LGG subtypes based on the activity changes of immunologic and hallmark gene sets in cancer

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Research Article

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Abstract

Purpose: When glioma is in WHO grade II-III, glioma is of low grade. Gliomas in this period have the opportunity for surgical treatment and can be treated with a range of targeted therapies to enhance patient survival.

Methods: In this study, we downloaded low-grade glioma data from TCGA database and GSEA database. Cancer subtypes were classified by GSVA enrichment method.

Results: By GSVA enrichment analysis, we obtain three low-grade gliomas (LGG) cancer subtypes. After further survival prognosis analysis and biological function analysis, we obtained 21 tumor microenvironment gene sets and 17 core genes that affect patients' survival prognosis, and these genes have the potential to become targets for targeted therapies and disease detection.

Conclusion: We screened a total of 21 gene sets through a series of enrichment analyses, statistical and prognostic analyses, etc. Among them, 17 core genes were identified, namely: TOP2A, KIF20A, CCNB2, AURKA, KIF11, CDK1, BUB1B, CCNA2, BUB1, CDC20, CDCA8, TPX2, KIF2C, POLA2, POLE2, POLA1 and POLE. TOP2A.

1. Introduction

Glioma is the most common primary tumor of the brain, which originates from glial cells. Glial cells nourish and support neuronal cells, but under the induction of some physicochemical factors, neuronal cells can deteriorate into glioma cells[1]. Numerous studies have confirmed that the progression of glioma is closely related to the Tumor microenvironment (TME). The tumor microenvironment can induce differentiation of normal cells into tumor cells through a series of physicochemical mechanisms, so the current study focused on the direct relationship between microenvironmental cells and glioma[1-3]. According to the World Health Organization (WHO), gliomas with pathological grading in grades II and III are defined as low-grade gliomas (LGG), in which patients could be treated surgically and have the possibility to further improve the treatment outcome. In the current study we are dedicated to the study of LGG Tumor microenvironment constitutive genes, working to find targets to improve LGG survival prognosis and detect predictive genes for LGG disease[4]. With the establishment of databases such as TCGA, more and more studies are using big data to analyze therapeutic targets as well as genes available for screening. In the current study, enrichment analysis was used to screen tumor microenvironment-related genes and classify LGG into three subtypes, and finally to screen the gene set and core genes that affect the survival prognosis of LGG patients[5]. In conclusion, we mined 21 sets of microenvironmental gene sets and 17 core genes affecting LGG survival prognosis through a series of statistical analysis and enrichment analysis[6].

2. Methods

2.1 Data Collection

For the present study, the included genetic and clinical data were downloaded from the TCGA database. We collected 529 cases of gene expression data, and 515 cases of clinical data from LGG patients. In addition, we downloaded 4922 immune gene datasets from Gene Set Enrichment Analysis (GSEA) (<https://www.gsea-msigdb.org/gsea/msigdb/index.jsp>) [7].

2.2 Functional enrichment analysis using GSVA

Gene set variation analysis (GSVA) can be used to assess the degree of enrichment of a specific gene set in a sample population and thus observe changes in the activity of a set of gene sets. Enrichment analysis of the above gene set was performed using GSVA to assess the relevant biological activity [8].

2.3 Statistical analysis

All statistical analyses were performed with R software (version 4.1.2). p-values <0.05 were considered statistically significant. p<0.01 was considered a significant difference. heatmap and subtype classification of LGG samples were analyzed by the Heatmap and CancerSubtys packages of the R software. Apply NMF package to cancer genomic dataset for NMF. Cox regression model (COX) was used to screen for sets of genes that potentially affect patient survival prognosis. $\text{riskscore} = \sum \text{The } Exp_i \text{ indicated the expression level for each gene and the } Coe_i \text{ indicated the corresponding multivariable Cox regression coefficient.}$

2.4 Protein Interaction Networks and Biological Function Networks

STRING (<https://cn.string-db.org/>) was used to analyze the interaction links between genes, and then the core genes of the protein interaction network were obtained using the plug-in MCODE of Cytoscape software (version 3.9.0). the Clue GO plug-in was used to generate the biological functional interaction network [9].

3. Results

3.1 Immunological activity of the hallmark gene set in the LGG samples.

Because GSVA can detect even subtle pathway activity, we use GSVA to detect pathway activity in selected sets of genes. We downloaded 4922 immunologically relevant genes from GSEA to provide a comprehensive picture of the changes in the immune activity of LGG. gene expression of LGG was downloaded from the TCGA database (from 529 LGG patients). Figure 1 is a diagram of our research process. Immunological microarrays can define the immunological genome. The gene expression of LGG was visualized by heatmap (Figure 2).

After obtaining gene expression amounts, we tried to classify LGG patients into different subtypes. Because survival prognosis data were available for only 515 patients in TCGA, after collation, we screened the data from 508 patients who had both gene expression data and clinically relevant data. Using the COX regression model [Nonnegative matrix factorization and CancerSubtypes package, we classified LGG into 3 subtypes (Figure 3E). The average Silhouette width value was 0.88 (the closer the value is to 1 the more accurate it is, and 0.88 is already a very accurate value) (Figure 3D). The factoextra package of R software can classify cases into the best groups (Figure 3A and 3B). Kaplan-Meierplotter analysis was used to construct a survival model. Among the three subtypes of LGG, subtype 1 had the worst prognosis, subtype 2 was slightly better, while subtype 3 had the best prognosis among the three subtypes (Figure 3C).

3.2 Relationship between LGG tumor subtypes and clinical information.

We visualized the relationship between clinical information and LGG gene expression by heat map. The results showed that cancer subtypes were strongly correlated with LGG grade, $P < 0.001$, and cancer subtypes were correlated with patient age, $P < 0.05$. The above two clinical information were statistically significant between different cancer subtypes. (Figure4) The specific information is shown in Table1. Visualization of the differential gene sets of the three cancer subtypes by Venn diagram showed that there were 74 differential gene sets among the three cancer subtypes (Figure 5). Visual analysis of these 74 gene sets showed significant differences in the expression of the 74 gene sets in the three different cancer subtypes (Figure6).

3.3 Linking gene expression and survival prognosis of LGG patients.

The COX regression analysis model allows a good assessment of the relationship between variables on survival and posterior. By COX regression analysis, we concluded that a total of 21 gene sets were associated with the survival prognosis of LGG patients (Figure7). the risk scores derived from COX regression were divided into high and low risk based on median, with the high-risk group having a significantly worse survival prognosis than the low-risk group (Figure8).

3.4 Screening and biological function analysis of core genes.

Searching the above 21 sets of gene sets in GSEA's, we obtained 4107 immunology-related genes. The protein interaction network was constructed by STRING database (<https://cn.string-db.org/>). The results were imported into Cytoscape (version 3.9.0), and the biological functions of the protein interaction network were analyzed using the Clue Go plugin (Figure9 A). Finally, the core modules and core genes in the protein interaction network were identified using the MCODE plugin. The results showed that a total of 17 core genes and 2 core modules were filtered out. They are TOP2A, KIF20A, CCNB2, AURKA, KIF11, CDK1, BUB1B, CCNA2, BUB1, CDC20, CDCA8, TPX2, KIF2C, POLA2, POLE2, POLA1 and POLE (Figure9 B, C).

4. Discussion

Glioma is a common primary tumor of the central nervous system. The microenvironment of the glioma tissue area consists of tumor cells, immune cells and various factors secreted by them. Among them, various factors secreted by tumor cells or immune cells, such as growth factors, chemokines, pro-inflammatory factors and anti-inflammatory factors, form the microenvironmental network, which interact with each other to regulate and influence the process of tumor[10].

Glial cells support nerve cells in their associated neural activities and keep them healthy. However, glial cells can also give rise to a malignant tumor, glioma, which is the most common primary malignant tumor of the brain. The World Health Organization classifies gliomas as grades I, II, III, and IV. II, III are classified as lower-grade gliomas (LGGs). Gliomas can present with many symptoms, such as Headaches, Mental Status Changes, Motor/Movement Changes, Seizures, and Sensory Changes. The differences in symptoms are mainly related to the location where the glioma occurs. In addition to causing many painful symptoms, gliomas can also greatly reduce the survival time of patients. However, there is still a great deal of research into the treatment and detection of gliomas in the brain. With the establishment of databases like TCGA and GSEA, more and more studies are using big data and AI to analyze many valuable research results. Many studies have now found that immunologically relevant activities of tumors, play an important role in both suppressing and promoting tumor progression. The present study will focus on immunology-related activities to analyze LGG-related mechanisms and clinical prognosis. In this study, we used a database with each analysis software to analyze the big data of LGG patients, aiming at obtaining some gene sets that can predict the prognosis of patients' survival. These gene sets are expected to be new targets for detection or treatment.

In this study, we screened the gene expression transcripts of LGG in TCGA's GDC database and downloaded their corresponding clinical data. We downloaded gene expression data for a total of 529 patients, but their corresponding clinical data were available for only 515 cases. Therefore, we deleted 14 cases of gene expression data without clinical data. We downloaded immune-related gene sets from GSEA and then enriched 3 different

cancer subtypes by GSVA. Among the three different cancer subtypes, subtype 1 has the worst survival prognosis, subtype 3 has the best prognosis, and subtype 2 is in between. The closer the Silhouette width value is to 1, the higher the accuracy of the model is represented. Among the three different cancer subtypes, the highest Silhouette width value was 0.93 for subtype 1 and subtype 2, and 0.83 for subtype 3. The average Silhouette width value of the three subtypes was 0.88, which represents the high accuracy of our model. With the nonnegative matrix factorization (NMF) method, we can clearly see that the 3 cancer subtypes have different Clustering displays. This also represents that there is a significant difference in gene expression among the three cancer subtypes (Figure 3). The heat map shows that there are significant differences in gene expression profiles among the three cancer subtypes (Figure 4). According to the analysis, the main reasons for this difference were the age of the patients and the grade of the cancer. Using the Venn diagram, we can find 74 common differential gene sets for the 3 cancer subtypes (Figure 5). Also, the heat map can show that the three cancer subtypes have significantly different expressions in these 74 gene sets (Figure 6). By COX regression analysis, we obtained 21 gene sets that affect the prognosis of LGG patients (Table2). K-M curves allow analysis of the relationship between gene set expression and patient survival prognosis. By the median of gene set expression, we divided them into high-risk and low-risk groups, and the results showed that in the 21 gene sets, the survival prognosis of the high-risk group was significantly worse than that of the low-risk group (Figure 7). The gene set expression was multiplied by the Coef value of the gene set by COX regression analysis, relying on the median to classify them into high-risk and low-risk groups. K-M curve analysis showed that the survival prognosis of the high-risk group was significantly worse than that of the low-risk group (Figure 8). We listed the gene data (4107) from 21 gene sets to construct their biological function enrichment network. The results show that the core functions of the network are: outer kinetochore α DNA polymerase: primase complex $\rightarrow$ attachment of mitotic spindle microtubules to kinetochore $\rightarrow$ positive regulation of chromosome separation $\rightarrow$ Cell cycle $\rightarrow$ spindle midzone $\rightarrow$ mitotic spindle midzone $\rightarrow$ protein localization to chromosome, centromeric region $\rightarrow$ protein localization to condensed chromosome. The 21 gene sets were placed into the STRING database and their protein interaction networks were analyzed. The core modules in the protein interaction network were then analyzed by the Cytoscape (3.9.0) plugin MCODE. Finally, we analyzed 17 core genes, which are: TOP2A, KIF20A, CCNB2, AURKA, KIF11, CDK1, BUB1B, CCNA2, BUB1, CDC20, CDCA8, TPX2, KIF2C, POLA2, POLE2, POLA1 and POLE. TOP2A is a major target for many targeted therapies, and it is overexpressed in many tumors. It has been shown that inhibition of TOP2A expression inhibits the proliferation of tumor cells in cellular experiments. However, the research on this gene has been limited to basic experiments and has not been well applied to clinical studies. [11, 12]. A related study showed that tumor specimens from patients with glioma were used for gene sequencing and showed that patients with increased KIF20A expression had a poorer survival prognosis. However, the study of this gene in glioma remains to be further explored[13, 14]. CCNB2 is a member of the cell cycle protein family, specifically the B-type cell cycle proteins. Current studies support that LGG patients with high CCNB2 expression have a significantly worse survival prognosis than those with low CCNB2 expression. However, the exact mechanism is not clear. It is simply described to be closely related to the tumor microenvironment[15-18]. AURKA and KIF11 are used as a target in many tumors for targeted therapy, and these genes are also microenvironment constituent genes of tumors[19-22]. CKD1 has not been studied much in glioma. It has been reported that gliomas can develop resistance to Temozolomide by immune escape through the CDK1/survivin signaling pathway[23]. BUB1B may provide a marker to predict aggressive and effective drug response[24]. CCNA2 has been little studied in glioma, and its mechanism of action in glioma needs to be further investigated[18]. Glioma cells proliferate and rely on the BUB1B / BubR1 pathway for mitosis[25]. CDC20 overexpression and its associated gene modules were characteristically elevated, signifying increased genomic instability in gliomas[26]. At present, there are few studies of other core genes in glioma to conclude the mechanisms involved.

Conclusion

In summary, we screened a total of 21 gene sets through a series of enrichment analyses, statistical and prognostic analyses, etc. Among them, 17 core genes were identified, namely: TOP2A, KIF20A, CCNB2, AURKA, KIF11, CDK1, BUB1B, CCNA2, BUB1, CDC20, CDCA8, TPX2, KIF2C, POLA2, POLE2, POLA1 and POLE. TOP2A.

Abbreviations

COX: Cox regression model; GSVA: Gene set variation analysis; LGG: low-grade gliomas; WHO: World Health Organization; TME: tumor microenvironment; OS: overall survival; GSEA: gene set enrichment analysis; HR: hazard ratio; TCGA: The Cancer Genome Atlas

Declarations

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Author contributions

Sihan Chen guided and revised the manuscript. All authors contributed equally to this manuscript.

Competing Interests

The authors declare no competing interests.

Ethics approval and consent to participate

There were no human subject studies, cell, tissue,, or animal studies. No ethical requirements are involved.

Data Availability Statement

The submitting author has read and agreed to this statement on behalf of all authors on this paper.

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Tables

Table 1. The relationship between LGG subtypes and clinical features.

Covariates	Total	C1	C2	C3	P-value
Age					0.0362
<=65	478(93.73%)	130(90.28%)	104(92.04%)	244(96.44%)	
>65	32(6.27%)	14(9.72%)	9(7.96%)	9(3.56%)	
Gender					0.5333
FEMALE	228(44.71%)	60(41.67%)	55(48.67%)	113(44.66%)	
MALE	282(55.29%)	84(58.33%)	58(51.33%)	140(55.34%)	
Grade					
G2	248(48.63%)	49(34.03%)	30(26.55%)	169(66.8%)	0.00012
G3	261(51.18%)	94(65.28%)	83(73.45%)	84(33.2%)	
Unknow	1(0.2%)	1(0.69%)	0(0%)	0(0%)	
First presenting symptom					
Headaches	105(20.59%)	34(23.61%)	20(17.7%)	51(20.16%)	0.1188
Mental Status Changes	39(7.65%)	12(8.33%)	7(6.19%)	20(7.91%)	
Motor/Movement Changes	38(7.45%)	8(5.56%)	12(10.62%)	18(7.11%)	
Seizures	245(48.04%)	71(49.31%)	58(51.33%)	116(45.85%)	
Sensory Changes	18(3.53%)	4(2.78%)	5(4.42%)	9(3.56%)	
Visual Changes	12(2.35%)	7(4.86%)	1(0.88%)	4(1.58%)	
Unknow	1(0.2%)	1(0.69%)	0(0%)	0(0%)	
Unknow	52(10.2%)	7(4.86%)	10(8.85%)	35(13.83%)	
Laterality					
Left	248(48.63%)	70(48.61%)	55(48.67%)	123(48.62%)	0.8295
Midline	6(1.18%)	3(2.08%)	1(0.88%)	2(0.79%)	
Right	251(49.22%)	69(47.92%)	57(50.44%)	125(49.41%)	
Unknow	5(0.98%)	2(1.39%)	0(0%)	3(1.19%)	
Tumor location					
Posterior Fossa, Brain Stem	1(0.2%)	1(0.69%)	0(0%)	0(0%)	0.1589
Posterior Fossa, Cerebellum	2(0.39%)	1(0.69%)	0(0%)	1(0.4%)	
Supratentorial, Frontal Lobe	300(58.82%)	74(51.39%)	67(59.29%)	159(62.85%)	
Supratentorial, Not Otherwise Specified	8(1.57%)	4(2.78%)	1(0.88%)	3(1.19%)	
Supratentorial, Occipital Lobe	8(1.57%)	2(1.39%)	4(3.54%)	2(0.79%)	
Supratentorial, Parietal Lobe	47(9.22%)	11(7.64%)	12(10.62%)	24(9.49%)	
Supratentorial, Temporal Lobe	143(28.04%)	51(35.42%)	28(24.78%)	64(25.3%)	
Unknow	1(0.2%)	0(0%)	1(0.88%)	0(0%)	

Table 2. Results of COX regression analysis regarding 21 gene sets affecting the survival prognosis of LGG patients.

Id	Coef	HR	HR.95L	HR.95H	p-value
T_GSE14415_INDUCED_TREG_VS_FAILED_INDUCED_TREG_DN	49.62146	3.55E+21	2.86E+10	4.40E+32	0.00014
T_HALLMARK_G2M_CHECKPOINT	77.5229	4.65E+33	7.59E+15	2.85E+51	0.000207
T_GSE9650_NAIVE_VS_EFF_CD8_TCELL_DN	38.75154	6.75E+16	0.000117	3.91E+37	0.012132
T_GSE37532_WT_VS_PPARG_KO_VISCERAL_ADIPOSE_TISSUE_TREG_UP	-94.9046	6.07E-42	1.91E-62	1.93E-21	8.14E-05
T_GSE27241_WT_VS_RORGT_KO_TH17_POLARIZED_CD4_TCELL_UP	39.39034	1.28E+17	6517.725	2.51E+30	0.011658
T_GSE33162_HDAC3_KO_VS_HDAC3_KO_MACROPHAGE_DN	-66.5605	1.24E-29	5.36E-44	2.87E-15	8.00E-05
T_GSE25088_WT_VS_STAT6_KO_MACROPHAGE_IL4_STIM_DN	-40.7207	2.07E-18	6.87E-35	0.062128	0.035423
T_GSE24634_TREG_VS_TCONV_POST_DAY3_IL4_CONVERSION_UP	-46.4434	6.76E-21	4.59E-39	0.009958	0.029562
T_GSE22886_UNSTIM_VS_IL2_STIM_NKCELL_DN	-57.048	1.68E-25	1.21E-42	2.33E-08	0.004616
T_GSE30962_PRIMARY_VS_SECONDARY_ACUTE_LCMV_INF_CD8_TCELL_UP	-43.4696	1.32E-19	8.20E-35	0.000213	0.014972
T_GSE36476_CTRL_VS_TSST_ACT_72H_MEMORY_CD4_TCELL_OLD_DN	-88.1892	5.01E-39	4.22E-63	5.95E-15	0.001821
T_GSE19941_LPS_VS_LPS_AND_IL10_STIM_IL10_KO_MACROPHAGE_UP	67.2787	1.65E+29	3.2E+13	8.55E+44	0.000268
T_GSE22601_DOUBLE_POSITIVE_VS_CD4_SINGLE_POSITIVE_THYMOCYTE_DN	39.84654	2.02E+17	7.53E-07	5.41E+40	0.047695
T_GSE24634_TREG_VS_TCONV_POST_DAY7_IL4_CONVERSION_UP	-41.8642	6.59E-19	9.90E-34	0.000438	0.006214
T_GSE45365_WT_VS_IFNAR_KO_BCELL_DN	-40.4809	2.63E-18	3.08E-27	2.24E-09	0.000114
T_GSE36476_CTRL_VS_TSST_ACT_72H_MEMORY_CD4_TCELL_YOUNG_DN	92.92481	2.27E+40	2.47E+18	2.09E+62	0.000317
T_GSE21063_CTRL_VS_ANTI_IGM_STIM_BCELL_NFATC1_KO_8H_DN	67.73301	2.61E+29	7.8E+11	8.71E+46	0.001002
T_GSE25088_WT_VS_STAT6_KO_MACROPHAGE_DN	35.21672	1.97E+15	0.027354	1.42E+32	0.025364
T_KAECHE_NAIVE_VS_DAY8_EFF_CD8_TCELL_DN	-38.2487	2.45E-17	8.55E-40	700892	0.0017122
T_GSE39110_DAY3_VS_DAY6_POST_IMMUNIZATION_CD8_TCELL_DN	35.6956	3.18E+15	0.073798	1.37E+32	0.047761
T_GSE22313_HEALTHY_VS_SLE_MOUSE_CD4_TCELL_DN	-19.772	2.59E-09	3.42E-17	0.19599	0.032677

Figures

Figure 1
Flowchart about our research.

Figure 2
Heat map of the enrichment fraction of immunological and marker genomes in LGG tumor samples. Immunological and marker genomes were downloaded from GSEA.

Differential gene sets' expression of clinical features and cancer subtypes.

Figure 5
Venn diagram, a common set of differential genes for the three cancer subtypes.

Figure 6

Heat map of the relationship between the expression of gene sets affecting patient survival prognosis, and individual clinically relevant information.

Figure 7
High risk score among LGG patients were associated with low overall survival. p-value < 0.05 was considered statistically significant (Various sets of genes affecting patient survival prognosis).

Figure 8