Research Article

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Ferroptosis-associated gene SLC7A11 is upregulated in NSCLC and correlated with patient's poor prognosis: An integrated bioinformatics analysis

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Abstract

Objective – Ferroptosis is a type of programmed cell death dependent on iron and characterized by the accumulation of lipid peroxides, which was involved in the progression of malignant tumors including non-small cell lung cancer (NSCLC).

Material/methods – Ferroptosis inhibiting gene solute carrier family 7 member 11 (SLC7A11) mRNA expression was investigated in the database of TCGA and Oncomine and compared between the cancer tissue and the normal corresponding tissue of NSCLC patients. SLC7A11 gene mutation of NSCLC was investigated in the TCGA database by the online data analysis tool of Catalog of Somatic Mutations in Cancer (COSMIC) and cBioPortal. The protein–protein interaction (PPI) network of SLC7A11 and associated genes were constructed with the STRING database. Gene ontology (GO) and the KEGG pathway of genes involved in the PPI network were explored and demonstrated by a bubble plot. Progression-free survival (PFS), overall survival (OS) and postprogression survival (PPS) between SLC7A11^{high} and SLC7A11^{low} expression groups were compared and demonstrated by the survival curve.

Results – SLC7A11 mRNA was upregulated in cancer tissues compared to paired normal tissues in colorectal adenocarcinoma, esophageal squamous cell carcinoma, lung squamous cell carcinoma rectum adenocarcinoma and uterine corpus endometrial carcinoma. Missense and

synonymous substitutions were 66.67% and 16.67% for lung squamous cell carcinoma. For lung adenocarcinoma, the missense and synonymous substitutions were 66.67% and 33.33% respectively. In the case of single nucleotide mutation, A>T, C>G, G>A, G>T for lung squamous cell carcinoma and G>T, C>A, G>A, T> for lung adenocarcinoma were the most common mutations in the SLC7A11 coding strand. Fifty-one genes were included in the PPI network with an edge number of 287, average node degree of 11.3 and local clustering coefficient of 0.694, which demonstrated that the PPI network was enriched significantly ($p = 1.0 \times 10^{-16}$). In terms of the KEGG pathway, the SLC7A11 and PPI-involved genes were mainly enriched in ferroptosis, NSCLC, pathways in cancer, tp53 signaling pathway, etc. The overall survival (OS) in the SLC7A11^{high} group was significantly lower than those of SLC7A11^{low} groups in NSCLC (HR = 1.15, 95% CI: 1.02–1.31, $p = 0.027$). However, the progression-free survival (PFS) (HR = 1.17, 95% CI: 0.97–1.42, $p = 0.098$) and postprogression survival (PPS) (HR = 1.00, 95% CI: 0.78–1.29, $p = 0.97$) between SLC7A11^{high} and SLC7A11^{low} expression groups were not statistically different.

Conclusion – SLC7A11 was upregulated in NSCLC and correlated with the patient's poor overall survival. SLC7A11 may be a potential target for NSCLC treatment through the ferroptosis pathway.

Keywords: ferroptosis, SLC7A11, NSCLC, prognosis

1 Introduction

It has been reported that 2.1 million newly diagnosed lung carcinoma and 1.8 million lung cancer deaths cases were identified in the year 2018, which take part in nearly 1 in 5 (18.4%) of all malignant carcinoma caused death [1]. However, the molecular carcinogenesis of non-small cell lung cancer (NSCLC) was not clear yet. In recent

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Figure 1: SLC7A11 mRNA expression analysis in different tissues: (a) SLC7A11 mRNA expression in human normal tissues; (b) SLC7A11 mRNA expression in different carcinoma; (c) SLC7A11 mRNA expression between cancer tissue and paired normal tissues of lung adenocarcinoma and lung squamous cell carcinoma; and (d) SLC7A11 mRNA expression between the cancer tissue and paired normal tissue of pan-cancer based on the Oncomine database.

years, with the rapid development of tumor molecular biology technology and relevant cancer databases, the lung cancer diagnosis, prognosis and targeted therapy had been improved especially for advanced cases [2–5].

Recently, a new cell death pathway, named ferroptosis, a form of regulated cell death induced by excessive lipid peroxidation was first reported by Dixon *et al.* [6]. Ferroptosis can eliminate the adaptive characteristics of malignant cells, remove the cells that are unable to obtain key nutritional factors or are infected or damaged due to environmental changes, which plays a key role in tumor suppression [7–10]. It had been reported that solute carrier family 7 member 11 (SLC7A11) was upregulated in multiple cancers and can activate cancer cell growth by inhibiting ferroptosis [11–13]. In the present work, we investigate SLC7A11 gene expression and its prognosis for NSCLC by using the relevant databases.

2 Material and methods

2.1 SLC7A11 expression analysis in relevant databases

The SLC7A11 gene mRNA expression level between the NSCLC tumor tissue and the corresponding normal lung tissue was explored in TCGA and Oncomine databases. The mean expression level and range were demonstrated by the box plot.

2.2 SLC7A11 gene mutation analysis

The mutation frequency of the SLC7A11 gene was explored in the TCGA databases by the online analysis tool cBioPortal. Catalogue of Somatic Mutation in Cancer (COSMIC) was

applied to identify the SLC7A11 gene mutation status in NSCLC and the mutation frequency was expressed by the Pie plot.

2.3 PPI network construction

The protein–protein interaction network (PPI) of SLC7A11 and relevant protein coding genes were established in the STRING databases. The PPI establishment requirements were as follows: active interaction source of textmining, experiments, database, co-expression, neighborhood, gene fusion and co-occurrence.

2.4 Go and KEGG pathway enrichment

The genes involved in the PPI network were gene ontology (GO) enriched in the aspects of the cellular component (CC), biology process (BP) and molecular function (MF). The Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment was also investigated for SLC7A11 and relevant genes.

2.5 Prognosis analysis

According to the median mRNA expression level of the SLC7A11 gene, NSCLC patients from the TCGA databases were divided into SLC7A11^{high} ($\geq$ median tumor expression level) and SLC7A11^{low} ($<$ median tumor expression level) expression groups. log-rank text was applied to compare the overall survival (OS) and disease-free survival (DFS) between SLC7A11^{high} and SLC7A11^{low} groups of NSCLC patients.

2.6 Statistical methods

The statistical analysis was generally based on the relevant databases and the corresponding online analysis tool. The Student’s *t*-test was applied in comparing continuous variables. Chi-squared test was used for categorical variables. The log-rank test was applied for survival analysis. Two-tail *p* values < 0.05 were considered statistically significant.

Figure 3: SLC7A11 gene mutation analysis through Catalog of Somatic Mutations in Cancer (COSMIC): (a) SLC7A11 gene mutation in lung squamous cell carcinoma; (b) SLC7A11 gene single nucleotide mutation in squamous cell carcinoma; (c) SLC7A11 gene mutation in lung adenocarcinoma; and (d) SLC7A11 gene single nucleotide mutation in lung adenocarcinoma.

Figure 5: The bubble plot of biology process enrichment for SLC7A11 and relevant genes involved in the PPI network.

3 Results

3.1 SLC7A11 mRNA expression

The SLC7A11 mRNA expression level was quite different across human normal tissues (Figure 1a). SLC7A11 mRNA was upregulated in the cancer tissue compared to the

paired normal tissue in colorectal adenocarcinoma, esophageal squamous cell carcinoma, lung squamous cell carcinoma rectum adenocarcinoma and uterine corpus endometrial carcinoma (Figure 1b and c). However, SLC7A11 was downregulated in acute myeloid leukemia compared to normal cells. This result was also confirmed by the Onco-mine database (Figure 1d).

Table 2: The cellular component enrichment for SLC7A11 and relevant genes involved in the PPI network

Description	Gene count	Background gene count	p-value
Plasma membrane part	23	2,651	1.02×10^{-5}
Integral component of the plasma membrane	17	1,564	2.67×10^{-5}
Melanosome	6	105	3.05×10^{-5}
Cell periphery	30	5,254	5.94×10^{-5}
Plasma membrane	29	5,159	0.00013
Cytoplasmic part	40	9,377	0.00022
Plasma membrane region	12	1,061	0.00036
Glutamate-cysteine ligase complex	2	2	0.00086
Cytosol	26	4,958	0.0015
Cell part	51	16,244	0.0015
Cytoplasm	42	11,238	0.0023
Apical plasma membrane	6	307	0.0023
Cell projection	13	1,969	0.017
Cell projection membrane	5	317	0.0177
Brush border	3	97	0.0257
Cell leading edge	5	371	0.031
Somatodendritic compartment	7	731	0.031
Plasma membrane-bounded cell projection	12	1,900	0.031
Membrane	32	8,420	0.0344

Figure 6: The bubble plot of cellular component enrichment for SLC7A11 and relevant genes involved in the PPI network.

3.2 SLC7A11 gene mutation

SLC7A11 mutation that was frequently seen in NSCLC was analyzed in the TCGA database through cBioPortal (Figure 2). The SLC7A11 mutation in NSCLC was investigated by the online data analysis tool of Catalog of Somatic Mutations in Cancer (COSMIC). Missense and synonymous substitutions

were 66.67% and 16.67% for lung squamous cell carcinoma. For lung adenocarcinoma, missense and synonymous substitutions were 66.67% and 33.33%, respectively. In the case of single nucleotide mutation, A>T, C>G, G>A, G>T for lung squamous cell carcinoma and G>T, C>A, G>A, T> for lung adenocarcinoma were the most common mutations in the SLC7A11 coding strand (Figure 3).

Table 3: The molecular function enrichment for SLC7A11 and relevant genes involved in the PPI network

Description	Gene count	Background gene count	p-value
Amino acid transmembrane transporter activity	14	76	2.45×10^{-19}
L-Amino acid transmembrane transporter activity	12	52	1.20×10^{-17}
Carboxylic acid transmembrane transporter activity	15	151	1.20×10^{-17}
L-Glutamate transmembrane transporter activity	7	14	2.89×10^{-12}
Drug transmembrane transporter activity	10	92	3.74×10^{-12}
Secondary active transmembrane transporter activity	12	235	4.27×10^{-11}
Neurotransmitter transporter activity	8	54	1.11×10^{-10}
Neutral amino acid transmembrane transporter activity	7	31	1.77×10^{-10}
Symporter activity	10	146	1.92×10^{-10}
Amino acid:sodium symporter activity	6	17	5.07×10^{-10}
High-affinity glutamate transmembrane transporter activity	5	7	1.53×10^{-9}
Neurotransmitter:sodium symporter activity	6	29	5.69×10^{-9}
Solute:sodium symporter activity	7	82	4.37×10^{-8}
Sulfur amino acid transmembrane transporter activity	4	7	1.74×10^{-7}
Sodium ion transmembrane transporter activity	8	164	1.74×10^{-7}
Cation transmembrane transporter activity	11	652	9.28×10^{-6}
L-Glutamine transmembrane transporter activity	3	5	9.82×10^{-6}
Antioxidant activity	5	79	2.58×10^{-5}
Cofactor binding	9	481	4.11×10^{-5}

Figure 7: The bubble plot of molecular function enrichment for SLC7A11 and relevant genes involved in the PPI network.

3.3 PPI network construction

Fifty-one genes were included in the PPI network with an edge number of 287, an average node degree of 11.3 and local clustering coefficient of 0.694, which demonstrated that the protein–protein interaction network was enriched significantly ($p = 1.0 \times 10^{-16}$); Figure 4.

3.4 GO and KEGG pathway analysis

For the biological process, the SLC7A11- and PPI-involved genes were main enriched in the negative regulation of cell death, response to oxidative stress, amino acid import across the plasma membrane, etc. (Table 1 and Figure 5). In the case of the ceclular component, SLC7A11 and relevant

Figure 8: KEGG pathway analysis of SLC7A11 and PPI involved genes.

Figure 9: Survival curve of PFS, OS and PPS between the SLC7A11 high and low expression groups: (a) progression-free survival; (b) overall survival; (c) post and progression survival.

genes were enriched in the plasma membrane part, an integral component of the plasma membrane, melanosome, etc. (Table 2 and Figure 6). For the molecular function, the SLC7A11 and PPI involved genes were mainly enriched in amino acid transmembrane transporter activity, L-amino acid transmembrane transporter activity, carboxylic acid transmembrane transporter activity, etc. (Table 3 and Figure 7). In terms of the KEGG pathway, the SLC7A11- and PPI-involved genes were mainly enriched in ferroptosis, NSCLC, pathways in cancer, p53 signaling pathway, etc. (Table 4, Figure 8).

3.5 SLC7A11 expression and patient's survival

The overall survival (OS) in the SLC7A11 high expression group was significantly lower than those of low expression groups in NSCLC (HR = 1.15, 95% CI: 1.02–1.31, $p = 0.027$). However, the progression free survival (PFS) (HR = 1.17, 95% CI: 0.97–1.42, $p = 0.098$) and postprogression survival (PPS) (HR = 1.00, 95% CI: 0.78–1.29, $p = 0.97$) between SLC7A11 high and low expression groups was not statistically different (Figure 9).

4 Discussion

Lung carcinoma including small cell lung cancer (SCLC) and NSCLC was considered as the leading cause of malignant tumor-related death [14]. It has been reported that lung cancer was the most commonly diagnosed carcinoma (11.6% of all cancers) and the leading cause of

cancer-associated death (18.4% of the total cancer deaths), closely followed by female breast cancer (11.6%) and male prostate cancer (7.1%) [1]. Therefore, lung cancer had posed a heavy burden on human health. Clearly identifying lung cancer carcinogenesis and relevant molecular biological characteristics were of most importance for deeply understanding the lung cancer biological behavior and facilitating the tumor target drug development. SLC7A11 is a key gene in the pathway of ferroptosis, which was generally upregulated in cancer cells and promoted cancer cells growth partly by suppressing ferroptosis, a form of regulated cell death induced by excessive lipid peroxidation [15].

In our present work, we found that SLC7A11 mRNA was upregulated in cancer tissues compared to paired normal tissues in most cancers including lung cancer. These findings were in accordance with the previous publications [11,16,17]. We also found that SLC7A11 mutation frequently included missense and synonymous substitution in NSCLC. KEGG pathway enrichment indicated that SLC7A11- and PPI-involved genes were mainly enriched in ferroptosis, NSCLC, pathways in cancer and the p53 signaling pathway. It had been reported that tumor suppressor protein tp53 inhibited carcinogenesis partly through inhibiting SLC7A11 expression and promoting ferroptosis, while oncogenic KRAS and OTUB1 promoted tumor development partly by promoting SLC7A11 levels and inhibiting ferroptosis [18]. Survival analysis indicated that the overall survival (OS) in the SLC7A11 high expression group was significantly lower than those of low expression groups in NSCLC (HR = 1.15, 95% CI: 1.02–1.31, $p = 0.027$). This indicated that SLC7A11 can be applied as a molecular marker for poor overall survival of NSCLC.

Table 4: The KEGG pathway enrichment for SLC7A11 and relevant genes involved in the PPI network

Description	Count	Gene ratio	Q value
Ferroptosis	7	0.175	4.13×10^{-9}
Hepatocellular carcinoma	7	0.042945	1.23×10^{-5}
Fluid shear stress and atherosclerosis	6	0.045113	5.35×10^{-5}
Protein digestion and absorption	5	0.055556	0.00013
HIF-1 signaling pathway	5	0.05102	0.00015
Pathways in cancer	9	0.017476	0.00015
Prostate cancer	5	0.051546	0.00015
MicroRNAs in cancer	5	0.033557	0.00074
Longevity regulating pathway	4	0.045455	0.0013
Proteoglycans in cancer	5	0.025641	0.0021
Cysteine and methionine metabolism	3	0.068182	0.0028
Glutathione metabolism	3	0.06	0.0035
Cocaine addiction	3	0.061224	0.0035
Hepatitis B	4	0.028169	0.0051
Glioma	3	0.044118	0.0063
Non-small cell lung cancer	3	0.045455	0.0063
Central carbon metabolism in cancer	3	0.046154	0.0063
Selenocompound metabolism	2	0.125	0.007
Biosynthesis of amino acids	3	0.041667	0.007
Pancreatic cancer	3	0.040541	0.007
Melanoma	3	0.041667	0.007
EGFR tyrosine kinase inhibitor resistance	3	0.038462	0.0072
Viral carcinogenesis	4	0.021858	0.008
Endocrine resistance	3	0.031579	0.0115
PI3K-Akt signaling pathway	5	0.014368	0.0115
Insulin resistance	3	0.028037	0.0148
Metabolic pathways	9	0.0072	0.023
Glycine, serine and threonine metabolism	2	0.051282	0.0235
FoxO signaling pathway	3	0.023077	0.0235
Estrogen signaling pathway	3	0.022556	0.0235
Relaxin signaling pathway	3	0.023077	0.0235
Hepatitis C	3	0.022901	0.0235
Bladder cancer	2	0.04878	0.0235
Breast cancer	3	0.020408	0.0271
MAPK signaling pathway	4	0.013652	0.0278
Cushing's syndrome	3	0.019608	0.0286
Amyotrophic lateral sclerosis (ALS)	2	0.04	0.0289
Endometrial cancer	2	0.034483	0.0372
Mitophagy – animal	2	0.031746	0.0422
Cortisol synthesis and secretion	2	0.031746	0.0422
Amphetamine addiction	2	0.030769	0.0426
p53 signaling pathway	2	0.029412	0.0452
Epstein-Barr virus infection	3	0.015464	0.0452
Thyroid hormone synthesis	2	0.027397	0.0492

Apoptosis, a classic cell death pathway, played an essential role in cancer suppression and cell death resistance was considered a landmark of cancer. Recently, another cell death pathway known as ferroptosis has attracted attention in the field of cancer. It has been confirmed that SLC7A11 has emerged as a central hub linking ferroptosis to its proposed tumor suppression function [19,20].

Studies have shown that the tumor suppressor protein tp53 is related to the mechanism of ferroptosis [21]. tp53 can directly inhibit the transcription of SLC7A11, a key component of system X_c^- , and inhibit the uptake of cystine [22]. In addition, acetylation-deficient mutant mice lack the function of cell cycle arrest, apoptosis or aging, but can induce iron death by inhibiting the expression of SLC711A and still have tumor inhibition function [23]. The role of tp53 in the process of ferroptosis was achieved through different mechanisms, such as tp53 on metabolism gene transcription, posttranslational regulation or P53-P21 axis [24]. However, the bidirectional regulation of pt53 on ferroptosis and a cell-specific or environment-dependent manner needs further study.

SLC711A protein is a member of a heteromeric, sodium-independent, anionic amino acid transport system that is highly specific for cysteine and glutamate. In this system, designated X_c^- , the anionic form of cysteine, is transported in exchange for glutamate. SLC7A11 expression on the cell membrane is essential for the uptake of cystine required for the synthesis of intracellular glutathione (GSH), an antioxidant that plays an important role in maintaining intracellular redox balance [25]. Human aortic endothelial cells can import Hcy via at least four of the known cysteine transport systems, namely, XAG, L, ASC, and A SLC7A11, and are involved in the homocysteine-induced apoptosis promoted by amino acid starvation [26]. Homocysteine is a kind of sulfur-containing amino acid, which is an intermediate product in the process of methionine metabolism [27]. It metabolizes through methylation and trans sulfurization, maintaining the two major abilities of the human body: methylation and antioxidant. Studies also indicated that the SLC7A11 inhibitor, salazosulfapyridine, which is an amino acid transporter, protects against Hcy-induced apoptosis due to autophagy [28]. Combined with our findings, the SLC7A11 inhibitor may be a potential target drug that can inhibit cancer by Hcy-induced apoptosis due to autophagy.

5 Conclusion

In the present work, we found that SLC7A11 was upregulated in NSCLC and correlated with the patient's poor

overall survival. SLC7A11 may be a potential target for NSCLC treatment through the ferroptosis pathway. However, cellular or clinical experiments are further needed to validate our findings and unravel the molecular function of SLC7A11 in ferroptosis.

Conflict of interest: The authors state no conflict of interest.

Data availability statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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