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Regulatory role of SLC3A2 in Ferroptosis and its impact on head and neck squamous cell carcinoma: A bioinformatics study

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Head and Neck Squamous Cell Carcinoma (HNSCC) is a complex malignancy distinguished by poor prognosis and limited therapeutic options. Emerging evidence suggests that ferroptosis, a form of regulated cell death Persistent by iron-dependent lipid peroxidation, is a cornerstone in cancer biology. This exploration focuses on SLC3A2, a gene implicated in amino acid transport, as a potential regulator of ferroptosis in HNSCC. A bioinformatics approach was employed to investigate the role of SLC3A2 in HNSCC. Pan-cancer analysis was conducted using TIMER 2.0 to assess SLC3A2 expression across various cancer types. Prognostic gene expression analysis comparing normal and primary tumor tissues was performed using the UALCAN database. Genetic mutation analysis of SLC3A2 was examined in HNSCC patients. Protein-protein interaction (PPI) networks were erected using the STRING database and visualized with Cytoscape software. Functional annotation and pathway analysis were conducted using the KEGG database to elucidate the biological pathways linked with SLC3A2. SLC3A2 was determined to be markedly overexpressed in HNSCC compared to other cancer types. High SLC3A2 expression correlated with poor overall survival in HNSCC patients, indicating its potential as a prognostic biomarker. Mutation analysis revealed frequent genetic alterations in SLC3A2 in HNSCC. PPI network analysis identified key interacting proteins, highlighting SLC3A2central role in the network. Functional annotation and KEGG pathway analysis implicated SLC3A2 in ferroptosis regulation and other critical cancer-related pathways. Our bioinformatics analysis suggests that SLC3A2 is a key regulator of ferroptosis in HNSCC, with significant implications for prognosis and therapeutic targeting.

Keywords: Ferroptosis, Glutathione peroxidase 4, Glutathione, Reactive oxygen species, Solute carrier family 3 member 2

Head and neck squamous cell carcinoma (HNSCC) is a recurring and formidable malignancy originating from the epithelial cells lining the mucosal surfaces of the head and neck region. Despite the strides made in diagnostic techniques and treatment modalities, the prognosis for patients with HNSCC remains poor, with a five-year survival rate of approximately 50%[1]. According to GLOBOCAN 2020, India is projected to see 2.1 million new cancer cases by 2040, marking a 57.5% increase from the figures reported in 2020. In India, the risk of developing head and neck cancer (HNC) is significant, with 1 in 33 males and 1 in 107 females affected. Among the various types of HNC, mouth and tongue cancers are particularly common in both genders across the country[2,3]. These cancers are mainly squamous cell carcinomas and are strongly linked to risk factors including tobacco use, alcohol consumption, and human papillomavirus (HPV) infection. Despite advancements in treatment modalities, head and neck cancer remains a significant health burden due to its high morbidity and mortality rates[4,5]. This dismal outcome is often attributed to late-stage diagnosis, high recurrence rates, and the development of resistance to conventional therapies. Thus, it is crucial to discover new therapeutic targets and create more effective treatment strategies for HNSCC[6].

Recent research has underscored the potential role of ferroptosis, a regulated form of cell death induced by iron-dependent lipid peroxidation, in cancer therapy. Unlike apoptosis, necrosis, and autophagy, ferroptosis is characterized by the accumulation of lethal lipid reactive oxygen species (ROS) and is modulated by distinct genetic and biochemical pathways[7,8]. Key regulators of ferroptosis include glutathione peroxidase 4 (GPX4), which suppresses ferroptosis by decreasing lipid hydroperoxides, and system Xc-, a cystine/glutamate antiporter that supplies cystine for glutathione synthesis[9]. Targeting

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these regulators to induce ferroptosis has become a potential strategy for overcoming therapy resistance in various cancers, including HNSCC.

solute carrier family 3-member 2 (SLC3A2), also known as 4F2 heavy chain (4F2hc) or CD98, is a vital component of the heteromeric amino acid transporters (HATs) family. This protein is essential for the transport of neutral and basic amino acids across the plasma membrane. SLC3A2 is a type II membrane glycoprotein with a large extracellular domain[10,11]. The extracellular domain of SLC3A2 is characterized by a series of conserved cysteine residues, which are crucial for forming disulfide bonds and maintaining the protein's structural integrity[12]. This domain also interacts with the light chains of the HAT family, such as LAT1 (SLC7A5) and LAT2 (SLC7A8), facilitating the formation of functional amino acid transport systems[13,14]. The interaction between the heavy and light chains is mediated through a non-covalent bond, which is essential for the proper localization and function of the transporters on the plasma membrane[14]. Moreover, previous study reported as SLC3A2 is over expressed in various cancer types, such as osteosarcoma[15], and renal cell carcinoma[16], Lung cancer[17].

In this investigation, we conducted a comprehensive analysis of SLC3A2 in HNSCC using various bioinformatics tools and databases. These tools were chosen based on their reliability, reproducibility, and ability to provide accurate data interpretation, related with our study objectives of uncovering the role of SLC3A2 in disease progression and identifying potential therapeutic targets. We investigated the expression levels of SLC3A2 in normal versus primary tumor tissues, analyzed mutation frequencies, and assessed protein expression differences across different stages of metastasis. Additionally, we evaluated the impact of SLC3A2 expression on overall survival in HNSCC patients.

Material and Methods

Analysis of SLC3A2 expression in pan-cancer cohorts

Pan-cancer data were procured from the TIMER 2.0 (http://timer.cistrome.org/), focusing on the expression levels of the SLC3A2 gene across various cancer types. TIMER 2.0 provides comprehensive data on gene expression, immune infiltration, and clinical outcomes across multiple cancer datasets[18]. For this study, the SLC3A2 gene expression levels were retrieved and presented as log2 Transcripts Per Million (TPM). This normalization method ensures comparability across samples by accounting for sequencing depth and gene length. The data were processed and visualized using built-in analytical tools in TIMER 2.0, providing insights into the differential expression of SLC3A2 across different cancer types. This approach facilitated a robust and standardized comparison of SLC3A2 expression, highlighting its potential role in cancer biology.

Prognostic characteristics of SLC3A2

To evaluate the prognostic significance of SLC3A2, we analyzed its mRNA expression levels and metastatic potential in HNSCC using data retrieved from the UALCAN database (http://ualcan.path.uab.edu/)[19,20], which was chosen for its user-friendly interface and comprehensive clinical data, enabling easy access to gene expression and survival analysis in a various cancer. Additionally, overall survival analysis was conducted using the GEPIA database (http://gepia.cancer-pku.cn/)[21].

SLC3A2 gene mutation analysis

The cBio Cancer Genomics Portal (http://cbioportal.org) was utilized its in-depth analysis of genomic alterations and co-expression networks, supporting the exploration of genetic variations associated with cancer progression. In this study, we obtain data on the mutation and expression profiles of SLC3A2 in Head and Neck cancer samples from TCGA datasets. This platform offers a comprehensive analysis of genetic alterations, including the identification of mutations, amplifications, and deletions[22,23].

PPI network interaction

Protein-protein interaction (PPI) network networks were constructed to understand the functional associations among the identified genes. Here we determine the functional network for SLC3A2 using the STRING database, an online tool (https://string-db.org/)[24]. Interactions with a combined score exceeding 0.08 were deemed significant, reflecting the reliability of the protein connections. The visualizing and analyzing the PPI network due to its powerful network analysis plugins and user-friendly interfaceusing Cytoscape software (version 3.5.1; http://www.cytoscape.org)[25]. In the network, edge widths were proportional to the combined score, representing the strength of interactions. Hub genes, defined as nodes with a degree greater than 10, were identified as central elements in the network.

Furthermore, highly interconnected gene clusters, indicative of functional units or pathways, were identified using the cytoHubba plugin in Cytoscape.

Enrichment analysis and Kyoto encyclopedia of SLC3A2 and genomes pathways

Gene ontology (GO) and The Kyoto encyclopedia of genes and genomes (KEGG) pathways were of hub genes was obtained from Shiny Go 0.80 database (http://bioinformatics.sdstate.edu/go/)[26].High-level biological functions and pathways were predicted for targeted genes.

Statistical analysis

Gene expression analysis across the whole cancer model was performed using the Wilcoxon test to evaluate statistical significance. To perform a comparison between normal and tumor tissues in the TCGA dataset, the paired Student's *t*-test was employed. Additionally, the log-rank test was used to determine p-values for mRNA expression analysis and to generate Kaplan-Meier plots for evaluating overall survival. Statistical significance for group comparisons was defined as ***$P<$ 0.001 and ****$P<$ 0.0001.

Results

Pan cancer analysis of SLC3A2

The pan-cancer analysis of SLC3A2 expression revealed a significant variation in expression levels across different cancer types. Notably, SLC3A2 was expressed at particularly high levels in Head and Neck Squamous Cell Carcinoma (HNSCC) (Fig. 1). The log2 Transcripts Per Million (TPM) values indicated that SLC3A2 expression in HNSCC was substantially higher compared to other cancer types analyzed. This elevated expression indicates a potential function of SLC3A2 in the pathogenesis of HNSCC. Moreover, Overexpression of SLC3A2 is HNSCC tumor rather than HNSCC normal.

Prognostic makers of SLC3A2

To analyze the mRNA expression levels of SLC3A2 in normal versus HNSCC cancer patients, we conducted a comparative analysis, presented in (Fig. 2A). The results showed notable differences in SLC3A2 expression between healthy individuals and HNSCC patients. Additionally, we evaluated SLC3A2 expression across different stages of nodal metastasis in HNSCC patients, as depicted in (Fig. 2B). The findings revealed that SLC3A2 expression increases with advancing nodal stages, underscoring its crucial influence in the metastasis and progression of HNSCC. Elevated SLC3A2 expression was linked to a more aggressive disease course and poorer prognosis for patients. SLC3A2 overexpression was linked to tumor progression and reduced survival. SLC2A3 expression showed significant variation across nodal stages ($P<$ 0.0001, $P<$ 0.001). Specifically, overexpression of SLC3A2 was associated with altered metabolic processes in cancer cells, enabling evasion of cell death and promoting tumor invasion and metastatic spread[27]. This dysregulation correlated with reduced survival rates

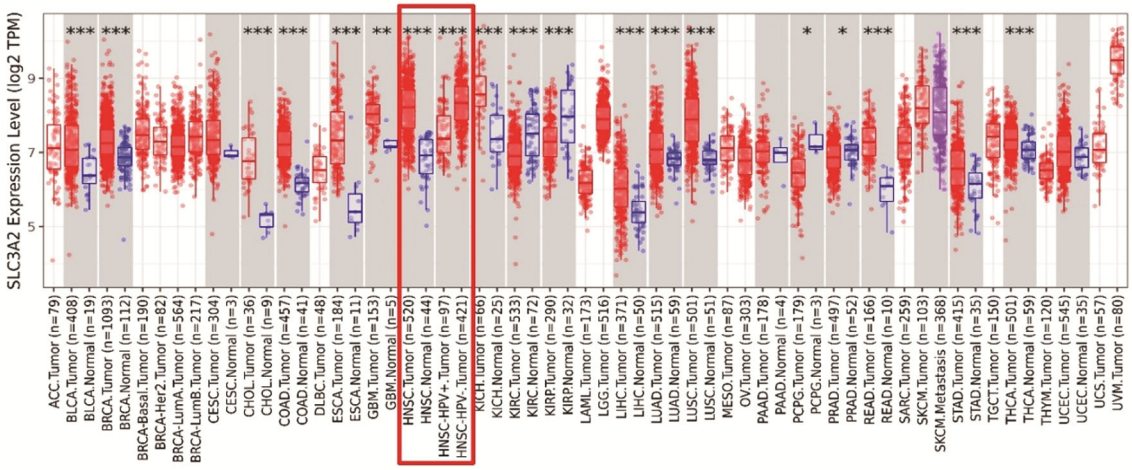

Fig. 1 – Pan-cancer analysis of SLC3A2 expression was conducted using data from the TCGA database, with expression levels presented in TPM. Blue bars represent normal samples, while red bars indicate tumor samples. Red box highlighted represents HNSCC. SLC3A2; TCGA, The Cancer Genome Atlas; TPM, Transcripts Per Million; The statistical significance computed by the Wilcoxon test is annotated (*: *P*-value < 0.05; **: *P*-value <0.01; ***: *P*-value <0.001)

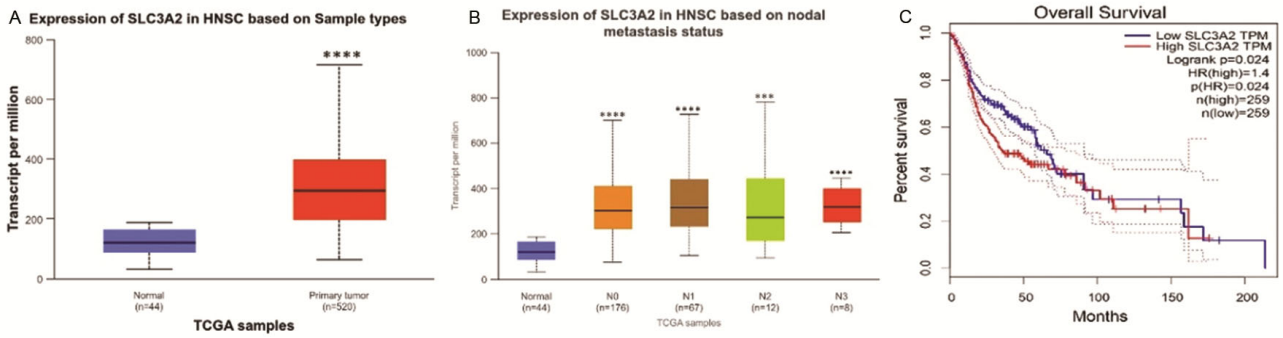

Fig. 2 — Expression status of SLC2A3 in Head and Neck cancer. (A) mRNA expression of SLC2A3 in Head and neck cancer were retrieved from TCGA samples using UALCAN database for normal (n=44; blue colour) and primary tumor (n=520; red colour); (B) nodal metastasis property (normal, n=44; N0, n=176; N1, n=67; N2, n=12; N3, n=8) for SLC2A3 was visualized. The '****'P< 0.0001 and '***'P< 0.001 denotes the statistical significance were determine by student t test; and (C) The overall survival rate of SLC2A3 (HR=1.4, p=0.024) in HNSCC was depicted using the Kaplan-Meier method in the KM plot. The colour blue represents low expression, whereas red represents great expression. The overall survival (OS) curve was validated based on probability (%) and time (months)

among HNSCC patients, as shown in (Fig. 2C). These findings imply that SLC3A2 could be a useful prognostic indicator and a possible target for treatment in the treatment of HNSCC.Kaplan–Meier analysis revealed high SLC2A3 expression was associated with lower survival (HR = 1.4, p = 0.024).

Mutation analysis

Figure 3 depicts the frequencies and types of genetic mutations observed in the SLC3A2 gene across head and neck cancer samples. The analysis showed that approximately 5.3% of the samples exhibited mutations. Mutation plots of the SLC3A2 gene in these cancers, based on data from The Cancer Genome Atlas (TCGA), revealed a mutation rate exceeding 1.8% in patient samples, with missense mutations being the predominant type.

PPI network interaction

The protein-protein interaction (PPI) network analysis of SLC3A2 revealed a complex interaction map involving multiple members of the solute carrier (SLC) family. Using the STRING database, we identified 11 nodes and 45 edges forming a tightly connected network (Fig. 4A). The SLC family members identified in this network include SLC3A2, SLC7A8, SLC7A7, SLC7A6, SLC7A5, SLC43A1, SLC7A11, SLC7A10, BSG, LCN2 and SLC7A9. These interactions suggest a coordinated role in amino acid transport and cellular metabolism. Moreover, we employed the cytohubba plugin in Cytoscape to identify the top 5 hub genes within this network. The hub genes, based on their degree of connectivity, are SLC3A2, SLC7A8, SLC7A7, SLC7A6, and SLC7A5

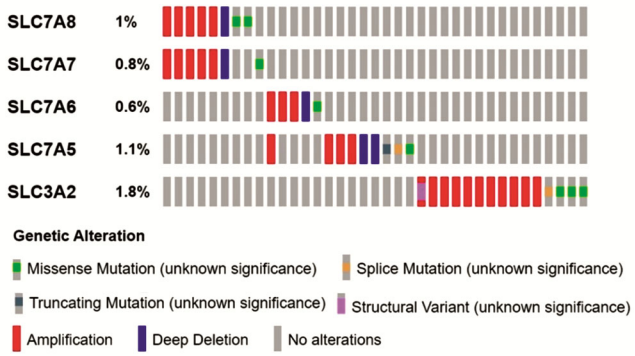

Fig. 3 — Hub gene SLC3A2 gene mutation frequencies in HNSCC-TCGA datasets obtained from the cBioPortal database. Gene amplifications are shown by the red bar, deep deletion by the blue bar, missense mutations by the green bar, and truncating mutations by the grey bar

(Fig. 4B). These genes demonstrate high interaction scores, indicating their central role in the network and potential importance in regulating key biological processes.

Functional annotation of SLC3A2

In this study, we observe the biological processes of hub genes retrieved from cytoscape. In Figure 5, revealed that SLC3A2 and their hug genes are mostly involved in the ferroptosis, protein digestion and absorption, Central carbon metabolisms in cancer, mTOR signalling pathway, and IL-17 Signalling pathway are predicated by the fold enrichment.

Kyoto encyclopedia of SLC3A2

The Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis for SLC3A2 elucidates its involvement in several criticalbiological processes

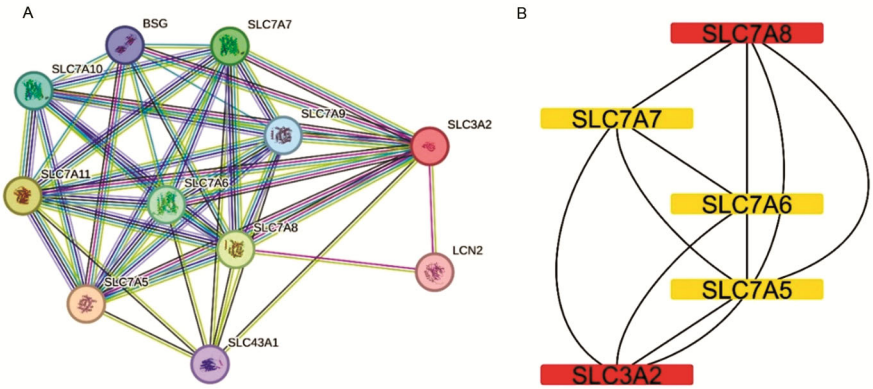

Fig. 4 — SLC3A2 interacts with hub genes in HNSCC. (A) Using the STRING web server and Cytoscape, the protein-protein interaction (PPI) network was visualized, displaying 11 nodes and 45 edges, with high nodal strength;and (B) The cytoHubba plugin was used to identify the top 5 hub genes based on their rank (1), resulting in a network of 5 nodes and 10 edges

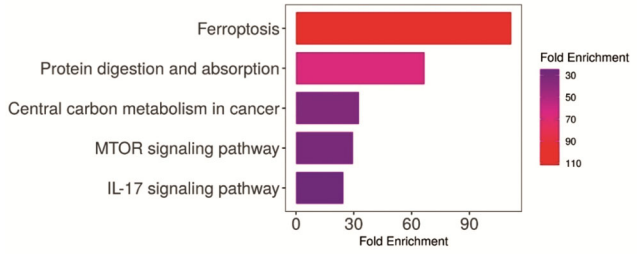

Fig. 5 — The functional annotation (GO) were visualized in bubble chart (BP) according to their fold enrichment. GO – Gene Ontology; BP, Biological Processes

and pathways, with a primary focus on the role of the SLC3A2 gene in ferroptosis. In Figure 6, we observe that the SLC3A2 gene inhibits the ferroptosis pathway *via* GPX4-mediated hydroperoxides reduction.

Discussion

In this study, we employed a range of bioinformatics approaches to elucidate the role of SLC3A2 as a key regulator of ferroptosis in head and neck squamous cell carcinoma (HNSCC). Through anextensive analysis encompassing pan-cancer expression data, tumor stage-specific expression patterns, mutation analysis, protein-protein interaction (PPI) network construction, and functional annotation, we have provided significant insights into the potential of SLC3A2 as a therapeutic target in HNSCC.

Our pan-cancer analysis revealed that SLC3A2 is ubiquitously expressed across various cancer types, with notably high expression in HNSCC. This widespread expression conveys that SLC3A2 Might act as a fundamental role in cancer biology. However, the particularly elevated levels in HNSCC highlight its potential as a specific marker for this cancer type. The differential expression patterns observed between normal and primary tumor tissues further underscore the involvement of SLC3A2 in tumorigenesis. Our analysis of SLC3A2 expression in normal versus primary tumor tissues of HNSCC patients demonstrated a significant upregulation in tumor tissues. This upregulation is indicative of the gene's role in tumor development and progression. The overexpression of SLC3A2 in tumor tissues may enhance amino acid transport, supporting the increased metabolic demands of rapidly proliferating cancer cells. Moreover, the high expression levels of SLC3A2 could be associated with the suppression of ferroptosis, thereby promoting tumor cell survival. Moreover, we further analysis the SLC3A2 expression across different pattern, with the highest expression observed in advanced metastatic stages. This indicates that SLC3A2 may have a pivotal function not only in primary tumor growth but also in the metastatic spread of HNSCC. The increased expression of SLC3A2 in metastatic stages may facilitate enhanced nutrient uptake and metabolic adaptability, which are essential for the survival and proliferation of metastatic cancer cells in new microenvironments. Additionally, the regulation of ferroptosis by SLC3A2 in metastatic cells could influence oxidative stress-induced cell death, further promoting the metastatic process.

Our mutation analysis revealed that 1.8% of HNSCC patients exhibit missense mutations in the SLC3A2 gene. While this mutation rate is relatively low, the presence of such mutations could have significant functional implications. Previously,

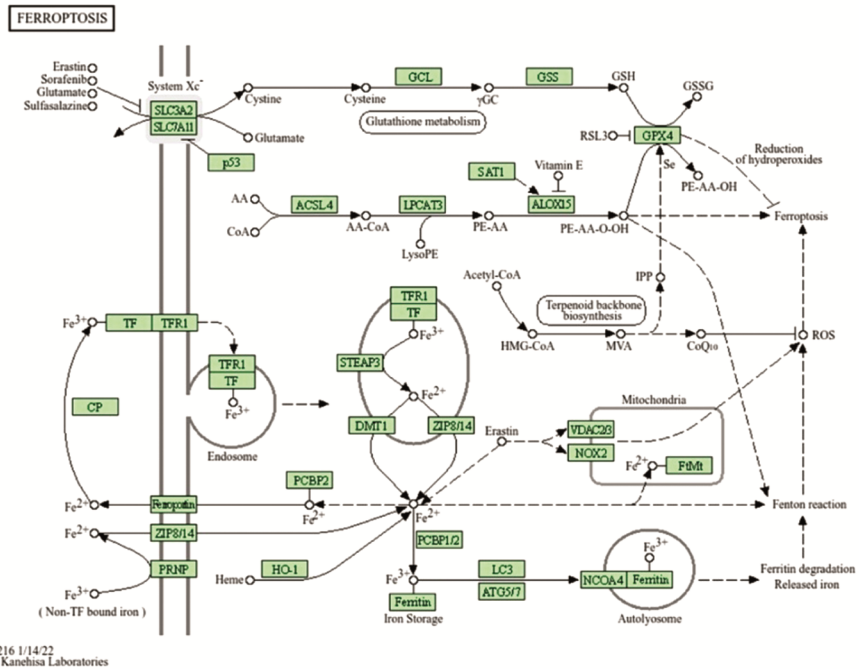

Fig. 6 — KEGG flowchart (https://www.kegg.jp/kegg/kegg1.html) for ferroptosis (Pathway ID: hsa04216)

Desai *et al*. identified a missense mutation in the novel gene IRAK1 in Indian HNSCC patient samples[28]. Moreover, the well-known P53 mutation in cancer is also a missense mutation[29]. Similarly, our bioinformatics data indicate that missense mutations in SLC3A2 may alter its transporter activity, interaction with binding partners, or regulatory mechanisms, potentially impacting its role in ferroptosis and cancer progression. Additional analysis is needed to elucidate the specific effects of these mutations on SLC3A2 function and their contribution to HNSCC pathology.

Using the STRING database, we predicted the protein-protein interaction (PPI) network for SLC3A2, identifying 11 nodes and 45 edges. This network imparts noteworthy understanding of functional interactions and pathways in which SLC3A2 is involved. The PPI network underscores the central role of SLC3A2 in a complex web of interactions that regulate various cellular processes, including amino acid transport, cell proliferation, and survival.To refine our analysis, we input the PPI network data into Cytoscape and identified the top five interacting genes based on rank, betweenness, and other network metrics. These top five genes—identified as key nodes in the network—are likely critical regulators that interact closely with SLC3A2 and may play significant roles in modulating ferroptosis.

Functional annotation of the top interacting genes revealed their involvement in various biological processes and pathways, with a prominent emphasis on the ferroptosis signalling pathway. This finding is particularly noteworthy, as it provides a mechanistic link between SLC3A2 and ferroptosis regulation in HNSCC. The identified genes include key regulators of lipid peroxidation, iron metabolism, and antioxidant defenses, all of which are critical components of the ferroptosis pathway.Our KEGG pathway analysis highlighted the interaction between SLC3A2 and GPX4, a well-known inhibitor of ferroptosis through the sequence signalling. SLC3A2, also known as CD98 or 4F2hc, is a key player in amino acid transport across the plasma membrane. This protein, in association with various light chain subunits, facilitates the exchange of extracellular cystine with intracellular glutamate[30]. Cystine is the oxidized dimeric form of cysteine, an amino acid essential for the synthesis of GSH. Upon entering the cell, cystine is hastily reduced to cysteine, which then serves as a precursor for GSH synthesis[31]. The first step in GSH synthesis is catalyzed by gamma-glutamylcysteine synthetase (GCL), also known as glutamate-cysteine ligase. This enzyme catalyzes the condensation of cysteine with glutamate to form gamma-glutamylcysteine. This reaction is the rate-limiting step in GSH synthesis and is tightly regulated by cellular conditions, such as oxidative stress. In the

second step, gamma-glutamylcysteine is combined with glycine by the enzyme glutathione synthetase (GSS) to form GSH[32]. GSH is a tripeptide composed of glutamate, cysteine, and glycine, and it consider as a major antioxidant in cells by neutralizing reactive oxygen species (ROS) and maintaining redox balance. Glutathione is essential for safeguarding cells against oxidative damage, primarily through its involvement with glutathione peroxidase 4 (GPX4)[33]. GPX4 is a unique enzyme that reduces lipid hydroperoxides to their corresponding alcohols, thereby preventing the propagation of lipid peroxidation and subsequent cell death. GPX4 reduces lipid hydroperoxides (ROOH) to lipid alcohols (ROH) using GSH as a cofactor. During this process, GSH is oxidized to glutathione disulfide (GSSG)[34]. This reaction is essential for regulating lipid homeostasis and avoiding the buildup of lipid peroxides, which can initiate ferroptosis. In the absence of adequate GSH levels, GPX4 activity is compromised, leading to the accumulation of lipid hydroperoxides and the initiation of ferroptosis[35]. The regulation of GPX4 by SLC3A2 suggests thatSLC3A2 may modulate ferroptosis by influencing GPX4 activity. This interaction presents a potential therapeutic target, where inhibiting SLC3A2 could lead to reduced GPX4 activity, increased lipid peroxidation, and induction of ferroptosis in HNSCC cells.

The comprehensive bioinformatics analysis presented in this study suggests that SLC3A2 is a promising therapeutic target in HNSCC. By targeting SLC3A2, it may be possible to disrupt its interaction with GPX4 and other key regulators, thereby inducing ferroptosis and promoting cancer cell death. This approach could be particularly effective in overcoming therapy resistance, as cancer cells that evade apoptosis may still be susceptible to ferroptosis.Furthermore, the high expression of SLC3A2 in metastatic stages of HNSCC indicates that targeting this gene could also inhibit metastatic spread, providing a dual benefit of reducing primary tumor growth and preventing metastasis. The development of SLC3A2 inhibitors or modulators could thus represent a novel and effective strategy for treating HNSCC.

Conclusion

In conclusion, our bioinformatics approaches have elucidated the critical role of SLC3A2 in regulating ferroptosis in HNSCC. The upregulation of SLC3A2 in HNSCC tumor and its dynamic expression across metastatic stages highlight its potential as a therapeutic target. Targeting SLC3A2 to induce ferroptosis could enhance the efficacy of existing cancer therapies, warranting further experimental studies to validate these findings and explore therapeutic potential.

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Conflict of interest

All authors declare no conflict of Interest.

References

1 Johnson DE, Burtness B, Leemans CR., Lui VWY, Bauman JE & Grandis JR, Head and neck squamous cell carcinoma. *Nat Rev Dis Primers*, 6 (2020) 92.

2 Sathishkumar K, Chaturvedi M, Das P, Stephen S & Mathur P, Cancer incidence estimates for 2022 & projection for 2025: Result from National Cancer Registry Programme, India. *Indian J Med Res*, 156 (2022) 598.

3 Bagal S, Budukh A, Thakur JS, Dora T, Qayyumi B, Khanna D, Fernandes D, Chakravarti P, Singh R, Patil S, Dikshit R & Chaturvedi P, Head and neck cancer burden in India: an analysis from published data of 37 population-based cancer registries. *Ecancermedicalscience*, 17 (2023) 1603.

4 Lechner M, Liu J, Masterson L & Fenton TR, HPV-associated oropharyngeal cancer: epidemiology, molecular biology and clinical management. *Nat Rev Clin Oncol*, 19 (2022) 306.

5 Barsouk A, Aluru JS, Rawla P, Saginala K & Barsouk A, Epidemiology, Risk Factors, and Prevention of Head and Neck Squamous Cell Carcinoma. *Med Sci (Basel)*, 11 (2023), 42.

6 Wang H, Zheng Z, Zhang Y, Bian C, Bao J, Xin Y & Jiang X, Locally advanced head and neck squamous cell carcinoma treatment efficacy and safety: a systematic review and network meta-analysis. *Front Pharmacol*, 14 (2023) 1269863.

7 Feng S, Tang D, Wang Y, Li X, Bao H, Tang C, Dong X, Li X, Yang Q, Yan Y, Yin Z, Shang T, Zheng K, Huang X, Wei Z, Wang K & Qi S, The mechanism of ferroptosis and its related diseases. *Mol Biomed*, 4 (2023) 33.

8 Zhang C, Liu X, Jin S, Chen Y & Guo R, Ferroptosis in cancer therapy: a novel approach to reversing drug resistance. *Mol Cancer*, 21 (2022), 47.

9 Li J, Cao F, Yin HL, Huang ZJ, Lin ZT, Mao N, Sun B & Wang G, Ferroptosis: past, present and future. *Cell Death Dis*, 11 (2020), 88.

10 Pizzagalli MD, Bensimon A & Superti-Furga G, A guide to plasma membrane solute carrier proteins. *FEBS J*, 288 (2021) 2784.

11 Kahlhofer J & Teis D, The human LAT1-4F2hc (SLC7A5-SLC3A2) transporter complex: Physiological and

pathophysiological implications. *Basic Clin Pharmacol Toxicol*, 133 (2023) 459.

12 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*, 18 (2013) 522.

13 Wu D, Yan R, Song S, Swansiger AK, Li Y, Prell JS, Zhou Q & Robinson CV, The complete assembly of human LAT1-4F2hc complex provides insights into its regulation, function and localisation. *Nat Commun*, 15 (2024) 3711.

14 Kahya U, Köseer AS & Dubrovska A, Amino Acid Transporters on the Guard of Cell Genome and Epigenome. *Cancers*, 13 (2021)125.

15 Zhu B, Dongdong C, Lei H, Shumin Z, Tao Y & Qingcheng Y, "SLC3A2 is upregulated in human osteosarcoma and promotes tumor growth through the PI3K/Akt signaling pathway." *Oncol Rep*, 37 (2017) 2575.

16 Prager GW, Poettler M, Schmidinger PR, Mazal M, Susani CC, Zielinski & Haitel A, "CD98hc (SLC3A2), a novel marker in renal cell cancer." *Eur J Clin Invest,* 39 (2009) 304.

17 Liu D, A, M, Wen G, Xing Y & Xia P, Both *In Situ* and Circulating SLC3A2 Could Be Used as Prognostic Markers for Human Lung Squamous Cell Carcinoma and Lung Adenocarcinoma. *Cancers*, 14 (2022) 5191.

18 Li T, Fan J, Wang B. Traugh N, Chen Q, Liu JS, Li B & Liu XS, TIMER: A Web Server for Comprehensive Analysis of Tumor-Infiltrating Immune Cells. *Cancer Res*, 77 (2017) e108.

19 Chandrashekar DS, Karthikeyan SK, Korla PK, Patel H, Shovon AR, Athar M, Netto GJ, Qin ZS, Kumar S, Manne U, Creighton CJ &Varambally S, UALCAN: An update to the integrated cancer data analysis platform. *Neoplasia*, 25 (2022) 18.

20 Chandrashekar DS, Bashel B, Balasubramanya SAH, Creighton CJ, Ponce-Rodriguez I, Chakravarthi BVSK & Varambally S, UALCAN: A Portal for Facilitating Tumor Subgroup Gene Expression and Survival Analyses. *Neoplasia*, 19 (2017) 649.

21 Tang Z, Li C, Kang B, Gao G, Li C & Zhangv Z, GEPIA: a web server for cancer and normal gene expression profiling and interactive analyses. *Nucleic Acids Res*, 45 (2017), W98.

22 Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, Jacobsen A, Byrne CJ, Heuer ML, Larsson E, Antipin Y, Reva B, Goldberg AP, Sander C & Schultz N, ThecBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov*, 2 (2012) 401.

23 Gao J, Aksoy BA, Dogrusoz U, Dresdner G, Gross B, Sumer SO, Sun Y, Jacobsen A, Sinha R, Larsson E, Cerami E, Sander C & Schultz N, Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. *Sci Signal*, 6 (2013) l1.

24 Szklarczyk D, Kirsch R, Koutrouli M, Nastou K, Mehryary F, Hachilif R, Gable AL, Fang T,Doncheva NT, Pyysalo S, Bork P, Jensen LJ & von Mering C, The STRING database in 2023: protein-protein association networks and functional enrichment analyses for any sequenced genome of interest. *Nucleic Acids Res.*, 51 (2023) D638.

25 Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, Amin N, Schwikowski B & Ideker T, Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome Res*, 13 (2003) 2498.

26 Ge SX, Jung D & Yao R, ShinyGO: a graphical gene-set enrichment tool for animals and plants. *Bioinformatics*, 36 (2000) 2628.

27 Nachef M, Ali AK, Almutairi SM & Lee SH, Targeting SLC1A5 and SLC3A2/SLC7A5 as a Potential Strategy to Strengthen Anti-Tumor Immunity in the Tumor Microenvironment. *Front Immunol*, 12 (2021) 624324.

28 Desai SS, Raksha RK, Jain A, Bawa PS, Dutta P, Atre G, Subhash A, Rao Vishal USR, Suvratha J, Srinivasan S & Choudhary B, Multidimensional Mutational Profiling of the Indian HNSCC Sub-Population Provides IRAK1, a Novel Driver Gene and Potential Druggable Target. *Front Oncol*, 11 (2021) 723162.

29 Li M, Sun D, Song N, Chen X, Zhang X, Zheng W, Yu Y & Han C, Mutant p53 in head and neck squamous cell carcinoma: Molecular mechanism of gain-of-function and targeting therapy. *Oncol Rep*, 50 (2023) 162.

30 Lee J & Roh JL, SLC7A11 as a Gateway of Metabolic Perturbation and Ferroptosis Vulnerability in Cancer. *Antioxidants (Basel, Switzerland)*, 11 (2022) 2444.

31 Forman HJ, Zhang H & Rinna A, Glutathione: overview of its protective roles, measurement, and biosynthesis. *Mol Aspects Med*, 30 (2009) 1.

32 Lu SC, Regulation of glutathione synthesis. *Mol Aspects Med*, 30 (2009) 42.

33 Pizzorno J, Glutathione!. *Integr Med (Encinitas)*, 13 (2014) 8.

34 Xie Y, Kang R, Klionsky D J & Tang D, GPX4 in cell death, autophagy, and disease. *Autophagy*, 19 (2023) 2621.

35 Yu Y, Yan Y, Niu F, Wang Y, Chen X, Su G, Liu Y, Zhao X, Qian L, Liu P & Xiong Y, Ferroptosis: a cell death connecting oxidative stress, inflammation and cardiovascular diseases. *Cell Death Discov*, 7 (2021) 193.