Original Article

Identification of an IFN-β-associated gene signature for the prediction of overall survival among glioblastoma patients

Lijing Cheng[1,2#], Meiling Yuan[1,2#], Shu Li[3], Zhiying Lian[4], Junjing Chen[5], Weibiao Lin[6], Jianbo Zhang[6], Shupeng Zhong[7]

[1]Department of Neurology, The First Affiliated Hospital of Dali University, Dali University, Dali, China; [2]Clinical Medical School, Dali University, Dali, China; [3]Department of Neurology, Jinshan Hospital, Benxi Jinshan Affiliated Hospital of Dalian Medical University, Benxi, China; [4]Second Clinical Medical College, Southern Medical University, Guangzhou, China; [5]Department of Radiation Oncology, Jiangxi Cancer Hospital of Nanchang University, Nanchang, China; [6]Department of Neurosurgery, Zhongshan City People's Hospital, Zhongshan, China; [7]Department of Oncology, Zhongshan City People's Hospital, Zhongshan, China

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[#]These authors contributed equally to this work.

Correspondence to: Shupeng Zhong. Department of Oncology, Zhongshan City People's Hospital, No. 2 Sunwen Road East, Zhongshan 528403, China. Email: zhongshupeng@163.com; Jianbo Zhang. Department of Neurosurgery, Zhongshan City People's Hospital, No. 2 Sunwen Road East, Zhongshan 528403, China. Email: zjb20191031@163.com.

Background: Brain glioblastoma multiforme (GBM) is the most common primary malignant intracranial tumor. The prognosis of this disease is extremely poor. While the introduction of β-interferon (IFN-β) regimen in the treatment of gliomas has significantly improved the outcome of patients; The mechanism by which IFN-β induces increased TMZ sensitivity has not been described. Therefore, the main objective of the study was to elucidate the molecular mechanisms responsible for the beneficial effect of IFNβ in GBM.

Methods: Messenger RNA expression profiles and clinicopathological data were downloaded from The Cancer Genome Atlas (TCGA) GBM and GSE83300 dataset from the Gene Expression Omnibus. Univariate Cox regression analysis and lasso Cox regression model established a novel 4-gene IFN-β signature (peroxiredoxin 1, Sec61 subunit beta, X-ray repair cross-complementing 5, and Bcl-2-like protein 2) for GBM prognosis prediction. Further, GBM samples (n=50) and normal brain tissues (n=50) were then used for real-time polymerase chain reaction experiments. Gene set enrichment analysis (GSEA) was performed to further understand the underlying molecular mechanisms. Pearson correlation was applied to calculate the correlation between the long non-coding RNAs (lncRNAs) and IFN-β-associated genes. An lncRNA with a correlation coefficient $|R^2|>0.3$ and $P<0.05$ was considered to be an IFN-β-associated lncRNA.

Results: Patients in the high-risk group had significantly poorer survival than patients in the low-risk group. The signature was found to be an independent prognostic factor for GBM survival. Furthermore, GSEA revealed several significantly enriched pathways, which might help explain the underlying mechanisms. Our study identified a novel robust 4-gene IFN-β signature for GBM prognosis prediction. The signature might contain potential biomarkers for metabolic therapy and treatment response prediction for GBM patients.

Conclusions: In the present study, we established a novel IFN-β-associated gene signature to predict the overall survival of GBM patients, which may help in clinical decision making for individual treatment.

Keywords: The Cancer Genome Atlas (TCGA); Gene Expression Omnibus (GEO); Chinese Glioma Genome Atlas (CGGA); β-interferon (IFN-β); glioblastoma; prognostic model

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Introduction

Brain glioblastoma multiforme (GBM) is the most common primary malignant intracranial tumor (50%), and is associated with high morbidity and mortality in both adults and children (1-4). A histopathological from low-grade to high-grade transformation is associated with poor overall survival (5). Currently, surgery, radiation, and chemotherapy are the main treatment modalities of GBM. Chemotherapy is a critical process in the postsurgical treatment of GBM (6-8). Alkylating agents, such as temozolomide, remain the standard of care in GBM chemotherapy, but response remains poor (9).

DNA repair protein, O6-methylguanine-DNA methyltransferase (MGMT), plays an essential role in cellular resistance to alkylating agents (10). Clinically, chemoresistance occurs frequently in patients with GBM that exhibit an aberrant activation of MGMT. β-interferon (IFN-β) can act as a drug sensitizer, enhancing toxicity against various neoplasias, and is widely used in combination with other antitumor agents, such as nitrosoureas (11-13). IFN-β sensitizes glioma cells that harbor the unmethylated MGMT promoter and are resistant to temozolomide (11,14,15). Likewise, IFN-β induces loss of spherogenicity and overcomes therapy resistance of glioblastoma stem cells (16). Nevertheless, the specific mechanisms and molecules associated with this phenomenon have not yet been completely elucidated. Therefore, the main objective of the study was to elucidate the molecular mechanisms responsible for the beneficial effect of IFNβ in GBM.

So far, studies have focused mainly on one gene is related with the other. In the present study, we firstly explored and analyzed all differentially expressed IFN-β-associated genes [gene set enrichment analysis (GSEA) M2567] and IFN-β-associated lncRNAs by systematic bioinformatics analysis. In total, 596 GBM patients were included in The Cancer Genome Atlas (TCGA) GBM to construct the prognostic model. Univariate Cox regression model found 5 survival-related genes. Lasso-penalized Cox analysis then identified 5 genes to construct the prognostic model. Using the methodology previously described, the result is validated on the Gene Expression Omnibus (GEO) datasets (GSE83300). We found that a 4 IFN-β-associated gene [peroxiredoxin 1 (*PRDX1*), Sec61 subunit beta (*SEC61B*), X-ray repair cross-complementing 5 (*XRCC5*), and Bcl-2-like protein 2 (*BCL2L2*)] signature was a robust marker of seizure prognosis in patients with GBM. Using data from the Chinese Glioma Genome Atlas (CGGA), we found that 4 IFN-β-associated genes were independent biomarkers of prognosis. Pathway enrichment analysis results demonstrated that several modules are enriched in GBM-related pathways.

Long non-coding RNA (lncRNA) has been demonstrated to play an important role in human diseases (17), especially in GBM. LncRNA AC003092.1 regulates tissue factor pathway inhibitor-2 (TFPI-2) expression through the competing endogenous RNA mechanism, and lncRNA SOX2OT (SOX2 overlapping transcript) interacts with RNA-binding proteins to promote the expression level of SOX2, which is involved in glioma chemotherapy (18,19). However, the relevance between IFN-β and lncRNA has not been fully elucidated in GBM. Pearson correlation was applied to calculate the correlation between lncRNAs and IFN-β-associated genes. An lncRNA with a correlation coefficient $|R^2|>0.3$ and $P<0.05$ was considered to be an IFN-β-associated lncRNA. Univariate and multivariate Cox regressions were used for the survival analysis, which indicated that AC093278.2, AC004067.1, LINC01116, and AC017104.1 were independent prognostic factors for the overall survival of GBM patients.

The findings of the present study may lay the foundation for future studies investigating GBM. We present the following article in accordance with the REMARK reporting checklist (available at http://dx.doi.org/10.21037/atm-21-1986).

Methods

Clinical specimens and data collection

Fifty human glioma tissue samples and 50 normal brain tissues were obtained from the Jiangxi Cancer Hospital of Nanchang University, China. Samples were frozen in liquid nitrogen after surgical resection. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised

in 2013). The present study was approved by the Ethics Committee of the Jiangxi Cancer Hospital of Nanchang University. Informed consent was obtained from patients or guardians.

Messenger RNA (mRNA) expression profiles and clinical data were obtained from TCGA GBM (https://cancergenome.nih.gov/), the GEO (GSE83300) database (https://www.ncbi.nlm.nih.gov/geo/), and the CGGA (http://www.cgga.org.cn/). The IFN-β-associated gene set (M2567) was obtained by GSEA using the gene set database (http://www.gsea-msigdb.org/). All data were analyzed using R software (version 4.0.2) (http://www.r-project.org).

Identification of differentially expressed genes in TCGA GBM

The limma package was used to screen the differentially expressed genes of interest with R software version 4.0.2. The expression pattern of the 120 IFN-β-associated genes was then investigated in TCGA. Genes were selected as consistently altered IFN-β-associated genes for subsequent prognostic analysis if they demonstrated a consistent expression pattern in TCGA cohort and if they were listed in the GSE83300 dataset.

Construction of the prognostic IFN-β-associated gene signature

Univariate Cox regression analysis and lasso-penalized Cox regression analysis were used to identify the prognosis-related IFN-β-associated genes and to construct the prognostic gene signature. $P<0.05$ in the univariate Cox regression analysis was considered statistically significant. The prognostic gene signature was shown as risk score=(coefficient $mRNA_1$×expression of $mRNA_1$)+(coefficient $mRNA_2$×expression of $mRNA_2$)+…+(coefficient mRNAn×expression mRNAn). R package "survival" and "survminer" were used to explore the optimal cut-off of the risk score and to draw the Kaplan-Meier survival curve. In particular, the "surv_cutpoint" function of the "survminer" R package was used to determine the optimal cut-off value to divide patients into the high- and low-risk groups. R package "survivalROC" was used to investigate the time-dependent prognostic value of the gene signature. A 2-sided log-rank $P<0.05$ was considered significant for the survival analysis.

IFN-β-associated lncRNA screening

The profiles of the lncRNAs and IFN-β-associated genes were obtained from TCGA RNAseq dataset. Pearson correlation was applied to calculate the correlation between the lncRNAs and differential genes. An lncRNA with a correlation coefficient $|R^2|>0.3$ and $P<0.05$ was considered to be an IFN-β-associated lncRNA.

Construction of the prognostic IFN-β-associated lncRNA signature

Construction of the prognostic IFN-β-associated lncRNA signature was performed as previously described.

GSEA

GSEA was applied to investigate potential mechanisms underlying the influence of differential gene expression on GBM prognosis. GSEA was also applied to detect whether a priori-defined set of genes showed statistically significant differential expression between the high and low-risk groups. Gene sets with a standard $P<0.05$ were considered to be significantly enriched.

Immunohistochemical staining

The paraffin-embedded glioma tissues were cut into thin slices and then placed on glass slides for the immunohistochemical experiments. The specimens were incubated with rabbit anti-*BCL2L2*, anti-*PRDX1*, anti-*XRCC5*, and *SEC61B* antibody (1:200 dilutions; Abcam, Cambridge, MA, USA) at 4 ℃ overnight, followed by 1-h incubation of biocatalyst secondary antibody (1:200 dilutions, Santa Cruz Biotechnology, Santa Cruz, CA, USA) at room temperature. The avidin-biotin complex method was used to determine the target protein's location and relative expression to visualize the bound antibodies.

Statistical analysis

R 4.0.2 (www.r-project.org/) and SPSS.22 (www.ibm.com/software/it/analytics/spss/) were used to compute statistical analyses. The association between the IFN-β-associated genes and clinicopathologic features was tested using the chi-square test. Comparison of two independent groups was made by two-tailed Students t test. A one-way analysis

of variance (ANOVA) was used to determine differences among groups. Statistical significance was set at *P<0.05, **P<0.01, ***P<0.001. P<0.05 was considered to indicate statistical significance.

Results

Construction and validation of the prognostic IFN-β-associated gene signature

In total, 596 GBM patients and 121 IFN-β-associated genes (70 upregulated and 51 downregulated) were included in TCGA GBM to construct the prognostic model. Differential gene expression analysis identified 14 downregulated and 53 upregulated IFN-β-associated genes, respectively (Table S1). First, the heat map shows the differential genes and analyzed these significant genes further (*Figure 1A*). Univariate Cox regression model found 5 survival-related genes (Table S2). Lasso-penalized Cox analysis identified 5 genes to construct the prognostic model (Table S3). Using the methodology previously described, the result is validated on the GEO datasets (GSE83300) (Table S4). Patients were divided into high- and low-risk groups depending on their risk score. GBM patients with high-risk scores had poor prognosis (*Figure 1B*,*C*). The increased expression of the 4 different signature genes (*PRDX1*, *SEC61B*, *XRCC5*, and *Troxerutin (TXN)* and reduced expression of the 1 signature gene (*BCL2L2*) was observed as the risk value increased (*Figure 1D*,*E*). Taking all of our results together, 4 genes were found to be correlated with unfavorable clinical outcomes.

Prognostic significance of the 4 signature gene expression in GBM

To further validate the expression of the prognostic genes constructing the gene signature, Kaplan-Meier survival analysis was used. The findings indicated that the high expression of *SEC61B* and *XRCC5* was associated with poor prognosis in the GEO dataset (*Figure 2A*,*B*). Moreover, the high expression of SEC61B, *XRCC5*, and *PRDX1* was associated with poor prognosis, and the low expression of *BCL2L2* was associated with poor prognosis in TCGA dataset (*Figure 2C*,*D*,*E*,*F*). To further verify whether the expression of *SEC61B*, *XRCC5*, *BCL2L2*, and *PRDX1* was associated with prognosis in GBM, the Gene Expression Profiling Interactive Analysis (GEPIA) database (https://gepia.cancer-pku.cn/) was used. *SEC61B*, *XRCC5*, and *PRDX1* had significantly high expression in tumor samples compared with normal samples, and *BCL2L2* had significantly low expression in tumor samples compared with normal samples (*Figure 2G*). GBM samples (n=50) and normal brain tissues (n=50) were then used for real-time polymerase chain reaction (PCR) experiments. The results were consistent with the GEPIA database (*Figure 2H*). Taken together, the 4 signature gene expression is considered to be of clinical significance in GBM.

Validation of the 4 signature genes in the CGGA database

To further validate these results, we used the CGGA. Kaplan-Meier survival analysis of the CGGA dataset showed that the high expression of *SEC61B*, *XRCC5*, and *PRDX1*, and the low expression of *BCL2L2* indicated poor patient prognosis (*Figure 3A*,*B*,*C*,*D*). The expression level of *BCL2L2* significantly decreased with higher-grade gliomas (*Figure 3E*). Moreover, the expression of *SEC61B*, *XRCC5*, and *PRDX1* significantly increased with higher-grade gliomas (*Figure 3F*,*G*,*H*). To further validate these results, we performed immunohistochemical experiments. The immunohistochemical results obtained in the present study were consistent with the results of the CGGA database (*Figure 3I*). The expression of the 4 signature genes was considered to be of clinical significance in GBM.

GSEA analysis of the 4 signature genes

To further clarify the impact of the 4 signature genes on GBM, gene ontology and pathway enrichment analyses were performed using GSEA. The results revealed that these genes are mainly enriched in 14 pathways based on TCGA GBM database, including the calcium signaling pathway, cell cycle, epidermal growth factor receptor family (ERBB) signaling pathway, glyceraldehyde-3-phosphate dehydrogenase (GAP) junction, glioma, inositol phosphate metabolism, mitogen-activated protein kinase (MAPK) signaling pathway, oxidative phosphorylation, phosphatidylinositol signaling system, purine metabolism, ribosome, RNA degradation, spliceosome, and vascular endothelial growth factor (VEGR) signaling pathway (*Figure 4A*). Moreover, in the GEO dataset, these genes were mainly enriched in 9 pathways as follows: the calcium signaling pathway, cell cycle, extracellular matrix receptor interaction, ERBB signaling pathway, inositol phosphate metabolism, oxidative phosphorylation, P53 signaling pathway, phosphatidylinositol signaling system,

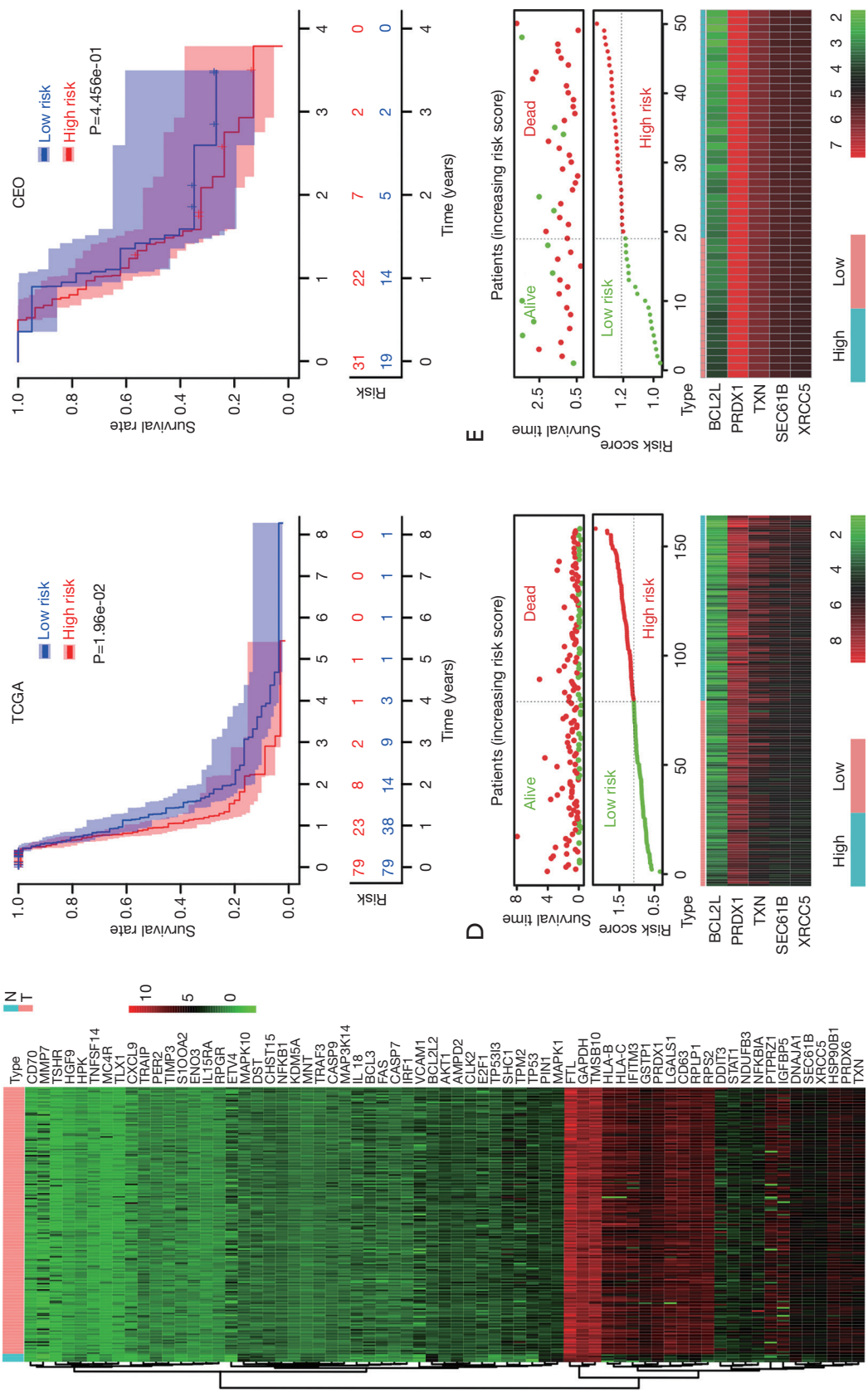

Figure 1 Construction and validation of the prognostic β-interferon (IFN-β)-associated genes signature. (A) Heatmap showing differential expression of 67 genes in normal brain tissues and glioblastoma multiforme (GBM) tissues, which differed significantly ($P<0.05$). (B) Survival curve of GBM patients based on risk score model in The Cancer Genome Atlas (TCGA). (C) Survival curve of GBM patients based on risk score model in TCGA. (D,E) Survival duration and status of GBM cases. IFN-β-associated gene risk score analysis of GBM patients in TCGA and the Gene Expression Omnibus (GEO). Heatmap of the 5 key genes expressed in GBM.

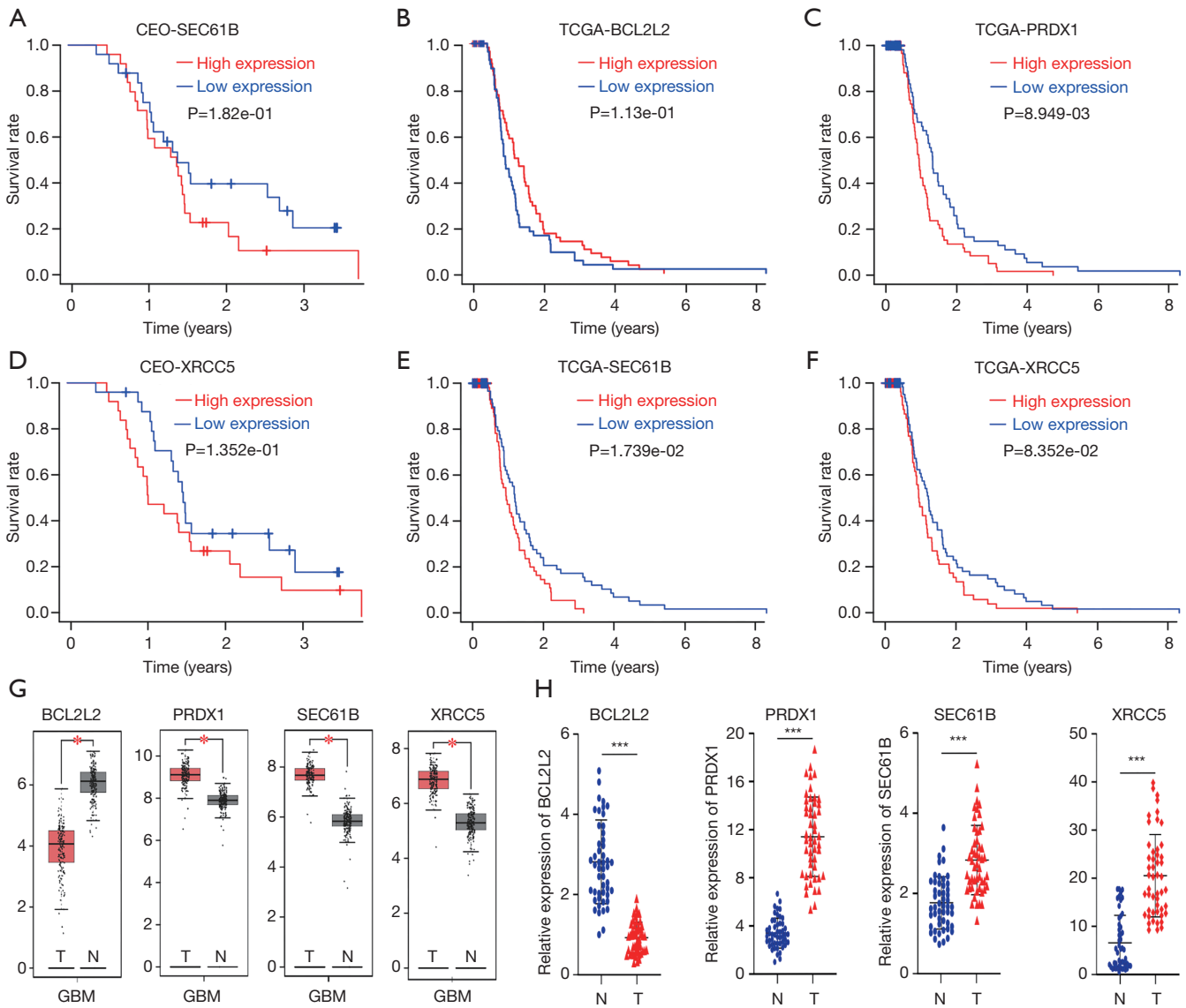

Figure 2 Prognostic significance of 4 signature gene expression in glioblastoma multiforme (GBM). (A,B) Survival analysis of the 2 prognostic β-interferon (IFN-β)-associated genes based on the Gene Expression Omnibus (GEO) database. (C,D,E,F) Survival analysis of the 4 prognostic IFN-β-associated genes based on The Cancer Genome Atlas (TCGA) database. (G) Expression analysis of 4 prognostic IFN-β-associated genes according to the Gene Expression Profiling Interactive Analysis database. (H) Real-time polymerase expression analysis of 4 prognostic IFN-β-associated genes in normal brain tissues (n=50) and GBM tissues (n=50). *P<0.05, ***P<0.001.

and pyrimidine metabolism (*Figure 4B*). These genes may be involved in the proliferation of GBM.

Prognostic impact of IFN-β-associated lncRNA signature for GBM

Considering the critical role of lncRNAs in GBM, the identification of important lncRNAs in cancer and developing lncRNA-based therapeutic strategies are important. Pearson correlation was applied to calculate the correlation between lncRNAs and IFN-β-associated genes. An lncRNA with a correlation coefficient $|R^2|>0.3$ and P<0.05 was considered to be an IFN-β-associated lncRNA. Univariate and multivariate Cox regressions were used for the survival analysis, and indicated that AC093278.2, AC004067.1, LINC01116, and AC017104.1

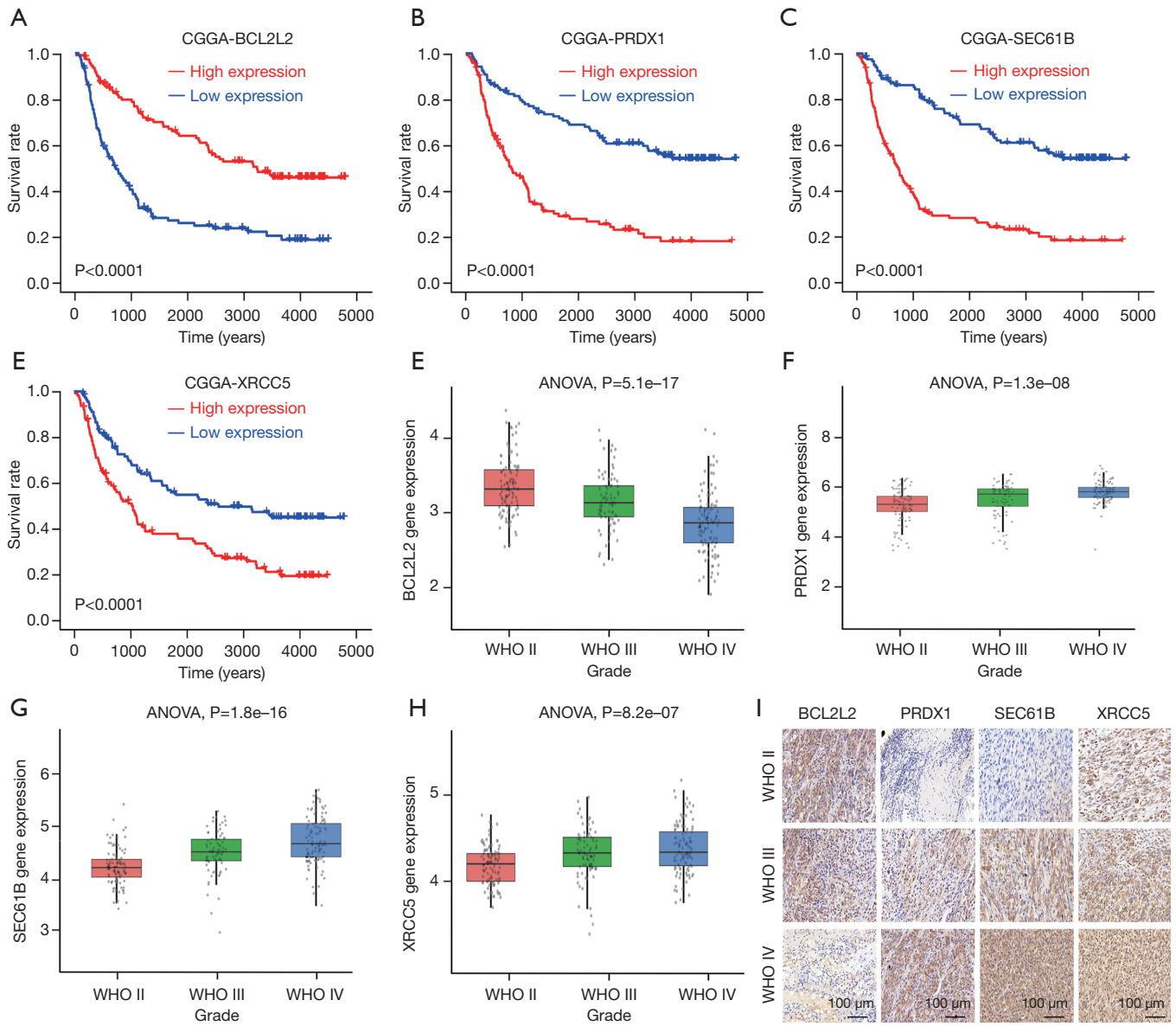

Figure 3 Validation of four signature-genes in the Chinese Glioma Genome Atlas (CGGA) database. (A,B,C,D) Survival analysis of the 4 prognostic β-interferon (IFN-β)-associated genes based on the CGGA database. (E,F,G,H) Expression analysis of 4 prognostic IFN-β-associated genes according to the CGGA database. (I) Immunohistochemistry of the 4 prognostic IFN-β-associated genes.

were independent prognostic factors for the overall survival of GBM patients (*Figure 5A,B,C*). Moreover, the high expression of the AC004067.1, AC017104.1, and LINC01116 is associated with poor prognosis, and the low expression of AC093278.2 is associated with poor prognosis in TCGA dataset (*Figure 5D,E,F,G*). GBM samples (n=50) and normal brain tissues (n=50) were then used for real-time PCR experiments to validate the expression of the IFN-β-associated lncRNAs in GBM. RT-PCR showed that, compared with the normal brain tissues, AC004067.1, AC017104.1, and LINC01116 were highly expressed and AC093278.2 and a low expression in GBM (*Figure 5H*). Therefore, IFN-β-associated lncRNAs have a high diagnostic value for GBM.

Discussion

With the development of high-throughput sequencing

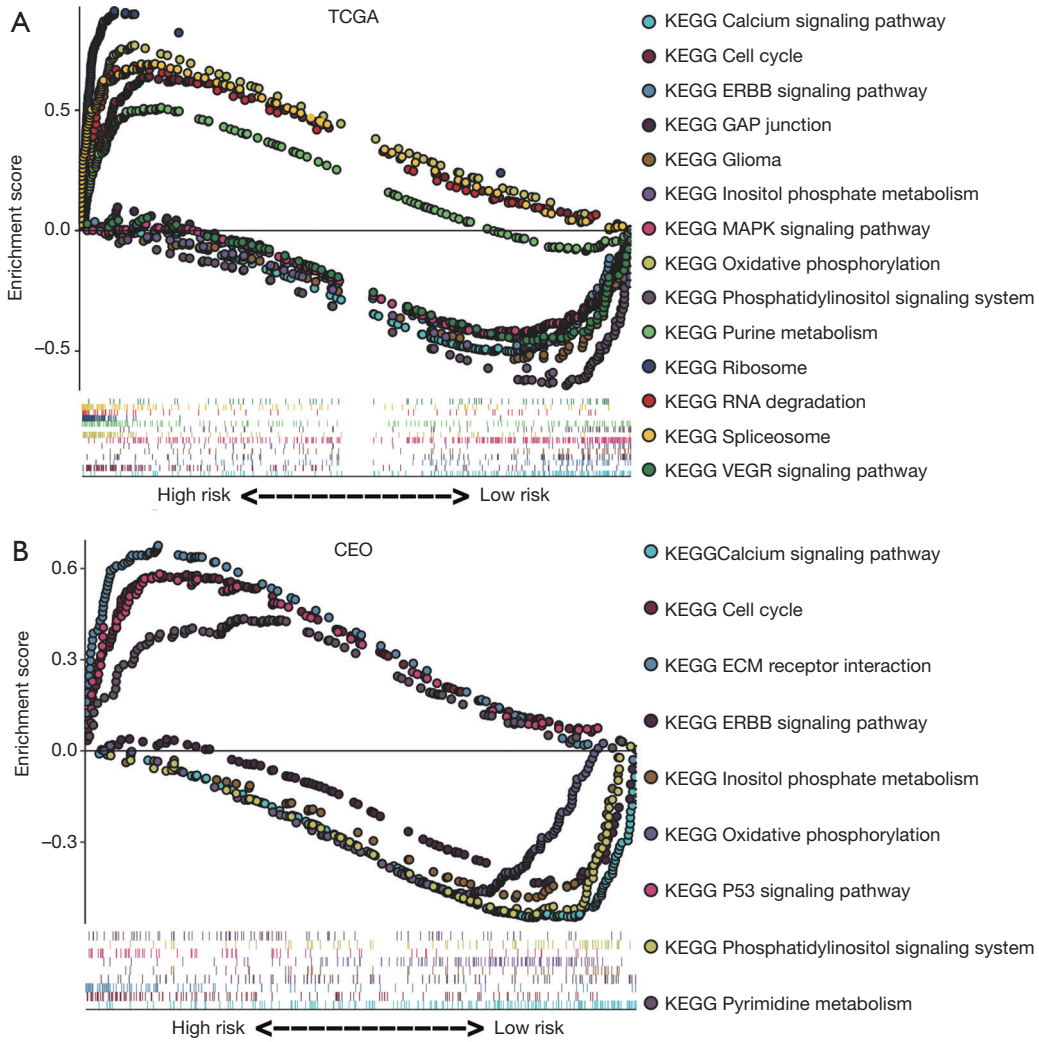

Figure 4 Gene set enrichment analysis (GSEA) analysis of the 4 signature genes. (A,B) GSEA analysis of the 4 prognostic β-interferon (IFN-β)-associated genes based on The Cancer Genome Atlas (TCGA) and the Gene Expression Omnibus (GEO) database.

technology, the understanding of cancer is becoming clearer. As the scope of analyzed genes and diseases expands, bioinformatics analysis is becoming increasingly important. In the present study, we analyzed the biological functions of a prognostic IFN-β-associated gene signature using bioinformatics analysis.

Univariate Cox regression model found 5 survival-related genes. Lasso-penalized Cox analysis identified 5 genes to construct the prognostic model. Using the methodology previously described, the result is validated on the GEO datasets (GSE83300). We found that 4 IFN-β-associated genes (*PRDX1*, *SEC61B*, *XRCC5*, and *BCL2L2*) signature was a suitable marker of seizure prognosis in patients with GBM. Using the CGGA data, we found that 4 IFN-β-associated genes are independent biomarkers of prognosis and play important roles in many biological processes. For example, *PRDX1* is a member of the peroxiredoxin family of antioxidant enzymes, which reduce hydrogen peroxide and alkyl hydroperoxides (20). *PRDX1* forms a heterodimer with p38α MAPK14, stabilizing phosphate-p38α in glioma cells (21), and epigenetic silencing of *PRDX1* is frequent in 1p/19q-deleted oligodendroglial tumors and likely contributes to radiosensitivity and chemosensitivity of these tumors (22). *XRCC5* is the 80-kD subunit of the Ku heterodimer protein, which is also known as ATP-dependent DNA helicase II or DNA repair protein *XRCC5*.

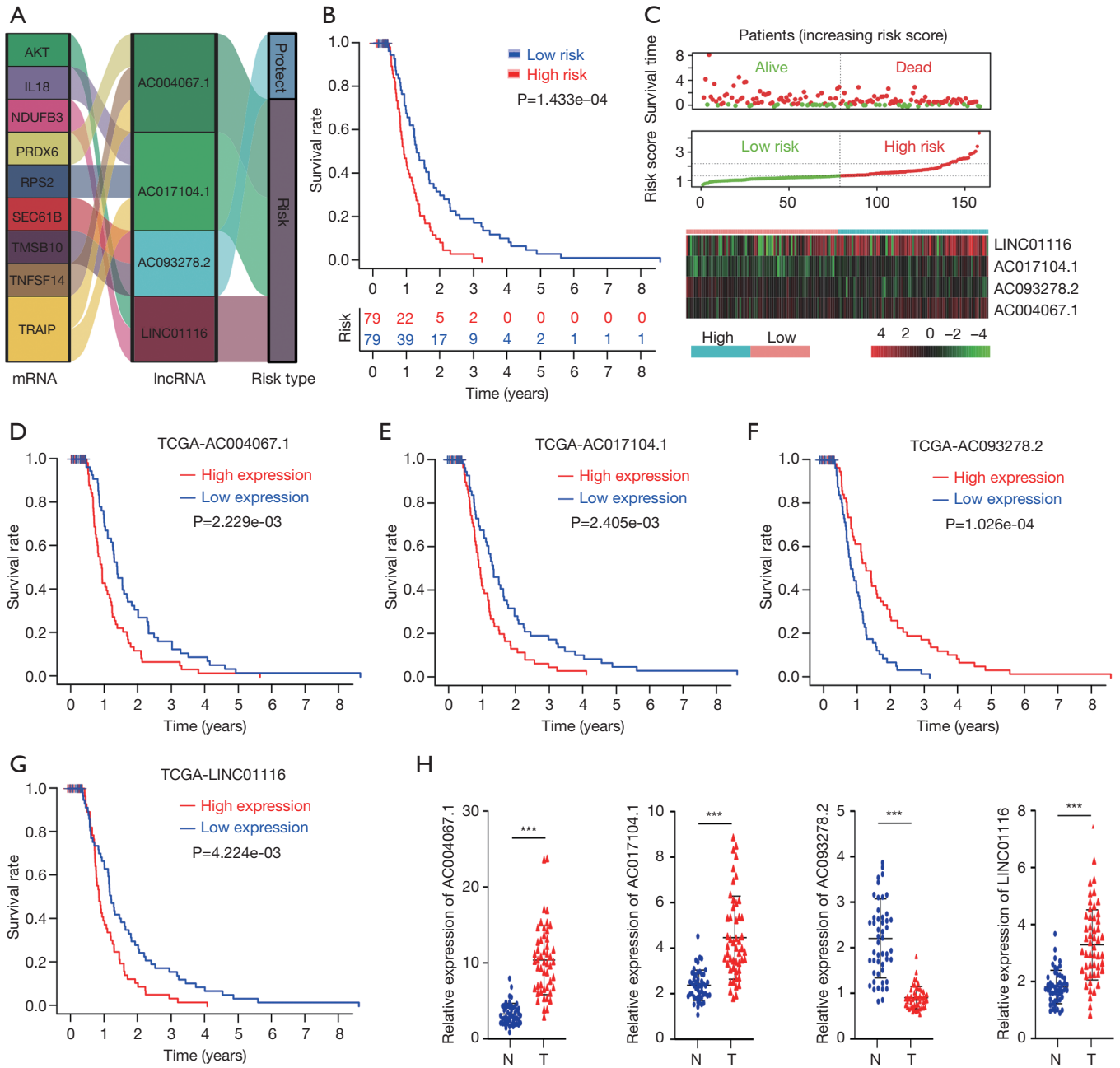

Figure 5 Prognostic impact of the β-interferon (IFN-β)-associated lncRNA signature for glioblastoma multiforme (GBM). (A) Network of prognostic lncRNAs with co-expressed IFN-β-associated lncRNAs in GBM. (B) Survival curve of GBM patients based on risk score model in The Cancer Genome Atlas (TCGA). (C) Survival duration and status of GBM cases. IFN-β-associated lncRNA risk score analysis of GBM patients in TCGA. Heatmap of the 4 key lncRNAs expressed in GBM. (D,E,F,G) Survival analysis of the 4 prognostic IFN-β-associated lncRNAs based on TCGA database. (H) Real-time polymerase chain reaction expression analysis of 4 prognostic IFN-β-associated lncRNAs in normal brain tissues (n=50) and GBM tissues (n=50). ***P<0.001.

The polymorphisms of *XRCC5* play an important role in astrocytoma prognosis in the Chinese Han population, which could be used in the determination of astrocytoma prognosis in clinical research (23). Elevated XRCC5 expression level can promote temozolomide resistance and predict poor prognosis in glioblastoma (24). *BCL2L2* is a member of the Bcl-2 protein family. The proteins of this family form heterodimers or homodimers and act as anti- and pro-apoptotic regulators. The expression of (24) in various cancer cell types. Interestingly, *BCL2L2* mRNA is highly expressed in the mesenchymal type of GBM (25). Through the wide variety of studies published to date, no clear consensus for the BCL2L2 is correlated with radiotherapy and chemotherapy in GBM. *SEC61B* is the central component of the protein translocation apparatus of the endoplasmic reticulum membrane (26). However, to the best of our knowledge, the expression pattern and function of SEC61B in GBM have not been previously reported; the role of the BCL2L2, XRCC5, SEC61B in glioma radiotherapy still remains unclear. Therefore, further study is warranted.

Considering the critical role of lncRNAs in GBM, the identification of important lncRNAs in cancer and developing lncRNA-based therapeutic strategies will be important in the future. Univariate and multivariate Cox Pearson correlation was applied to calculate the correlation between the lncRNAs and IFN-β-associated genes. regressions were used for the survival analysis, and indicated that AC093278.2, AC004067.1, LINC01116, and AC017104.1 were independent prognostic factors for the overall survival of GBM patients. LncRNA genes play important roles in many biological processes. For example, LINC01116 promotes tumor proliferation, migration, and invasion in glioma cell (27,28). However, the role of AC093278.2, AC004067.1, and AC017104.1 in GBM has not been reported, and it is important that it is elucidated in future studies. All in all, a novel IFN-β-associated gene signature to predict the overall survival of GBM patients, which may help in clinical decision making for individual treatment.

Conclusions

In the present study, we explored and analyzed differentially expressed IFN-β-associated genes by systematic bioinformatics analysis and established a novel IFN-β-associated gene signature to predict the overall survival of GBM patients, which may help in clinical decision making for individual treatment.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-21-1986). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Jiangxi Cancer Hospital of Nanchang University. Informed consent was obtained from the patients or guardians.

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