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# **1. S100A10 Is a New Prognostic Biomarker Related to the Malignant Molecular Features and Immunosuppression Process of Adult Gliomas**

<https://pubmed.ncbi.nlm.nih.gov/35779750/>

## **Abstract**

**Objective:** Previous studies have demonstrated the role of S100A10 in the progression of several tumors; however, few studies have investigated its immunological characteristics in adult gliomas. In this study, we systematically explored its biological features and clinical significance in adult gliomas.

**Methods:** Altogether, 325 glioma cases from the Chinese Glioma Genome Atlas and 699 glioma cases from The Cancer Genome Atlas were included as the training and validation cohorts. R software was used for data analysis and mapping using the RNA sequencing data from these cases. One-way analysis of variance and Student's t-test were used to assess the differences between the groups. Differences were considered statistically significant at P < 0.05.

**Results:** We found that S100A10 was remarkably highly expressed in high-grade glioma, isocitrate dehydrogenase wild type, 1p19q noncodeletion type, O6-methylguanine-DNA methyltransferase promoter unmethylation type, and mesenchymal-like molecular subtype. S100A10 specifically and sensitively indicates the mesenchymal-like molecular subtype. Upregulated S100A10 levels were independently correlated with poor survival. S100A10-related biological processes in gliomas mainly concentrate on immunoreaction and inflammatory response. We then proved that S100A10 was positively related to most inflammatory metagenes, except IgG, including HCK, LCK, MHC II, STAT1, and interferon. More importantly, the levels of glioma-infiltrating immune cells were positively associated with the expression of S100A10, especially in tumor-related macrophages, regulatory T cells, and myeloid-derived suppressor cells.

**Conclusions:** S100A10 is closely related to malignant pathological subtypes, worse prognosis, and immunosuppressive immune cell infiltration in adult gliomas, making it a promising biomarker and potential target in the diagnosis, treatment, and prognostic assessment of gliomas.

# 2. **CD93 is Associated with Glioma-related Malignant Processes and Immunosuppressive Cell Infiltration as an Inspiring Biomarker of Survivance.**

**Full Text:** [**https://link.springer.com/content/pdf/10.1007/s12031-022-02060-4.pdf**](https://link.springer.com/content/pdf/10.1007/s12031-022-02060-4.pdf)

* **Previous reports have confirmed the significance of CD93 in the progression of multiple tumors; however, there are few studies examining its immune properties for gliomas. Here, we methodically investigated the pathophysiological characteristics and clinical manifestations of gliomas. Six hundred ninety-nine glioma patients in TCGA along with 325 glioma patients in CGGA were correspondingly collected for training and validating**
* **We analyzed and visualized total statistics using RStudio. One-way ANOVA and Student's t-test were used to assess groups' differences. All differences were considered statistically significant at the level of P < 0.05**
* **We examined the associations of CD93 with immune-related meta-genes, and CD93 positively correlated with HCK, LCK, MHC I, MHC II, STAT1 and IFN, while adverse with IgG. Association analyses between CD93 and gliomas-infiltrating immunocytes indicated that the infiltrating degrees of most immunocytes exhibited positive correlations with CD93, particularly these immunosuppressive subsets such as TAM, Treg, and MDSCs. CD93 is markedly associated with adverse pathology types, unfavorable survival, and immunosuppressive immunocytes infiltration among gliomas, thus identifying CD93 as a practicable marker and a promising target for glioma-based precise diagnosis and therapeutic strategies.**
* **We downloaded the total RNA-seq data, molecular pathology information, and survival time of former training sets from the website http:// cance rgeno me. nih. gov/, while the corresponding data for the latter validation set were obtained from http:// www. cgga. org. cn.**
* **Statistical Analysis**

**Statistical analyses together with figure visualization were performed using RStudio with corresponding application packages such as “survival,” “survminer,” “ggplot2,” “pROC,” “pheatmap,” “devtools,” “corrplot,” “ggpubr”, and “corrgram” that were obtained from the website http:// www.r- proje ct. org. Logarithmic transformations were applied to the transcriptome sequencing data that were analyzed in this study prior to further analysis. Kaplan–Meier survivorship curvilinear analyses together with multivariable Cox analyses were performed to compare survival differences among the included patients. Spearman correlation analyses were used for sequencing and for sifting genes that were markedly related to CD93. Pearson’s association analyses were similarly applied for correlational degree assessments. Gene ontology function analysis of gene biological processes and molecular functions together with cellular components was conducted via the website of DAVID Bioinformatical Resource (https:// david. ncifc rf. gov/). AmiGO2 version 2.5.17 was utilized for downloading analyzing immunogene subsets to investigate the functions of CD93 among glioma-associated immunity responses (http:// amigo. geneo ntolo gy. org/ amigo). Single factor variance analyses were applied for difference testing using no fewer than three statistical clusters, while the difference testing for each of the two statistical clusters was completed using Student’s t-test. A P value of less than 0.05 was considered to be statistically significant**

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# **3.The CDK1-Related lncRNA and CXCL8 Mediated Immune Resistance in Lung Adenocarcinoma**

<https://www.mdpi.com/2073-4409/11/17/2688/htm>

* Lung adenocarcinoma (LUAD) is an important component of lung cancer, which is often accompanied by poor prognosis.
* The core of the cell cycle regulatory system is a group of cyclin-dependent kinases (CDKs) [[**4**](https://www.mdpi.com/2073-4409/11/17/2688/htm#B4-cells-11-02688)], each of which is activated at a specific time in the cell cycle and drives the completion of the cell cycle by phosphorylating the corresponding substrate. They are divided into two categories: (1) cell-cycle-associated CDKs (CDK1, CDK2, CDK4, and CDK6) that directly regulate cell cycle progression; and (2) transcriptionally associated CDKs (CDK7, CDK8, CDK9, CDK12, and CDK13) [[**5**](https://www.mdpi.com/2073-4409/11/17/2688/htm#B5-cells-11-02688)]

#### *Data Source and Processing*

A part of the clinical information and gene-sequencing data involved in this study were obtained from TCGA database ([**https://portal.gdc.cancer.gov/**](https://portal.gdc.cancer.gov/), accessed on 17 March 2022). Another part of clinical specimens and hematological specimens were collected from lung adenocarcinoma patients who fulfilled the research conditions at the Department of Oncology, the First Affiliated Hospital of Chongqing Medical University.

#### *Exploration of CDK1-Associated lncRNAs*

#### 1.. Exploration of CDK1-Associated Differentially Expressed Genes (DEGs)

RNAseq data of lung adenocarcinoma patients in TCGA were obtained with R software, and single gene differential expression analysis about CDK1 was performed with DEseq2 package of R [[**15**](https://www.mdpi.com/2073-4409/11/17/2688/htm#B15-cells-11-02688)]. The differential expression profiles of 56,493 DEGs were obtained.

.2. Dentification of Hub-lncRNA

we used differentially expressed miRNAs to predict potentially relevant lncRNAs, respectively. Meanwhile, the VennDiagram package [[**19**](https://www.mdpi.com/2073-4409/11/17/2688/htm#B19-cells-11-02688)] in R software was used to compare the predicted genes with the previous lncRNAs of the DEGs, and the overlapped genes were included for the next analysis. LnCAR ([**https://lncar.renlab.org/explorer**](https://lncar.renlab.org/explorer), accessed on 14 May 2022) is a comprehensive database on lncRNAs [[**20**](https://www.mdpi.com/2073-4409/11/17/2688/htm#B20-cells-11-02688)], which was used to perform survival analysis of lncRNAs in the network. In addition, survivable lncRNAs were defined as Hub-lncRNAs.

#### . 3. Validation of RNA Expression Levels and Clinical Relevance

First, we utilized TCGA data to verify the expression profiles of Hub-lncRNA and CDK1 in tumor tissues and normal lung tissues. The normality test results showed that the selected samples did not satisfy the normality test (*p* < 0.05), so the Kruskal–Wallis test was further selected. The Bonferroni method was used to correct the results for multiple hypothesis testing (Dunn’s test) at the significance level. Further subgrouping was performed according to target molecular expression. Chi-squared test and t-test were used to explore the correlation between target molecular expression and clinical stage, gender, age, race, and smoking in lung adenocarcinoma patients (*p* < 0.05 was considered significant). Finally, we collected surgical specimens from patients with lung adenocarcinoma and used RT-qPCR method to validate the expression difference of CDK1 and Hub-lncRNA between lung adenocarcinoma tissues and adjacent noncancerous tissues.

2.2.4. Molecular Correlation Analysis

R software was used to call the data of lung adenocarcinoma patients from TCGA database. Next, the corrplot package was invoked to explore the correlation between the expression quantity of each molecule using spearman’s principle.

#### *2.3. CDK1 and the Immune Response*

#### 2.3.1. Prediction of Responsiveness to ICIs

We applied the ggplot2 and ggpubr packages to predict immune checkpoint inhibitor responsiveness using the Tumor Immune Dysfunction and Exclusion (TIDE) algorithm [[**21**](https://www.mdpi.com/2073-4409/11/17/2688/htm#B21-cells-11-02688)], based on lung adenocarcinoma RNAseq data from TCGA database. TISIDB ([**http://cis.hku.hk/TISIDB/**](http://cis.hku.hk/TISIDB/), accessed on 1 June 2022) [[**22**](https://www.mdpi.com/2073-4409/11/17/2688/htm#B22-cells-11-02688)] is a comprehensive repository portal for tumor immune system interactions, which is based on the publicly available PubMed literature data for deep analysis. We explored the relationship between CDK1 and immune regulators using TISIDB and found that CDK1 was closely related to the IL family. Further, we collected a total of 17 patients who were hospitalized and diagnosed with lung adenocarcinoma by pathological biopsy in the First Affiliated Hospital of Chongqing Medical University. IL levels were measured before and after immunotherapy. In addition, we judged the patients’ positive response and negative response to immunotherapy by iRECIST criteria.

#### 2.3.2. Immune Infiltration Analysis

#### RNAseq data and clinical information of lung adenocarcinoma were obtained from TCGA database. The ssGSEA algorithm was used to calculate the immune cell infiltration scores of the samples. When intergroup comparisons were performed, Student’s t-test was used if the data met the requirements of normality and homogeneity of variance. In addition, Welch's t-test was used if two groups of data only met the requirements of normality but not homogeneity of variance. Moreover, when the two groups of data do not conform to normality, the Wilcoxon rank sum test was used for testing. The above results were visualized with the ggplot2 package of R software.

#### 2.3.3. Clinical Relevance Analysis

Patients with lung adenocarcinoma in TCGA database were grouped according to the expression of target protein, and the correlation with clinical stage, gender, age, race, smoking, and other conditions was analyzed by chi-squared test and *t*-test.

#### *2.4. Pathway Correlation Analysis of Molecular*

We collected the set of genes contained in relevant pathways [[**23**](https://www.mdpi.com/2073-4409/11/17/2688/htm#B23-cells-11-02688)] and obtained RNAseq data and corresponding clinical information of lung adenocarcinoma from the TCGA database. Next, analysis was performed by the R software GSVA package, according to the ssGSEA algorithm [[**24**](https://www.mdpi.com/2073-4409/11/17/2688/htm#B24-cells-11-02688)]. An enrichment score was calculated for each sample on each pathway in turn. Later, we analyzed the correlation of genes with pathway scores by spearman correlation. On the other hand, Metascape is a gene-annotation and gene-list-enrichment analysis database and tool ([**https://metascape.org/**](https://metascape.org/), accessed on 5 June 2022) [[**25**](https://www.mdpi.com/2073-4409/11/17/2688/htm#B25-cells-11-02688)]. To further explore the differential gene roles, we obtained co-expressed genes simultaneously associated with CDK1 and CXCL8 by single-gene differential expression analysis. In addition, we imported the co-expressed genes to Metascape tool, built protein–protein interaction network (PPI), and used Metascape's online analysis function to perform gene ontology (GO) analysis and visualize the DEGs from biological process, molecular function, and KEGG pathway, respectively.

#### *2.5. Single-Cell Analysis*

Human Protein Atlas database ([**https://www.proteinatlas.org/**](https://www.proteinatlas.org/), accessed on 6 June 2022) is dedicated to providing tissue and cellular distribution information of various classes of human proteins, and we derived RNA expression of single-cell-type clusters in lung tissue with its help. Cancer Single-cell Expression Map ([**https://ngdc.cncb.ac.cn/cancerscem/**](https://ngdc.cncb.ac.cn/cancerscem/), accessed on 6 June 2022) [[**26**](https://www.mdpi.com/2073-4409/11/17/2688/htm#B26-cells-11-02688)] is a public database dedicated to collecting, analyzing, and visualizing single-cell RNA-Seq data from human cancers. We explored the single-cell expression landscape of target molecules using its online analysis part. CANCERSEA is an additional single-cell database ([**http://biocc.hrbmu.edu.cn/CancerSEA/home.jsp**](http://biocc.hrbmu.edu.cn/CancerSEA/home.jsp), accessed on 10 June 2022) [[**27**](https://www.mdpi.com/2073-4409/11/17/2688/htm#B27-cells-11-02688)], which aims to comprehensively decode distinct functional states of cancer cells at single-cell resolution. It can provide PCG/lncRNA repertoires that are highly related to functional states at single-cell resolution. We searched the correlation between RNAs and functional states through this database.

# 2..

# **4. Molecular Crosstalk between T Cells and Tumor Uncovers GBM-Specific T Cell Signatures in Blood: Noninvasive GBM Diagnosis Using Immunosensors**

<https://pubs.acs.org/doi/10.1021/acsnano.2c04160>

**Description**

* Currently, there exists no clinically validated biomarker for GBM diagnosis. T cells exhibit the potential to escape a leaky blood–brain barrier in GBM patients. These T cells infiltrating the GBM interact with the heterogeneous population of tumor cells, display a symbiotic interaction resulting in intertwined molecular crosstalk, and display a GBM-associated signature while entering the peripheral circulation.
* Therefore, we hypothesize that studying these distinct molecular changes is critical to enable T cells to be a diagnostic marker for accurate detection of GBM from patient blood. We demonstrated this by utilizing the phenotypic and immunological landscape changes in T cells associated with glioblastoma tumors.
* GBM exhibits a high level of heterogeneity with diverse subtypes of cells within the tumor, enabling immune infiltration and different degrees of interactions with the tumor. To accurately detect these subtle molecular differences in T cells, we designed an immunosensor with a high detection sensitivity and repeatability. Hence in this study, we investigated the characteristic behavior of T cells to establish two preclinically validated biomarkers: GBM-associated T cells (GBMAT) and GBM stem cell-associated T cells (GSCAT). A comprehensive investigation was conducted by mimicking the tumor microenvironment *in vitro* by coculturing T cells with cancer cells and cancer stem cells to study the distinct variation in GBMAT and GSCAT. Preclinical investigation of T cells from GBM patient blood shows similar characteristics to our established biomarkers (GBMAT, GSCAT).
* Further evaluating the relative attributes of T cells in patient blood and tissue biopsy confirms the infiltrating ability of T cells across the BBB. **A pilot validation using a SERS-based machine learning algorithm was accomplished by training the model with GBMAT and GSCAT as diagnostic markers**. **Using GBMAT as a biomarker, we achieved a sensitivity and specificity of 93.3% and 97.4%, respectively, whereas applying GSCAT yielded a sensitivity and specificity of 100% and 98.7%, respectively.** We also validated this diagnostic methodology by using conventional biological assays to study the change in expression levels of T cell surface markers (CD4 and CD8) and cytokine levels in T cells (IL6, IL10, TNFα, INFγ) from GBM patients.