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Original Article

Diagnostic and prognostic utility of eIF6 in glioblastoma: a study based on TCGA and CGGA databases

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Abstract: Background: Among various glioma types, glioblastoma multiforme (GBM) is one of those with the highest malignancy. Although overexpression of eukaryotic translation initiation factor 6 (eIF6), a factor that regulates protein translation initiation, is believed to promote tumor development, its function and potential molecular mechanisms in glioma progression remain uncharacterized. Consequently, we evaluated its diagnostic and prognostic utility in GBM patients. Methods: Sample data from two databases, The Cancer Genome Atlas (TCGA) and the Chinese Glioma Genome Atlas (CGGA), were utilized to investigate the role of eIF6 as well as its mechanism of action in gliomas. We analyzed eIF6 expression in normal tissues as well as cancerous samples of different stages of glioma. The diagnostic and prognostic value of eIF6 were analyzed using the Receiver Operating Characteristic Curve (ROC) and Kaplan-Meier analysis, respectively. Furthermore, its underlying molecular mechanism in GBM was further revealed by gene set enrichment analysis (GSEA). Results: Transcriptome data analyses of the two databases showed that eIF6 was upregulated in glioma tissues compared with normal counterparts. eIF6 was at high levels in WHO grade IV gliomas versus grade II and III gliomas ($P<0.05$). In addition, eIF6 was highly expressed in elderly and Asian glioma patients. Furthermore, eIF6 expression was found to be lower in isocitrate dehydrogenase (IDH)-mutated tumors. Patients with high eIF6 level presented shorter overall survival than cases with low eIF6 level ($P<0.05$), and eIF6 had favorable accuracy in predicting the prognosis of glioma patients. GSEA revealed that high eIF6 expression was mainly concentrated in cell cycle and DNA repair related pathways. Conclusions: eIF6 is highly expressed in gliomas and positively associated with the degree of malignancy. Patients with high eIF6 expression present poor survival. Therefore, eIF6 has the potential to be a diagnostic biomarker and a potential therapeutic target for glioma development and GBM.

Keywords: eIF6, glioma, overall survival, GSEA

Background and Introduction

Glioma is the most commonly seen primary intracranial tumor, and glioblastoma multiforme (GBM) is one of the most difficult to treat [1-3]. Pathologically, gliomas can be categorized as either astrocytoma, oligodendroglioma, ependymoma or mixed glioma, of which astrocytoma is the most common [4-6]. In terms of grading, gliomas are classified into four grades (I-IV) based on their malignancy degrees [7]. Among them, grade (G) I and II gliomas are low-grade tumors, which have a good prognosis if they can be completely resected; while G III and IV gliomas belong to high-grade tumors, with high malignancy, difficult resection, and easy recurrence. A glioma may evolve into GBM when it develops to an advanced stage (G IV) [8]. In elderly patients, approximately 90% of GBM progress rapidly with no clinical or histological evidence of less malignant precursor lesions [7]. The current treatment options for gliomas are limited and the post-diagnosis prognosis is often poor [8]. Although surgical resection, chemotherapy and radiotherapy are clinically considered the standard treatments for GBM, none of them can cure the disease when used alone [9, 10]. Therefore, early detection and treatment of GBM is the key to improve patient survival. In recent years, the diagnosis, prognosis assessment and treatment of GBM based on histology com-

bined with molecular markers has become an important milestone in the management of the disease [11]. Therefore, discovering early biomarkers for GBM has become extremely important, and better understanding the molecular mechanisms underlying glioma progression is equally crucial for developing new therapies that ultimately enhance patient outcomes.

According to research reports, the formation of glioma is closely related to the maladjustment of signal pathways [12], so finding biomarkers from maladjusted pathways has become the key to early diagnosis. Eukaryotic translation initiation factors (eIFs) are shown to be involved in protein translation initiation and help stabilize the formation of functional ribosomes around the initiation codons, playing a vital role in cell growth and proliferation [13]. Over activation of eIFs has been confirmed to be related to tumor proliferation and invasion, suggesting the role of eIFs as potential diagnostic markers and therapeutic targets [14]. eIF6 belongs to the eIFs family and has been indicated to interfere with the progression of a wide spectrum of tumors [15-21]. A recent study based on eIF6 and gliomas showed a non-significant increase of eIF6 expression in G I, II, and III gliomas compared with non-tumor cortical brain tissue [14], while a significant elevation in G IV gliomas. Therefore, we speculate that the high expression of eIF6 may be the key in the tumorigenesis of GBM.

Given the lack of bioinformatics analysis of eIF6 in GBM, we collected data from two databases, The Cancer Genome Atlas (TCGA) and the Chinese Glioma Genome Atlas (CGGA), focusing on the correlation of eIF6 with GBM progression as well as the potential mechanism. This study is conducive to understanding the possible correlation and mechanism of interaction between eIF6 and GBM, providing an important theoretical basis for GBM diagnosis and prognosis assessment. In addition, the findings provide a new theoretical foundation for understanding the potential role of eIF6 in enhancing GBM growth and invasiveness and render a feasible tactic to improve GBM diagnosis and patient outcomes.

Methods

Data sources

From TCGA and Genotype-Tissue Expression (GTEx) with the URL of https://portal.gdc.cancer.gov/and https://gtexportal.org/, respectively, 663 cases of gliomas [GBM + low grade glioma (LGG)] sample data and RNA-seq data as well as the data of 2,642 cases of normal tissues were downloaded for analysis. eIF6 expression profiles and follow-up data were retrieved from the mRNA-seq_325 dataset (Dataset ID: mRNAseq_325 (batch 2); Data Type: RNA-seq) of the CGGA database (http://www.cgga.org.cn/). The collected data were normalized, and samples with defective clinical information were eliminated. There were 641 samples left in TCGA database (509 for GBM and 132 for LGG) and 313 samples in CGGA database after filtration. The batch effect was removed using the remove Batch Effect function from the limma package to analyze the expression data of TCGA and GTEx data together.

Kaplan-Meier (K-M) survival analysis

P values and hazard ratios (HR) with 95% confidence intervals (CI) in the K-M curve analysis were determined by the Logrank test and univariate Cox proportional hazard regression. Time-dependent receiver operating characteristic (ROC) curve analysis was further carried out to identify the prediction accuracy of eIF6. Patients were grouped as high- or low-expression group according to its optimal cut-off value. R software packages and all the aforementioned analytical methods were executed with the use of R software version 4.0.3 (R Foundation for Statistical Computing, 2020). The significance threshold was $P<0.05$.

Gene set enrichment analysis (GSEA)

Datasets were classified as high- or low-expression of eIF6 according to the median value. Reference genesets (c2.cp.kegg.v7.4.symbols.gmt and h.all.v7.4.symbols.gmt) retrieved from the Molecular Signatures Database were allocated to high and low eIF6 expression groups based on the median expression value. GSEA software (*v*3.0, URL: http://www.gsea-msigdb.org/) was used to set random combination times of 1,000, and the genesets with $P<0.05$ & FDR <0.25 were considered significantly enriched ones.

Statistical analysis

SPSS *v*22.0 was utilized to process the retrieved data. Mean ± standard deviation was used to indicate the quantitative variables, and

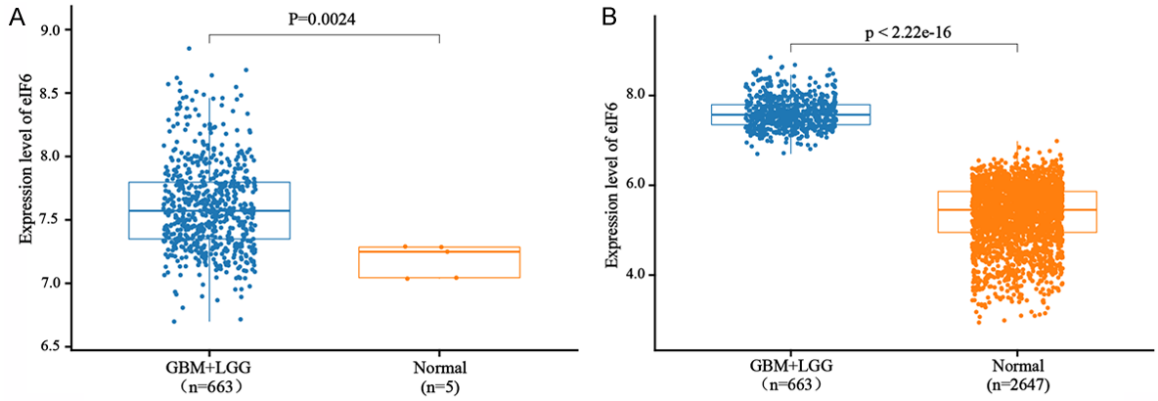

Figure 1. eIF6 expression in tumor tissue and normal counterparts. A. eIF6 in carcinoma tissue and normal counterparts from TCGA database; B. eIF6 in carcinoma tissue and normal counterparts from TCGA and GTEx databases.

differences between groups were analyzed by the Wilcoxon rank-sum test. K-M analysis was carried out for survival analysis. Statistical differences were indicated when $P<0.05$.

Results

eIF6 expression in glioma was higher than normal tissue

To analyze whether eIF6 is associated with glioma genesis, eIF6 expression in 663 glioma samples (GBM + LGG) and 5 adjacent counterparts in the TCGA database was analyzed. The results identified that eIF6 was significantly upregulated in cancer tissues compared with normal counterparts ($P<0.05$, **Figure 1A**). Due to the lack of normal counterparts in the TCGA database, 2,642 normal tissue specimens from the GTEx were further analyzed, and consistent results were obtained ($P<0.05$, **Figure 1B**).

eIF6 was upregulated in the elderly, Asians, and malignant gliomas based on the TCGA database

Data from TCGA were further analyzed to understand whether eIF6 expression in gliomas is affected by age, gender, ethnicity, and tumor grading. TCGA transcriptome data analysis determined a significant difference in eIF6 expression between patients ≤50 years old and those aged above 50 ($P<0.05$, **Figure 2A**), but no evident difference between different genders ($P>0.05$, **Figure 2B**). Besides, eIF6 levels differed significantly among Asians, Caucasians and Africans ($P<0.05$), but didn't among other races ($P>0.05$, **Figure 2C**). Finally, eIF6 was elevated significantly in G IV gliomas ($P<0.05$, **Figure 2D**). This suggests the potential of eIF6 upregulation as a high-risk factor for glioma progression among the elderly, Asians and those with G IV gliomas.

eIF6 expression was upregulated in the elderly and those with high-grade gliomas, but downregulated in isocitrate dehydrogenase (IDH)-mutated gliomas based on CGGA database

Similarly, we analyzed data from CGGA to determine whether eIF6 expression in gliomas is affected by age, gender, and tumor grading. Analysis of CGGA transcriptome data also identified an evident difference in eIF6 expression between patients younger than 50 years old and those aged >50 ($P<0.05$, **Figure 3A**), but no notable difference between different genders ($P>0.05$, **Figure 3B**). Furthermore, eIF6 showed statistically different expression among glioma patients with different WHO grades ($P<0.05$, **Figure 3D**). The above suggests that the development of gliomas in elderly patients, as well as the exacerbation of high-grade gliomas, are associated with upregulation of eIF6.

Additionally, tumor cells use the "metabolic reprogramming" caused by IDH mutations to create favorable growth conditions for themselves. Interestingly, statistical difference in eIF6 expression was observed in patients with different IDH mutation status ($P<0.05$, **Figure 3C**). eIF6 showed lower expression in IDH-mutated gliomas than in normal gliomas.

eIF6 upregulation reduced overall survival (OS) in glioma patients

Glioma development is closely linked to patients' OS. To understand whether eIF6 upregu-

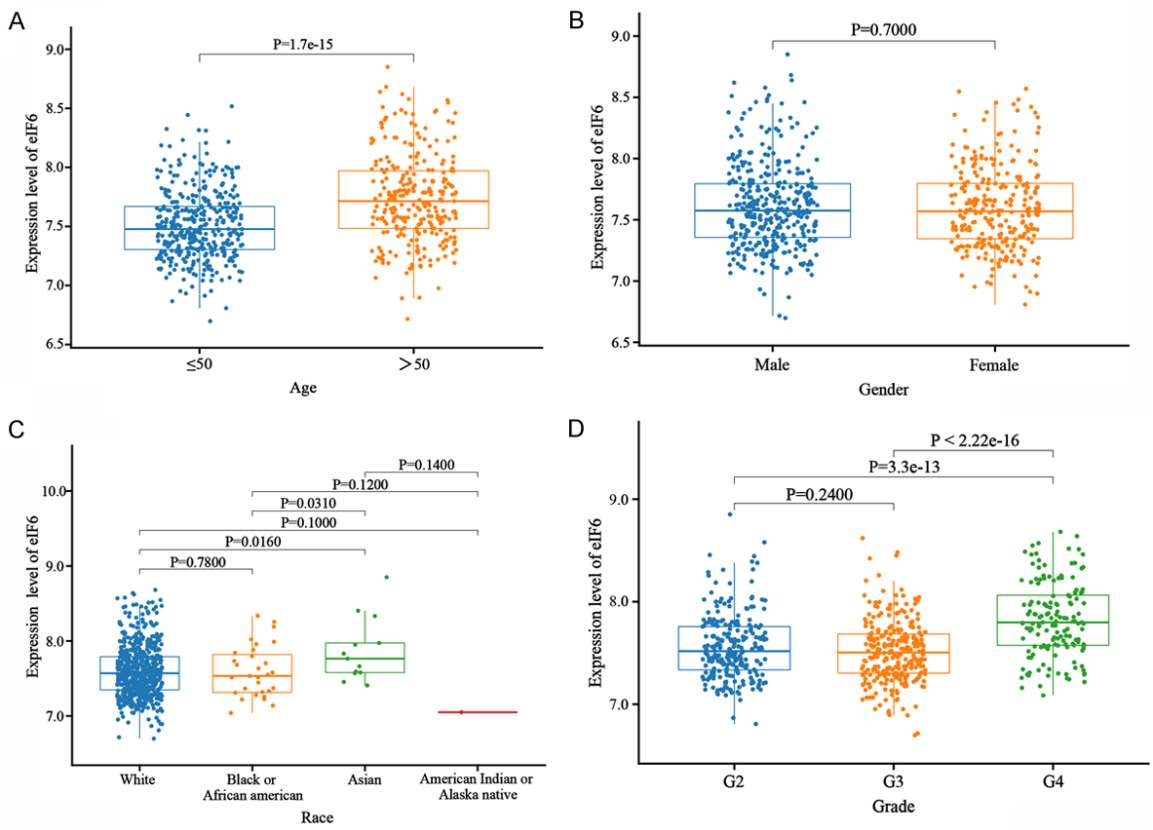

Figure 2. Expression in carcinoma tissue specimens from TCGA database. A. Expression of eIF6 in different age groups; B. Expression of eIF6 in different genders; C. Expression of eIF6 in different races; D. Expression of eIF6 in patients with different grades of gliomas.

lation affects OS, we analyzed the prognosis and survival of patients. Cases were grouped into either the high or low expression group based on optimal cut-off value of eIF6. In GBM and LGG patients from the TCGA database, high expression level of eIF6 predicted worse prognosis in GBM patients, while no statistical difference in eIF6 expression was observed regarding prognosis in LGG patients (**Figure 4A**, **4C**). Notably, worse prognoses were determined by K-M analysis in cases with high eIF6 expression in both TCGA and CGGA databases, compared with those with low expression (P<0.05, **Figure 4E**, **4G**). In addition, the sensitivity and specificity of eIF6 in predicting patients' OS were verified by ROC curves. We found that in the TCGA database, the area under the curve (AUC) values of eIF6 in predicting 1-, 3- and 5-year prognosis of GBM patients were 0.68, 0.65, and 0.64, respectively, and those for 1- and 3-year prognosis of LGG patients were 0.53, and 0.58, respectively (**Figure 4B**, **4D**). While taking GBM and LGG patients as a whole, the AUC values of eIF6 in predicting 1-, 3- and 5-year prognosis of glioma patients in TCGA were 0.63, 0.68, and 0.68, respectively; while in the CGGA database, the data were 0.72, 0.76, and 0.76, respectively. This suggests that eIF6 has high accuracy in predicting the prognosis and survival of glioma patients (**Figure 4F**, **4H**).

eIF6 upregulation affected cellular metabolism, cycle, DNA repair, and oncogene expression

Given that the impact of eIF6 on glioma development remains unclear, we further analyzed its biological function in gliomas. GSEA was performed on its high and low expression datasets according to median eIF6 expression value (Median value =5.67). With FDR <0.25 and NOM p-value <0.05 as thresholds, KEGG and HALLMARK pathway enrichment associated with eIF6 overexpression are shown in **Table 1**. The top three KEGG and HALLMARK signal

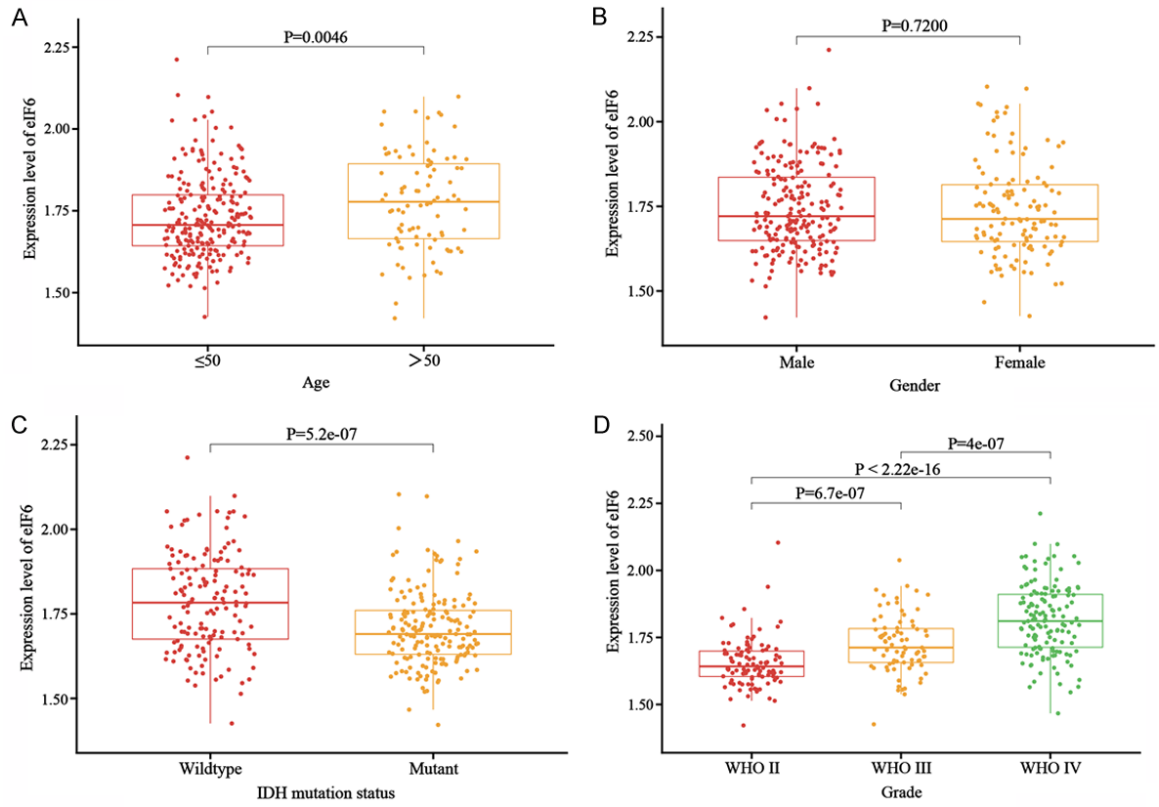

Figure 3. Expression of eIF6 in cancer tissue samples from CGGA database. A. Expression of eIF6 in different age groups; B. Expression of eIF6 in different genders; C. Expression of eIF6 in different IDH mutation status; D. Expression of eIF6 in patients with different WHO grades of gliomas.

pathways with the closest association with elevated eIF6 levels are listed in **Figure 5**. Of them, elevated eIF6 was mainly associated with Ribosome, Cell cycle and Spliceosome related pathways (**Figure 5A**); high eIF6 expression was positive in MYC targets, E2F targets and DNA repair signaling pathway (**Figure 5B**).

Discussion

Among central nervous system tumors, gliomas belong to the most frequently occurring type. Of gliomas, LGG is one of the most prevalent and aggressive types of primary malignant intracranial tumors, while GBM is considered the most common and invasive type [22, 23]. Accurate prognostic assessment, beyond all doubt, is critical for choosing the most suitable treatment at the early stage of the disease to improve the prognosis of patients [24]. Recent evidence has shown that biomarker-based cancer therapy can effectively improve the prognosis of some malignancies [25]. Therefore, this study mainly analyzed the association and underlying mechanism of eIF6 with GBM progression. Our results clearly show that eIF6 upregulation has a close association with the onset and development of gliomas. Besides, eIF6 generally highly expressed in high-grade tumors and susceptible populations. Moreover, upregulation of eIF6 reduces OS in glioma patients.

Translation initiation is an intricate and rate-determining step in protein synthesis that is conserved in eukaryotes and involves a wealth of eukaryotic initiation factors including eIFs. For a long time, eIFs have been considered rate-limiting for protein translation initiation. In recent years, their mechanisms of action in cancer have been gradually revealed, and the disturbance of their expression and localization has been considered the inducement of cancer progression and malignant phenotype of circulating cells [26]. eIFs participate in tumorigenesis, progression and invasion, and mainly regulate the classical or canonical translation initiation process, with either carcinogenic or tu-

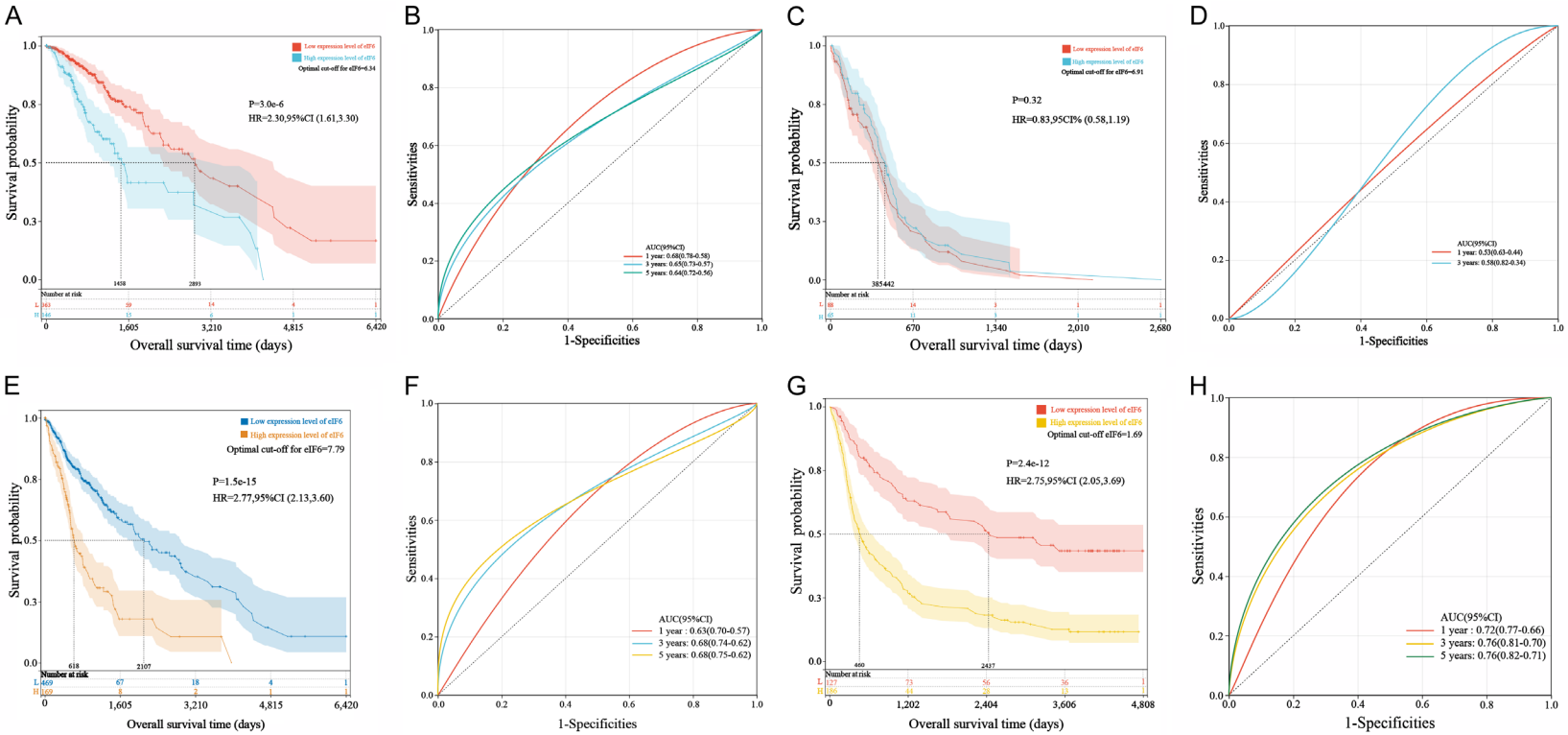

Figure 4. Correlation of eIF6 expression with glioma patient's overall survival. A. Correlation of eIF6 expression with overall survival of GBM patients in TCGA database; B. Time-dependent ROC curve of GBM patients in TCGA database; C. Correlation of eIF6 expression with overall survival of LGG patients in TCGA database; D. Time-dependent ROC curve of LGG patients in TCGA database; E. Correlation of eIF6 expression with glioma patients' overall survival in TCGA; F. Time-dependent ROC curve in the TCGA database; G. Relationship between eIF6 expression and glioma patients' overall survival in CGGA; H. Time-dependent ROC curve in the CGGA database.

Table 1. KEGG and HALLMARK pathway enrichment

GS follow link to MSigDB	Size	NES	NOM *p*-value	FDR q-value
KEGG_RIBOSOME	73	3.72	0.000	0.000
KEGG_CELL_CYCLE	54	2.61	0.000	0.000
KEGG_SPLICEOSOME	25	2.52	0.000	0.000
KEGG_DNA_REPLICATION	19	2.30	0.000	0.000
KEGG_P53_SIGNALING_PATHWAY	24	2.23	0.000	0.000
KEGG_PYRIMIDINE_METABOLISM	31	1.96	0.000	0.006
KEGG_N_GLYCAN_BIOSYNTHESIS	17	1.60	0.035	0.062
KEGG_ANTIGEN_PROCESSING_AND_PRESENTATION	30	1.47	0.034	0.134
HALLMARK_MYC_TARGETS_V1	66	3.01	0.000	0.000
HALLMARK_E2F_TARGETS	100	2.70	0.000	0.000
HALLMARK_DNA_REPAIR	36	2.46	0.000	0.000
HALLMARK_G2M_CHECKPOINT	90	1.32	0.000	0.001
HALLMARK_INTERFERON_GAMMA_RESPONSE	91	1.65	0.000	0.038
HALLMARK_P53_PATHWAY	67	1.45	0.025	0.133

mor-suppressive functions [27, 28]. Of them, eIF6 was discovered in mammals more than 3 decades ago, which is a 27 kDa conserved protein in eukaryotes [29] that participates in protein synthesis regulation [30]. In addition to a small fraction of eIF6 in eukaryotes' nucleus, most eIF6 exists in the cytoplasm [31]. Therefore, subcellular localization may be the key to the regulation of eIF6 function. In recent years, eIF6 dysregulation has been reported in various cancers like colorectal [28], breast [32], and non-small cell lung carcinoma [33]. However, its expression in gliomas and relationship with patient prognosis are still unclear, as there is a scarcity of research on eIF6 in gliomas. Based on the two major glioma gene profiles, TCGA and CGGA, this study explored the expression characteristics and clinical significance of eIF6 in gliomas, and preliminarily discussed its function in molecular mechanisms. First, the expression characteristics of eIF6 in gliomas were explored through transcriptome data of glioma patients from TCGA and CGGA. The results showed eIF6 was highly expressed in gliomas, with an increasing trend in glioma patients with higher WHO grade. In addition, high eIF6 expression was associated with poor prognosis. Therefore, the abnormally over-expressed eIF6 has a great clinical relationship with the occurrence and clinical prognosis of gliomas, which indicates its potential to be a characteristic marker of gliomas, especially GBM. Sun et al. [18] also found that eIF6 expression increased notably in hepatocellular carcinoma (HCC), and the increase was related to the pathological progression of HCC, indicating the role of eIF6 in HCC as both a novel diagnostic biomarker and an independent risk factor for patients' OS. In gliomas, this study also found consistent characteristics of eIF6.

Finally, the functional enrichment analysis of high and low eIF6 expression revealed that high eIF6 expression was abundantly enriched in biological processes and molecular axis related to cell proliferation like ribosomes and cell cycle signaling pathways. Reportedly, as a double factor, eIF6 promotes ribosome biogenesis and blocks the assembly of 40S and 60S ribosome subunits [34, 35], with a unique role in suppressing biological growth and development [36]. Notably, earlier studies have demonstrated that overexpression of eIF6 can lead to ocular dysplasia through G1/S phase arrest of the Xenopus cell cycle [37], while in Saccharomyces cerevisiae, eIF6 deletion reduces cell proliferation and viability [38]. In mice with eIF6 knockout, MYC-induced lymphatic injury was prevented and tumour-free survival was extended [31]. Moreover, it acts on lipogenic transcription factors (ATF4, C/EBPb, C/EBPd, etc.) in mammals, thus influencing lipometabolism and glycolysis levels [39]. All these studies have demonstrated the vital role played by eIF6 in cell cycle progression and tumorigenesis.

However, this study has some limitations. First, this research has only studied the characteristics of eIF6 in gliomas at the human gene transcriptome level, but not further studied its func-

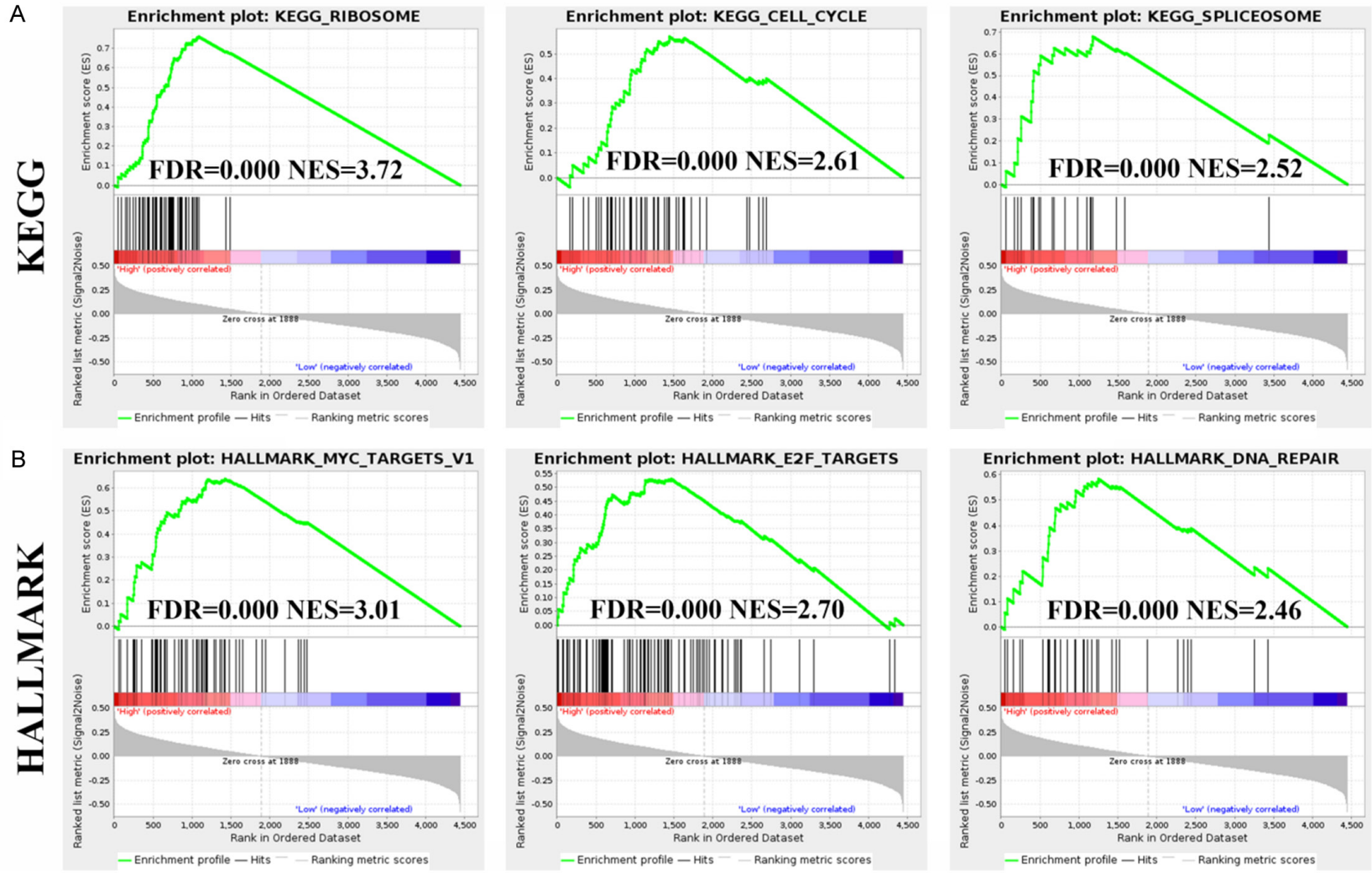

Figure 5. Pathways involved in the eIF6 enrichment analysis. A. KEGG enrichment analysis; B. HALLMARK enrichment analysis.

tion *in vivo* or *in vitro*. Second, the specific molecular mechanism of eIF6 in these processes needs further exploration. Therefore, more basic biological experiments are warranted for *in vivo* or *in vitro* validation of the conclusions obtained in this study.

In summary, eIF6 is highly expressed in gliomas, and higher eIF6 expression indicates high malignancy of gliomas and worse survival. Therefore, we believe that eIF6 is a key gene in the onset and development of gliomas and GBM, with the potential to be a biomarker and therapeutic target for GBM.

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Disclosure of conflict of interest

None.

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