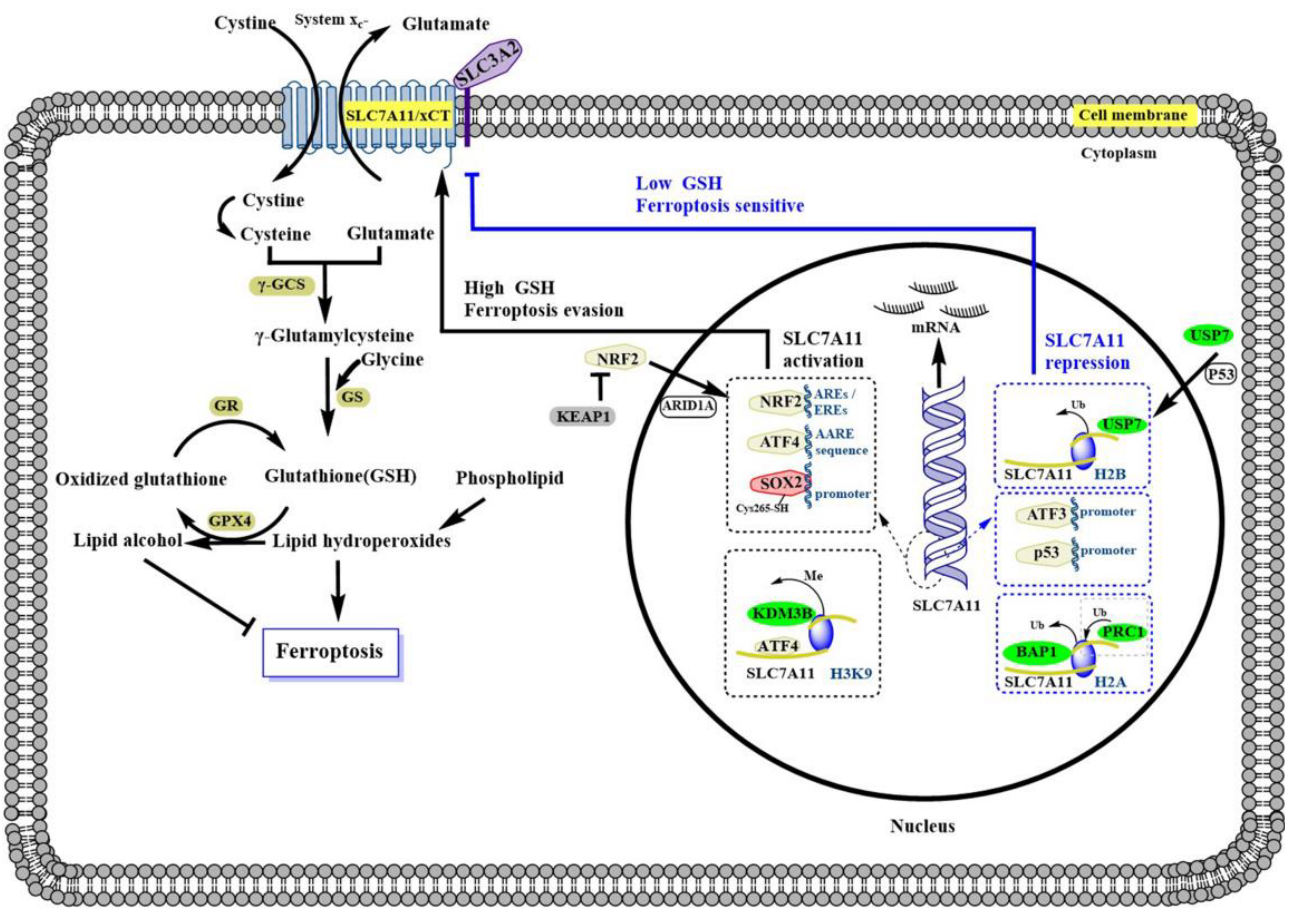

Figure 1. Regulations of SLC7A11/ xCT in ferroptosis. SLC7A11 imports extracellular cystine and exports intracellular glutamate. Imported cystine covers to cysteine which is then utilized to synthesize GSH through the addition of glycine. Subsequently, the accumulation of lipid hydroperoxides in cellular membrane induced ferroptosis. Whereas ferroptosis is suppressed due to the production of lipid alcohols by GPX4 through utilizing GSH. NRF2, ATF4 and SOX2 bind to the SLC7A11 promoter and upregulate its expression. ATF3 and p53 bind to the SLC7A11 promoter and repress its expression. KDM3B cooperating with ATF4, upregulates SLC7A11 through removing methyl from H3K9. BAP1 removes H2Aub, PRC1 induces H2Aub. and USP7 increases H2B ubiqutination to suppress SLC7A11 expression. ATF4, activating transcriptional factor 4; NRF2, nuclear factor erythroid 2-related factor 2; SOX2, Sry-related HMG box protein 2; BAP1, BRCA1-associated protein 1; USP7, ubiquitin Specific Peptidase 7; AREs, antioxidant response elements; ARID1A, AT-rich interacting domain-containing protein 1A; H2Aub, H2A ubiquitination; H3K9, Histone H3 lysine 9.

pass transmembrane protein with both N- and C-termini located within the cytoplasm [14, 15] (**Figure 1**). SLC7A11 (the catalytic subunit) and SLC3A2 (the chaperon subunit) compose the system X_c^-, which takes up extracellular cystine in exchange for intracellular glutamate at a 1:1 ratio [16] (**Figure 1**). Both of these two subunits are essential for mediating the activity of system X_c^-. SLC7A11 is responsible for regulating cystine/ glutamate antiporter activity, whereas SLC3A2 primarily regulate trafficking of SLC7A11 to the plasma membrane [17]. As shown in Figure 1, extracellular cystine is transported into the cell through SLC7A11, and then is converted to cysteine. Subsequently, cysteine is utilized to synthesize GSH through the formation of γ-glutamylcysteine and the addition of glycine. Ferroptosis is induced by excessive accumulation of lipid hydroperoxides. Rather, GPX4 reduce lipid hydroperoxides to lipid alcohols through utilizing GSH, thereby suppressing ferroptosis.

3. Transcriptional regulation of SLC7A11

The expression and activity of SLC7A11 is regulated by various mechanisms, including transcriptional regulation, epigenetic modification and posttranslational modification [12]. Hereby, we primarily summarize the transcriptional regulation of SLC7A11 by diverse transcriptional and epigenetic factors under various physiological and pathological conditions.

3.1 Transcriptional regulation of SLC7A11 under stress conditions

Cells can respond to various stress conditions, such as oxidative stress [18], amino acid limitation and metabolic stress [19]. Under oxidative stress, the extracellular cystine is imported into cells through SLC7A11 to produce GSH resulting in suppression of ferroptosis [20]. Many transcriptional factors are involved in manipulating SLC7A11 expression and activity under stress conditions.

ATF4, a regulator of the cellular stress response, controls the expression of many adaptive genes that allow cells to endure stress [21]. It was found that ATF/ CEBP families bind the AARE sequence in gene promoters and activate transcription [22]. ATF4 is involved in SLC7A11 expression under amino acid starvation [23]. Overexpression of SLC7A11 regulated by ATF4 increases the sensitivity of cancer cells to glucose starvation-induced cell death [24], and confers resistance to ferroptosis in cancer cells [25]. ATF3, another member of ATF family, also can bind the promoter of SLC7A11. However, ATF3 decreases expression of SLC7A11, which thus promotes the erastin-induced ferroptosis [26].

NRF2, a critical modulator of oxidative homeostasis, is produced in response to elevated oxidative stress [27]. It negatively regulates ferroptosis via modulating SLC7A11 expression levels [28]. Various genes on the ferroptosis cascade are targets of NRF2 [29]. NRF2 binds to the AREs, and stimulates the expression of ARE-dependent genes to maintain homeostasis of cellular redox [30]. The activity of NRF2 is directly regulated by a negative regulator Keap1 [31]. The NRF2-Keap1 pathway was reported to accelerate oncogenic progression [32]. The upregulation of NRF2 and inhibition of Keap1 promote resistance to ferroptosis by activating SLC7A11 [32].

3.2 Transcriptional regulation of SLC7A11 in cancer

It is well established that SLC7A11 is a central hinge connecting ferroptosis and tumor suppression [12]. p53, the most mutated tumor suppressor in human cancers, is discovered to repress SLC7A11 expression and thus induce ferroptosis [33]. BAP1, another tumor suppressor, promotes ferroptosis by suppressing SLC7A11 transcription [34, 35]. Cancer-associated BAP1 mutations could abrogate their abilities to suppress SLC7A11 expression and induce ferroptosis [35]. KRAS, one of the most mutated oncogenes in human cancers, promotes SLC7A11 transcription resulting in the inhibition of ferroptosis [36, 37]. SLC7A11 inactivation can significantly attenuate KRAS-induced tumor growth [37].

Epigenetic modification of SLC7A11 in cancer cells plays a crucial role in governing ferroptosis. H2Aub is a histone modification that is generally associated with transcriptional repression. BAP1 removes H2Aub on the SLC7A11 promoter to repress SLC7A11 expression [34, 35] (**Figure 1**). PRC1, a major ligase of H2Aub ubiquitin, promotes H2A ubiquitination on the SLC7A11 promoter [38]. Moreover, SLC7A11 expression is activated by H2Bub1 (mono-ubiquitination of histone H2B on lysine 120) [39]. The nuclear translocation of USP7 decreases H2Bub1 on the SLC7A11 regulatory region and thus suppresses SLC7A11 expression [39] (**Figure 1**). H3K9 methylation on SLC7A11 promotor can regulate its expression. KDM3B, cooperating with ATF4, activates SLC7A11 through decreasing H3K9 methylation on SLC7A11 promoter [40] (**Figure 1**). Furthermore, ARID1A, a subunit of SWI/SNF chromatin remodeling complex, could enhance the SLC7A11 transcription [41, 42]. Taken together, epigenetic modification plays a considerable part in the SLC7A11 regulation and ferroptosis.

3.3 Transcriptional regulation of SLC7A11 in cancer stem cells

Interestingly, SLC7A11 expression is recently shown to be tightly relevant to cancer cell stemness. Cancer stemness is the main cause of metastasis and drug resistance [43]. It was reported that miR-375 directly targets SLC7A11 and attenuates the stemness of gastric cancer stemness through triggering SLC7A11-dependent ferroptosis [44]. Overexpression of lncRNA SLC7A11-AS1 (the anti-sense transcript of SLC7A11) promotes cancer stemness and chemoresistance by scavenging ROS in gemcitabine-resistant PDAC (pancreatic ductal adenocarcinoma) cells [45]. Recently, SOX2 was reported to confer ferroptosis resistance and maintain cancer cells stemness in lung cancer via upregulation of SLC7A11 [46].

SOX2, a transcriptional factor expressed in embryonic and stem cells [47, 48], is crucial in maintaining the stemness of embryonic cells and various adult stem cells [49] and reprogramming human or murine induced pluripotent stem cells from terminally differentiated somatic cells [50]. SOX2 regulates cancer stemness through PRKCI-SOX2-HHAT signaling axis, which is activated by the coordinated overexpression of SOX2 and PRKCI [51]. The aberrant SOX2 expression is associated with various types of cancer [49, 52]. SOX2 maintains glioma stem cells stem-like properties and tumorigenicity via activating TGF-β signaling [53]. Furthermore, SOX2 was confirmed to sustain cancer stem cells in osteosarcomas by interfering with tumor-suppressive Hippo pathway [54].

Recently, we deciphered a SOX2-SLC7A11 regulatory axis [46], which greatly contributed to the mechanism of tumor stemness and ferroptosis resistance. High expression of SOX2 in lung cancer cells transcriptionally activated SLC7A11 expression to increase cystine uptake and GSH synthesis, which protected lung cancer from ferroptosis. Interestingly, upregulated GSH blocked the oxidative modification of SOX2-Cys265, resulting in enhanced SOX2 activity and maintaining cancer cells stemness. We uncovered a novel posttranslational mechanism of SOX2 that oxidation at Cys265 can inhibit its transcriptional activity and a new type transcriptional regulation of SLC7A11 by SOX2. Taken together, our study provides a mechanism by which cancer cells evade ferroptosis and suggests SOX2 could be a potential therapeutic target for cancer with ferroptosis resistance.

4. Modulation of ferroptosis by targeting SLC7A11

A wealth of studies suggests that ferroptosis plays a pivotal role in human diseases. Pharmacological modulation of ferroptosis in cancers, by either inhibitors or inducers, may contribute to significant clinical benefit for certain diseases. To date, numerous inducers of ferroptotic death through interrupting SLC7A11-involved pathway has been discovered **(Figure 2)**. In 2003, Dolma et al. identified the first inducer of ferroptosis, erastin, which is an inhibitor of system X_c^-. Erastin selectively kills engineered tumor cells through a nonapoptotic mechanism [55]. Whereafter, imidazole ketone erastin (IKE) and piperazine erastin (PE) are identified as better inhibitors of system X_c^-, which both are suitable for *in vitro* and *in vivo* studies [56, 57]. Sorafenib and sulfasalazine, two FDA-approved drugs, can inhibit SLC7A11 transporter activity, and induce ferroptosis and suppress tumor growth *in vivo* [58, 59]. HG106 was identified to markedly decrease cystine uptake and intracellular glutathione biosynthesis by inhibited SLC7A11 [36].

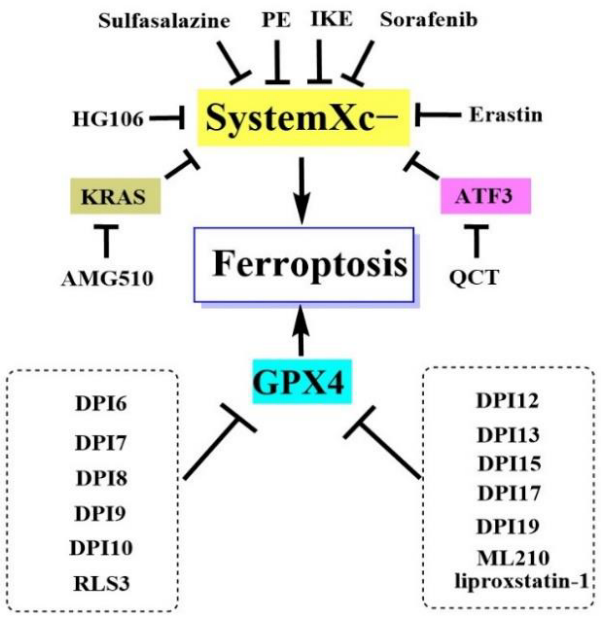

Figure 2. Inhibitors regulate ferroptosis. Erastin, IKE, PE, Sorafenib and sulfasalazine and HG106 reduce ferroptosis by inhibiting system X_c^-. Liproxstatin-1, DPI6, DPI7/ML162, DPI8, DPI9, DPI12, DPI13, DPI15 and DPI19, DPI17, DPI10 and ML210 are GPX4 inhibitors to induce ferroptosis. AMG510 suppresses SLC7A11 through inhibiting KRAS. QCT represses SLC7A11 through inhibiting ATF3 expression.

Other than directly inhibiting SLC7A11, various studies identified inhibitors which target proteins regulating SLC7A11 expression and activity **(Figure 2)**. Inhibitors of GPX4, a protein utilizing GSH to reduce lipid hydroperoxides, are well established to induce ferroptosis. RLS3 is a widely used GPX4 inhibitor *in vitro*, whereas unfavorable pharmacokinetic properties impede its application *in vivo* [56, 60]. Other inhibitors of GPX4 also have been discovered, including liproxstatin-1 [61], DPI6, DPI7/ML162, DPI8, DPI9, DPI12, DPI13, DPI15 and DPI19, DPI17, DPI10 and ML210 [56, 60]. Besides, AMG510, a KRAS inhibitor in clinical development, is identified to reduce SLC7A11 expression [62]. QCT, a ATF3 inhibitor, can significantly inhibit the expression of ATF3 and induce ferroptosis [63]. Additionally, other approaches targeting SLC7A11 to induce nutrient dependency in cancer cells would not be discussed in this commentary.

5. Conclusion

Since the promising therapeutic functions in many human diseases, ferroptosis has aroused great interest. Cancer cells manipulate ferroptosis and resist oxidative stress through upregulating SLC7A11. Given the recent advances, we know that the expression and activity of SLC7A11 are modulated through various mechanisms, including transcriptional regulation by transcription factors and epigenetic regulators, and posttranslational regulatory mechanisms to control its mRNA levels, protein stability, subcellular localization, and transporter activity. In this commentary, we reviewed the transcriptional regulation of SLC7A11. NRF2, SOX2 and p53 directly bind to the promoter region of SLC7A11 and regulate its transcription. Epigenetically, BAP1 inhibits SLC7A11 expression through deubiquitinating H2A, while chromatin remodeling factor ARID1A increases SLC7A11 expression. KDM3B, cooperating with ATF4 activate SLC7A11 expression by decreasing H3K9 methylation on SLC7A11 promoter. Therefore, targeting SLC7A11 to discover therapeutic agents may contribute to clinical treatment for cancer therapy.

6. Author Contributions

Conceptualization, P.W. and P.Z.; writing manuscript, P.Z. and L.Y.; review and editing, X.W. and P.W. All authors have read and agreed to the published version of the manuscript.

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9. Conflicts of Interest

The authors declare no conflict of interest.

10. Reference

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