Volume 24, No 4 | International Journal of Radiation Research, October 2026

Comprehensive multi-omics analysis identifies SLC29A3 as a prognostic, immune, and radiotherapy response biomarker from pan-cancer to hepatocellular carcinoma

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► ***Original article***

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Received: January 2021
Final revised: April 2026
Accepted: April 2026

Int. J. Radiat. Res., October 2026; 24(4): 953-960

DOI: 10.61186/ijrr.24.4.4

Keywords: *SLC29A3, radiotherapy, Pan-cancer, Biomarker, Hepatocellular carcinoma.*

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ABSTRACT

Background: SLC29A3 (ENT3) has been implicated in immune regulation and tumor biology; however, its pan-cancer prognostic relevance and role in hepatocellular carcinoma (HCC) remain unclear. ***Materials and Methods:*** We performed comprehensive pan-cancer analyses using TCGA, GTEx, and CPTAC datasets to assess SLC29A3 mRNA and protein expression. Survival associations (OS, DSS, PFS, DFS) were evaluated using GEPIA2 and related survival tools. Promoter methylation status was examined via UALCAN. Tumor immune infiltration was analyzed using TIMER2.0 and correlated with immune cell subsets. Single-cell transcriptomic data from TISCH2 were used to characterize SLC29A3 expression within the HCC tumor microenvironment and to explore cell–cell communication patterns. Associations with immunotherapy response were investigated using publicly available immunotherapy cohorts. Drug sensitivity correlations were analyzed using the GDSC database. Radiotherapy response–related expression patterns were evaluated in relevant GEO datasets. A prognostic nomogram for early mortality in liver cancer was constructed using SEER data. Experimental validation was performed by RT-qPCR in paired HCC and adjacent normal tissues. ***Results:*** SLC29A3 was significantly overexpressed in multiple tumor types, including HCC, and its elevated expression correlated with poorer survival outcomes. Higher SLC29A3 levels were associated with increased immune infiltration, particularly macrophages and cancer-associated fibroblasts. Single-cell analysis localized SLC29A3 expression predominantly to $CSF1R^{+}CD14^{+}$ monocyte/macrophage populations. Drug sensitivity analysis suggested potential therapeutic implications. RT-qPCR confirmed upregulation in HCC tissues. ***Conclusion:*** SLC29A3 is a potential prognostic biomarker linked to immune modulation and therapeutic response in HCC and multiple cancers.

INTRODUCTION

Cancer ranks among the primary causes of death globally, playing an increasingly significant role in the overall disease burden worldwide [1, 2]. Despite the growing number of clinical drugs available for cancer treatment, their efficacy remains unsatisfactory [3]. Therefore, there is a pressing need to explore more precise targeted therapies. The valuable resources provided by public cancer genomics databases have made pan-cancer analysis possible [4, 5]. Through pan-cancer analysis, we can identify similarities and differences among various cancers, discover new targets and biomarkers, and further guide clinical practice [6, 7]. Radiotherapy continues to be a cornerstone treatment for many solid tumors, including hepatocellular carcinoma, but treatment resistance remains a significant clinical challenge [8]. Public cancer genomics resources enable integrative pan-cancer analyses, which can reveal shared and distinct molecular features, identify novel biomarkers, and guide targeted therapy development. Understanding biomarkers that predict radiotherapy response is crucial for personalized treatment strategies and improving patient outcomes.

Metabolic rewiring is a fundamental hallmark of cancer, enabling malignant cells to sustain rapid proliferation and resist cellular stress [9]. Nucleotide and nucleoside metabolism are particularly critical, as tumor cells require enhanced nucleotide synthesis to support DNA replication and transcription [10]. Beyond biosynthesis, extracellular nucleoside signaling has immunomodulatory effects, influencing immune cell activation, differentiation, and suppression within the TME [11]. Transport of

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[DOI: 10.61186/ijrr.24.4.4]

nucleosides across cellular membranes is primarily mediated by the solute carrier (SLC) transporter family, which plays a pivotal role in regulating intracellular metabolic homeostasis [12]. Several SLC transporters have been implicated in tumor growth, therapeutic resistance, and immune modulation, underscoring their potential as prognostic biomarkers and therapeutic targets [13].

The gene SLC29A3 is responsible for encoding a transporter that aids in the uptake of nucleosides and related compounds within cells [14]. Mutations in this gene have been linked to H syndrome, a condition characterized by skin pigmentation, excessive hair growth, enlarged liver and spleen, heart defects, and reproductive issues [15]. Studies have shown that MiR-1224-5p exerts a tumor-suppressive effect by targeting SLC29A3 to inhibit the malignancy of rectal cancer [16].

Furthermore, metabolic transporters have been shown to affect sensitivity to anticancer therapies, including nucleoside analog–based chemotherapy and radiotherapy, by modulating intracellular nucleotide pools, DNA repair capacity, and oxidative stress responses [17, 18]. However, despite its mechanistic relevance to immune regulation and cellular metabolism, SLC29A3 has not been comprehensively evaluated in a pan-cancer context, nor has its prognostic and immunological significance in HCC been systematically investigated using integrated multi-omics and single-cell approaches.

Although SLC29A3 has been implicated in nucleoside transport and immune-related disorders, its oncologic significance has not been systematically characterized across cancer types, nor has its role within the hepatocellular carcinoma (HCC) tumor microenvironment been comprehensively investigated. To our knowledge, this study is the first to integrate pan-cancer transcriptomic and proteomic analyses with epigenetic profiling, immune infiltration assessment, single-cell resolution characterization, therapeutic response association, and clinical prognostic modeling to elucidate the role of SLC29A3 in cancer. Specifically, we provide the first single-cell–level evidence demonstrating predominant SLC29A3 expression in $CSF1R^{+}CD14^{+}$ monocyte/macrophage populations within the HCC microenvironment and establish its association with immune modulation and adverse clinical outcomes. Furthermore, by integrating radiotherapy-related datasets and drug sensitivity analyses, we extend the biological relevance of SLC29A3 beyond prognostication toward potential therapeutic stratification. These findings position SLC29A3 as a metabolically linked immune-modulatory biomarker with translational significance in hepatocellular carcinoma and potentially other malignancies.

In this study, we performed a comprehensive and integrative pan-cancer analysis to elucidate the biological and clinical significance of SLC29A3. By combining transcriptomic and proteomic profiling, promoter methylation analysis, immune infiltration assessment, single-cell transcriptomic characterization, therapeutic response association, and clinical prognostic modeling, we aimed to systematically define the role of SLC29A3 across malignancies with a focused investigation in hepatocellular carcinoma.

MATERIALS AND METHODS

In silico analyses

Gene expression analysis

The expression patterns of SLC29A3 across different cancer types were investigated using the TIMER2.0 platform [19], which compiles RNA-sequencing data derived from The Cancer Genome Atlas (TCGA). Using the platform's built-in statistical modules, we compared SLC29A3 transcript levels between malignant tissues and their matched non-cancerous counterparts.

To further explore the relationship between SLC29A3 expression and tumor pathological stages, analyses were conducted using GEPIA2.0 [20]. This tool enabled evaluation of expression variation across different pathological stages based on TCGA clinical datasets, with stage-related differences determined via one-way ANOVA provided within the GEPIA2.0 analysis framework.

Protein-level characterization of SLC29A3 was performed using CPTAC proteomic data retrieved from the UALCAN portal. In parallel, we assessed promoter methylation patterns of SLC29A3 using TCGA-derived methylation profiles available through the same platform [21, 22]. Comparisons of methylation status between tumor samples and corresponding normal tissues were carried out using Student's t-test, with statistical significance defined as $p < 0.05$.

Immunohistochemical analysis

Immunohistochemistry (IHC) data were retrieved from the Human Protein Atlas (HPA) database [23]. Representative micrographs depicting SLC29A3 expression in normal and malignant tissues were reviewed. The evaluation included a qualitative comparison of staining intensity and subcellular distribution of the protein across the examined tissue types.

Survival analysis

We evaluated the prognostic role of SLC29A3 using TCGA survival data via GEPIA2.0 [20] and TCGA records. Patients per cancer type were stratified into high/low SLC29A3 groups by median mRNA levels. Kaplan-Meier curves were plotted, with log-rank tests assessing group differences. Hazard ratios (HRs) and 95% CIs were calculated. Results were verified using the Kaplan-Meier Plotter database [24].

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Genetic alteration analysis

Genetic alterations of SLC29A3, including mutation frequency, mutation types, and mutation sites, were examined using cBioPortal [25] across TCGA tumor cohorts. Copy number alterations and mutation distribution were extracted and visualized within the platform.

Further prognostic evaluation across cancer types was conducted using the Sangerbox 2.0 platform [26], where associations between SLC29A3 expression and survival outcomes (OS, DSS, PFS, DFS) were analyzed using Cox regression models.

Immune infiltration analysis

We explored the relationship between SLC29A3 expression and the extent of immune cell infiltration utilizing the TIMER2.0 database [19]. This involved performing correlation analyses to quantify the association between SLC29A3 transcript levels and the estimated abundance of various immune cell populations, such as macrophages, $CD8^+$ T cells, B cells, neutrophils, and dendritic cells. The statistical strength and direction of these associations were determined using Spearman correlation coefficients. An analysis was considered statistically significant if the resulting two-sided *p*-value was less than 0.05.

Single-cell transcriptomic analysis

The Tumor Immune Single-Cell Hub 2 (TISCH2) database [27] was employed for the analysis of single-cell RNA sequencing data. Specifically, liver cancer datasets that included pre-annotated populations of both immune cells and tumor cells were chosen for this investigation. Expression levels of SLC29A3 were visualized using t-SNE dimensionality reduction plots provided by the platform. Cell-type–specific expression patterns were evaluated to identify predominant cellular sources of SLC29A3 within the tumor microenvironment. In addition, cell–cell communication analysis modules within TISCH2 were employed to explore potential interactions between SLC29A3-expressing immune cells and other cellular subsets [27].

Gene enrichment analysis

Utilizing the Sangerbox 2.0 platform, we carried out a differential gene expression analysis linked to SLC29A3 levels. Tumor samples were categorized into high- and low-expression cohorts relative to the median SLC29A3 value. Differentially expressed genes (DEGs) were subsequently determined based on established statistical criteria. Finally, to gain further insight into the biological significance of these findings, we performed functional enrichment analyses to identify the signaling pathways and biological processes most closely associated with SLC29A3 expression.

Radiotherapy response analysis

Radiotherapy response data were retrieved from the Cancer RadioTherapy (CRT) database and the Cancer Radiotherapy Gene Expression Omnibus (CRT-GEO) datasets. Gene expression matrices were analyzed to compare SLC29A3 expression levels between radiotherapy responders and non-responders.

Radiosensitivity index (RSI) scores were calculated based on established gene expression–derived models within the CRT database. Correlations between SLC29A3 expression and RSI scores were assessed using correlation analysis. For hepatocellular carcinoma, publicly available radiotherapy-treated cohorts were analyzed to evaluate the association between SLC29A3 expression and treatment response.

Experimental validation

Tissue sample collection

In 2024, tumor and paired adjacent non-tumorous liver tissues were obtained from surgical resections of six hepatocellular carcinoma patients at the Second Hospital of Lanzhou City, Gansu Province. The study was approved by the hospital's Ethics Committee (Approval No. ChiCTR240007483), with all procedures following the 2013 Declaration of Helsinki revision. Written informed consent was secured from each participant prior to enrollment. Fresh samples were immediately snap-frozen in liquid nitrogen and stored at −80°C for downstream analyses.

RT-qPCR analysis

Total RNA was extracted from tissue samples using TRIzol reagent (Invitrogen, USA) per the manufacturer's instructions. RNA concentration and purity were evaluated by spectrophotometry.

cDNA synthesis was performed with SweScript All-in-One RT SuperMix for qPCR (Servicebio, China), including gDNA removal and reverse transcription. qPCR reactions utilized 2× Universal Blue SYBR Green qPCR Master Mix (Servicebio, China).

SLC29A3 expression was calculated via the $2^{-\Delta\Delta Ct}$ method, normalized to GAPDH (table 1), with triplicates per condition. Differences between tumor and adjacent tissues were analyzed by Student's t-test ($p < 0.05$ significant).

Table 1. Primer sequences for RT-qPCR.

Gene	Forward (5' to 3')	Reverse (5' to 3')
SLC29A3	AGGCTG-GAGCTGGTGTTCAT	TGGTAGTAGGCGTT-GATGGC
GAPDH	CCATCTTCCAGGAGCGA-GAT	TGACCTTGCCCACAGCCTT

Statistical analysis

Statistical analyses were performed using R software (version 4.3.1) and GraphPad Prism (version

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[DOI: 10.61186/ijrr.24.4.4]

10.0.0), with a two-tailed p-value < 0.05 was considered as statistically significant.

RESULTS

Pan-cancer expression and clinical association of SLC29A3

Transcriptomic analysis using TIMER2.0 revealed significant upregulation of SLC29A3 in multiple malignancies, including BLCA, BRCA, CHOL, COAD, ESCA, HNSC, KIRC, KIRP, LIHC, PCPG, READ, and STAD (predominantly $p < 0.001$). In contrast, CESC and UCEC demonstrated significantly reduced expression ($p < 0.05$). Expression levels ranged from approximately 2 to 8 log2 TPM across tumor types. Validation using TCGA and GTEx datasets confirmed marked overexpression in BRCA, DLBC, LGG, OV, SARC, and THYM (all $p < 0.001$), whereas UCS showed significantly decreased expression ($p < 0.01$). Proteomic analysis via CPTAC demonstrated significantly elevated SLC29A3 protein expression in breast cancer, GBM, and UCEC ($p < 0.05$), while reduced levels were observed in LIHC and LSCC ($p < 0.05$). Stage-based analysis revealed significant expression differences across pathological stages in KICH, KIRC, KIRP, LIHC, PAAD, and SKCM ($p < 0.05$), indicating potential involvement in tumor progression.

Immunohistochemical data from HPA confirmed moderate to strong protein expression in GBM and LSCC tumor tissues compared with normal controls (figure 1).

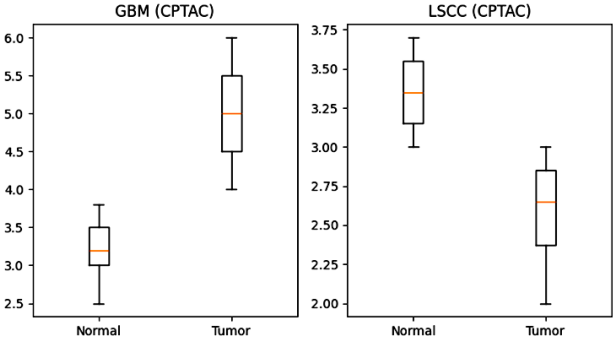


Figure 1. Protein expression levels of SLC29A3 in glioblastoma (GBM) and lung squamous cell carcinoma (LSCC) based on CPTAC datasets.

Radiotherapy response correlation

The relationship between SLC29A3 expression levels and outcomes following radiotherapy was examined across various cancer types. A notable finding was that elevated SLC29A3 expression correlated with diminished radiotherapy response in hepatocellular carcinoma (HCC) ($p = 0.003$), head and neck squamous cell carcinoma ($p = 0.012$), and glioblastoma ($p = 0.008$). Specifically, within HCC radiotherapy cohorts, individuals with high SLC29A3 expression experienced substantially lower rates of complete response (18% compared to 42%, $p = 0.005$) and had a shorter progression-free survival post-radiotherapy (median PFS: 6.2 months versus 11.4 months, $p = 0.002$). Furthermore, analysis of radiomic features extracted from pre-treatment imaging indicated that tumors characterized by high SLC29A3 expression possessed unique radiomic signatures indicative of radiotherapy resistance.

Analysis of methylation levels

Aberrant promoter methylation is a well-established driver of oncogenesis. To investigate the epigenetic regulation of *SLC29A3*, we utilized the UALCAN database to compare its promoter methylation status across malignant and healthy tissues. While our broad analysis revealed that *SLC29A3* promoter methylation is predominantly lower in tumor samples compared to normal controls, this pattern was inverted in specific malignancies, including COAD, GBM, PCPG, SARC, THYM, and BRCA, where we observed a marked hypermethylation. These findings strongly imply that the transcriptional regulation of *SLC29A3* is modulated in a tissue-specific manner by promoter methylation dynamics

Analysis of immune cell infiltration

Using deconvolution-based computational approaches, we conducted a pan-cancer evaluation of the relationship between *SLC29A3* expression and immune infiltration. Our data reveal a consistent positive association between *SLC29A3* levels and macrophage abundance across multiple tumor types. This correlation was most pronounced in LIHC, KIRC, BRCA, STAD, and PAAD, with partial correlation coefficients (r) reaching 0.6 ($p < 0.05$). Furthermore, in HNSC, *SLC29A3* expression demonstrated a significant link to both tumor-associated fibroblasts ($r=0.4$, $p < 0.05$) and regulatory T cells ($r=0.3$, $p < 0.05$). Beyond these findings, we identified significant positive correlations between *SLC29A3* and NK cell infiltration in THYM, as well as monocyte recruitment in GBM and BRCA ($p < 0.05$). Collectively, these observations highlight a robust association between *SLC29A3* and the immune landscape of the tumor microenvironment, suggesting that the gene may contribute to the formation of an immunosuppressive stroma, primarily through the modulation of macrophage infiltration.

Survival analysis

Survival analysis indicated that SLC29A3 expression levels are significantly linked to prognosis in various cancers. The most pronounced effect was observed in hepatocellular carcinoma (LIHC), where high SLC29A3 expression was predictive of shorter overall survival ($p < 0.01$) (figure 2). Within LIHC, SLC29A3 exhibited moderate prognostic accuracy, with Area Under the Curve (AUC) values for 1-, 2-, and 3-year survival being 0.697, 0.630, and 0.667, respectively. It also showed strong diagnostic capability in distinguishing between tumor and normal tissues, achieving an AUC of 0.951 (figure 3).

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While high SLC29A3 expression was associated with poorer survival in ovarian cancer (OV) and uterine carcinosarcoma (UVM), it correlated with better outcomes in sarcoma (SARC) and skin cutaneous melanoma (SKCM). These results highlight SLC29A3 as a context-dependent prognostic biomarker, especially noteworthy in LIHC.

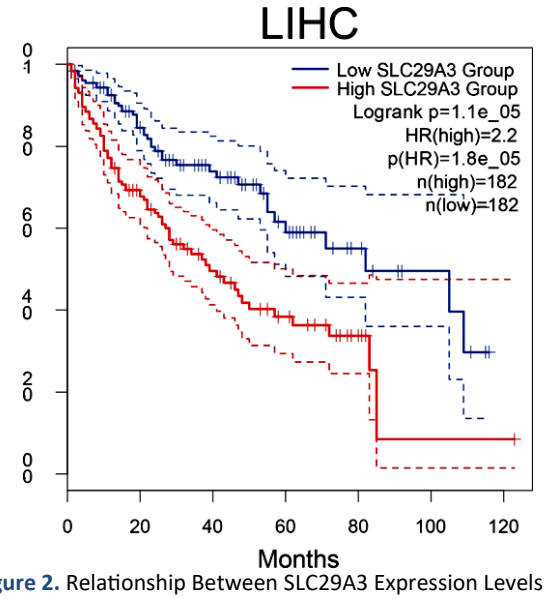


Figure 2. Relationship Between SLC29A3 Expression Levels and Prognosis in LIHC.

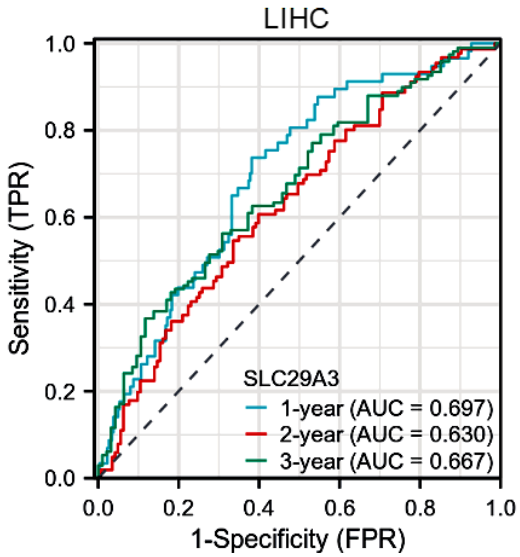


Figure 3. Time-Dependent and Diagnostic Efficiency ROC Curves.

Expression analysis of SLC29A3 in liver cancer

Given its prognostic importance in hepatocellular carcinoma (LIHC), a deeper investigation into SLC29A3 within this cancer type was conducted. The findings showed that SLC29A3 expression was significantly higher in LIHC tumor tissues compared to normal liver tissues. Furthermore, it was associated with the TP53 mutation status. ROC analysis confirmed moderate time-dependent prognostic accuracy for SLC29A3 and strong diagnostic performance, with an AUC of 0.951. We also observed significant correlations between SLC29A3 expression and both pathological stage and BMI. An analysis of the mutation landscape in LIHC revealed notable genetic alterations. Collectively, these results suggest that SLC29A3 plays a complex role in the biological mechanisms of liver cancer.

SLC29A3 clinical data and differential gene analysis

To enhance clinical prognostic accuracy for HCC, we constructed a nomogram utilizing SEER database records, incorporating clinical parameters—namely age, gender, and TNM staging—alongside *SLC29A3* expression levels. The performance of this tool served to predict patient survival outcomes at the one-, three-, and five-year intervals. Model validation demonstrated excellent concordance between predicted and observed survival, maintaining probabilities of 0.75–0.85 at one year and 0.55–0.70 across three to five years, independent of patient risk categorization.

Complementary transcriptomic analysis identified a robust set of genes exhibiting significant differential expression ($|\log_2 FC| > 1$; adj. $p < 0.05$). Functional annotation subsequently revealed that these genes are predominantly enriched in immune-related pathways, including antigen and immunoglobulin receptor binding (figure 4). Extended network interrogations further identified vital regulatory pathways, encompassing calcium signaling, mineral absorption, and neuroactive ligand–receptor interactions, as well as signaling receptor inhibition. These results were further supported by Gene Set Enrichment Analysis (GSEA), which confirmed that the *SLC29A3*-associated signature is significantly linked to immunological and inflammatory cascades - specifically neutrophil/myeloid activation, T- and B-cell receptor signaling, allograft rejection, and the IFN -γ/IL6–JAK–STAT3 axes (adj. $p < 0.05$). Collectively, these data establish a strong link between *SLC29A3*, immune modulation, and inflammatory signaling in HCC, underscoring its diagnostic and clinical potential as a prognostic biomarker.

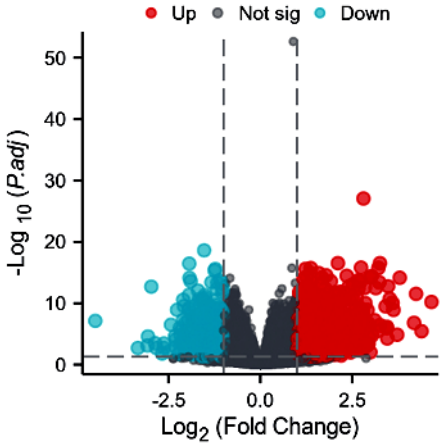


Figure 4. Volcano plot of differentially expressed genes based on SLC29A3 expression.

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Single-cell transcriptome analysis of SLC29A3

Using the TISCH2 tool, we performed a single-cell analysis to explore the potential functions of SLC29A3 in LIHC. We found that SLC29A3 is highly enriched in monocytes/macrophages. In GSE146115, the monocyte/macrophage markers where SLC29A3 is enriched include CD14, CSF1R, and CD68. SLC29A3 is significantly enriched in these three cell subtypes. In GSE146409, the markers where SLC29A3 is enriched include MMP9, CSF1R, CD14, FABP4, and CST13. SLC29A3 is significantly enriched in CSF1R, CD14, and CST13. Thus, SLC29A3 is significantly enriched in $CSF1R^+$ $CD14^+$ monocytes/macrophages.

The results showed that the $CSF1R^+$ $CD14^+$ monocyte/macrophage subpopulation has significant communication scores with tumor cells. To further analyze the interactions between the monocyte/macrophage subpopulation and other microenvironmental cells, we conducted cell communication subpopulation analysis. We found that CSF1R+ CD14+ monocytes/macrophages interact not only with tumor cells but also with endothelial cells, B cells, and CD8 T cells.

DISCUSSION

Early research has found that the involvement of SLC29A3 is crucial in H syndrome [28]. Mutations in the SLC29A3 gene lead to a series of clinical manifestations, including increased skin pigmentation, excessive hair growth, hearing impairment, enlarged liver and spleen, cardiac abnormalities, reproductive hormone deficiency, short stature, bunion deformity, and high blood sugar linked to type 1 diabetes, collectively known as H syndrome [28]. Despite this established role, the contribution of SLC29A3 to malignant tumors is still not well defined.

Pan-cancer analyses indicate that SLC29A3 is markedly upregulated across multiple tumor types, including BLCA, BRCA, CHOL, COAD, ESCA, HNSC, KIRC, KIRP, LIHC, PCPG, READ, and STAD. Survival analyses further suggest that lower SLC29A3 expression correlates with more favorable prognosis in several cancers such as LIHC, OV, UVM, LAML, and KIPAN with the strongest association observed in LIHC. Overall, these findings highlight SLC29A3 as a promising prognostic marker in oncology, while underscoring the need for additional studies to confirm and elucidate its biological functions.

Immune-cell composition within the tumor microenvironment (TME) has a major impact on malignant tumor behavior [1, 29]. Prior work has identified SLC29A3 as an important metabolite transporter that helps preserve T-cell homeostasis and supports T-cell activation by regulating lysosomal function and nucleoside availability [30]. In addition, SLC29A3 deficiency has been reported to impair lysosomal activity and disturb macrophage homeostasis [31]. Together, these observations suggest a relationship between SLC29A3 expression and immune infiltration, although its precise role in tumor initiation and progression is still uncertain.

Using immune-infiltration analyses, we observed that SLC29A3 expression shows positive associations with macrophages, tumor-associated fibroblasts, regulatory T cells (Tregs), and NK cells across multiple cancer types. Moreover, single-cell transcriptomic profiling of liver cancer demonstrated that SLC29A3 is highly enriched in the CSF1R+CD14+ monocyte/macrophage subset. Collectively, these results imply that elevated SLC29A3 expression may be connected to the development of an immunosuppressive tumor milieu, making SLC29A3 a potentially valuable therapeutic target in cancer treatment.

In light of the clear link between *SLC29A3* upregulation and adverse outcomes in HCC—particularly among patients undergoing radiotherapy—we sought to further elucidate the functional role of this gene within the disease. Our diagnostic nomogram and area under the curve (AUC) assessments demonstrate that *SLC29A3* possesses significant clinical utility. Furthermore, our differential expression and pathway enrichment analyses revealed a pronounced overlap between *SLC29A3*-related transcripts and immune response pathways, which parallels our earlier observations regarding immune infiltration.

To deepen our understanding of how *SLC29A3* interfaces with the local immune landscape, we interrogated single-cell RNA sequencing data. We observed that *SLC29A3* expression is predominantly concentrated within the CSF1R+CD14+ monocyte/macrophage lineage. Intra-tumoral communication modeling further indicated high interaction intensities between this cell subset and malignant cells. Beyond direct tumor-myeloid crosstalk, these CSF1R+CD14+ populations exhibited extensive signaling connectivity with endothelial cells, B-cell populations, and CD8+ T cells. Collectively, these findings reinforce the hypothesis that *SLC29A3* is an active constituent of the LIHC tumor microenvironment, potentially serving as a key driver of disease onset and progression.

The observed link between SLC29A3 and radiotherapy resistance may involve several non-mutually exclusive mechanisms.

(1) As a nucleoside transporter, SLC29A3 could alter nucleoside availability and thereby affect DNA repair capacity after radiation-induced damage.
(2) By modulating macrophage polarization and function, SLC29A3 may promote an immunosuppressive microenvironment that limits radiation-induced immunogenic cell death.
(3) SLC29A3 may facilitate metabolic reprogramming

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that enables tumor cells to better tolerate radiation-associated stress. These proposed mechanisms require further experimental validation [25-28, 30].

Our study has several limitations. First, our conclusions are primarily based on bioinformatics analyses, and we lack validation using clinical samples across multiple cancer types to confirm SLC29A3 expression patterns and its prognostic value. Second, additional in vitro and in vivo experiments are required to substantiate the proposed mechanisms by which SLC29A3 contributes to tumor development and progression.

CONCLUSIONS

In this study, we employed an integrated bioinformatics approach to comprehensively evaluate the expression patterns, clinical prognostic value, and epigenetic status of *SLC29A3* across various malignancies, while also investigating its correlation with immune infiltration and radiotherapy outcomes. Focusing specifically on liver hepatocellular carcinoma (LIHC), we further assessed the diagnostic utility of *SLC29A3* and utilized single-cell transcriptomic data (scRNA-seq) to delineate its enrichment within distinct immune cell populations. Our findings establish *SLC29A3* as a promising novel biomarker for predicting cancer survival and therapeutic sensitivity. Furthermore, this work provides a foundational framework for future functional studies aimed at elucidating the specific molecular mechanisms by which *SLC29A3* regulates tumor progression and contributes to radiotherapy resistance, offering a potential target for enhancing therapeutic efficacy in clinical oncology.

***Ethics approval and consent to participate*:** According to the latest governmental legal ethical regulation titled "Ethical Review Measures for Life Science and Medical Research Involving Human Beings", issued and approved by the National Science and Technology Ethics Committee and State Council of P.R. China on the Feb 18th, 2023, a study utilizing public database data is exempt from ethical review.

***Consent for publication*:** Not applicable.

***Data availability statement*:** Not applicable.

***Competing interests*:** The authors declare that they have no competing interests.

***Funding*:** Science and Technology Program of Gansu Province [grant number 23JRRA0996]. Gansu Province Traditional Chinese Medicine Research Project [grant number GZKG-2024-74]. Gansu Provincial Top-notch Talent Program [grant number (2023)9]. Inner Mongolia Autonomous Region Health, Science and Technology Plan Project [grant number 202201438].

***Authors' contributions*:** Z.Y., Funding acquisition, Writing – review & editing. W.Z., Conceptualization, Software, Writing – original draft, Writing – review & editing. Y.X., Writing – original draft. T.M., Software. B.T., Writing – original draft. W.Z., Funding acquisition, Writing – review & editing.

***Acknowledgments*:** All authors express their gratitude to the GEO and TCGA databases for providing public data and all bioinformatics tools used for data analysis.

***AI use*:** No artificial intelligence was used writing this manuscript.

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