·论　著·

TRIM5 高表达与胶质瘤患者不良预后和免疫浸润的相关性研究

陈悦，李琴，张洁，顾睿，李凯，赵岗，袁航，丰天宇，欧德琼，林苹

四川大学华西医院 实验肿瘤研究室（成都 610041）

【摘要】 三结构域蛋白家族 5（TRIM5）在自噬中起重要作用，并参与免疫和肿瘤进程，然而 TRIM5 在神经胶质瘤中的功能尚不清楚。本研究旨在通过生物信息学分析来评估 TRIM5 在胶质瘤中的作用。本研究神经胶质瘤数据库临床样本包括低级别神经胶质瘤（LGG）与多形性成胶质细胞瘤（GBM）。通过 Oncomine、基因表达谱交互分析（GEPIA）和癌症基因组图谱（TCGA）数据库探寻了 TRIM5 在胶质瘤组织中的表达。基于 TCGA 数据库，我们利用生存分析和多因素 Cox 回归分析评价 TRIM5 的预后作用。利用 STRING 数据库预测 TRIM5 相关蛋白网络，并通过 KEGG 富集分析预测 TRIM5 在胶质瘤中的潜在分子通路。此外，采用 CIBERSORT 和 TIMER 数据库进行免疫浸润分析。结果表明，与 Oncomine、GEPIA 和 TCGA 数据库中的正常样本相比，神经胶质瘤样本中的 TRIM5 表达明显上调。生存分析结果显示，较高的 TRIM5 表达与 LGG+GBM 患者以及 LGG 患者较差的总体生存（OS）有关，但与 GBM 患者 OS 无关。临床相关性分析结果显示，TRIM5 表达与年龄（χ^2=44.31，P<0.001）、病理学分级（χ^2=130.10，P<0.001）以及组织学类型（χ^2=125.50，P<0.001）具有相关性。多因素 Cox 风险分析结果显示 TRIM5 表达（HR=1.48，95% CI=1.20 ~ 1.80，P<0.001）、年龄（HR=1.05，95% CI=1.03 ~ 1.10，P<0.001）以及病理学分级（HR=3.11，95% CI=2.30 ~ 4.20，P<0.001）是胶质瘤患者（LGG+GBM）预后的独立危险因素；TRIM5 表达（HR=1.82，95% CI=1.42 ~ 2.32，P<0.001）、年龄（HR=1.06，95% CI=1.05 ~ 1.08，P<0.001）、病理学分级（HR=1.92，95% CI=1.22 ~ 3.01，P=0.005）以及组织学类型（HR=0.71，95% CI=0.57 ~ 0.89，P=0.003）是 LGG 患者的独立预后因素。相互作用网络分析发现，IRF3、IRF7、OAS1、OAS2、OAS3、OASL、GBP1、PML、BTBD1 以及 BTBD2 蛋白与 TRIM5 具有相互作用。此外，KEGG 分析还发现细胞凋亡、肿瘤以及免疫相关通路在 TRIM5 升高时显著富集。免疫浸润分析显示，TRIM5 表达可以影响胶质瘤中活化 NK 细胞、单核细胞、活化肥大细胞、巨噬细胞等免疫细胞浸润水平。以上结果提示，TRIM5 在胶质瘤组织中显著上调，并与预后不良和免疫浸润相关。TRIM5 可能作为神经胶质瘤预后与指导免疫治疗的生物标志物。

【关键词】 TRIM5；神经胶质瘤；生物标志物；预后；免疫浸润

Increased TRIM5 is associated with a poor prognosis and immune infiltration in glioma patients

CHEN Yue，LI Qin，ZHANG Jie，GU Rui，LI Kai，ZHAO Gang，YUAN Hang，FENG Tianyu，OU Deqiong，LIN Ping

Lab of Experimental Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu 610041, P.R.China

Corresponding author: LIN Ping, Email: linping@scu.edu.cn

【Abstract】 Tripartite motif 5 (TRIM5) plays a significant function in autophagy and involves in immune and tumor processes. While the function of TRIM5 remains poorly understood in glioma. We purpose to evaluate the possible prognostic role of TRIM5 in glioma via bioinformatics analyses. The database clinical samples of glioma in this study included low grade glioma (LGG) and glioblastoma multiforme (GBM). TRIM5 expression in glioma tissues were explored in Oncomine, GEPIA and The Cancer Genome Atlas (TCGA) databases. Survival analysis and the multivariate Cox regression analysis of TRIM5 based on TCGA were used to evaluate the prognostic role of TRIM5. The protein networks of TRIM5 was detected by STRING database. KEGG enrichment analyses were performed to predict the

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通信作者：林苹，Email：linping@scu.edu.cn

potential molecular pathways of TRIM5 in glioma. In addition, immune infiltration analysis was conducted by CIBERSORT and TIMER databases. We found that TRIM5 was strongly increased in glioma samples compared with normal samples in Oncomine, GEPIA and TCGA databases. Higher TRIM5 was significantly contributed to worse overall survival (OS) in LGG+GBM patients and LGG patients, while was no correlated with OS of GBM patients. Interaction networks analysis identified that IRF3, IRF7, OAS1, OAS2, OAS3, OASL, GBP1, PML, BTBD1 and BTBD2 proteins were contacted with TRIM5. Moreover, KEGG revealed that apoptosis and cancer- and immune-related pathways were enriched with elevated TRIM5. Specifically, TRIM5 could influence the immune infiltration levels, such as activated NK cells, monocytes, activated mast cells and macrophages in glioma. In conclusion, our data indicated that TRIM5 was upregulated in glioma tissues and associated with poor prognosis and immune infiltration. TRIM5 may be acted as a biomarker in prognosis and immunotherapy guidance of glioma.

【Key words】 TRIM5; glioma; biomarker; prognosis; immune infiltration

Introduction

Glioma is the most common brain tumor with high morbidity of 6 per 100 000 people each year[1-2]. Based on histopathology, gliomas can be classified into grades Ⅰ-Ⅳ. Of which, grade IV is regarded as glioblastoma multiforme (GBM), with shorter overall survival (OS) even with routine treatment[3]. Currently, postoperative radiotherapy and chemotherapy are the main treatment for glioma, but the prediction of clinical outcome is still inaccurate due to the histological grading variability, especially for low grade glioma (LGG) patients (grades Ⅰ-Ⅲ, including pilocytic astrocytoma, anaplastic astrocytoma, oligodendroglioma, oligodendrocytoma, anaplastic oligodendrocytoma and anaplastic oligodendroglioma and etc.)[4-5]. Therefore, efforts are needed to identify more biomarkers to evaluate the prognosis for glioma.

The tripartite motif (TRIM) family, constituted as immune-regulated proteins, played a general role in autophagy and involved in immune and tumor processes[6]. Tripartite motif 5 (TRIM5), well-known as a retrovirus limiting factor, has the function of autophagic degradation, protecting immune cells from HIV-1 infection[7]. Bioinformatics analysis by Srihari *et al.* found that TRIM5 was associated with BRCA1 and BRCA2 breast cancer[8]. A paper from Leal *et al.*, revealed that the restriction factor of TRIM5 may act as a significant role in defense against neuroinflammation[9]. Unfortunately, the function of TRIM5 remains much less explored in glioma.

In current study, we aimed to explore the prognostic role and potential mechanisms of TRIM5 in glioma. Firstly, we obtained the TRIM5 expression based on Oncomine, Gene Expression Profiling Interactive Analysis (GEPIA) and The Cancer Genome Atlas (TCGA) databases and analyzed the prognostics value of TRIM5 by TCGA database. Then, Oncomine, STRING databases and Kyoto Encyclopedia Genes and Genomes (KEGG) analysis were used to predict the possible pathways of TRIM5. Finally, immune infiltration analysis was performed between TRIM5 and glioma by using CIBERSORT and TIMER analyses.

1 Materials and Methods

1.1 Database

The TRIM5 mRNA expression in glioma was compared by the Oncomine (https://www.oncomine.org/) database[10] including Murat Brain and Sun Brain glioma studies[11-12]. TCGA (https://cancergenome.nih.gov/) database[13] was also searched to obtain TRIM5 expression and clinical data of glioma including 5 normal brain tissues, 529 LGG tissues and 169 GBM tissues. GEPIA (http://gepia.cancer-pku.cn/detail.php) database[14], an online webserver including 8 587 normal and 9 736 tumor samples, was utilized to analyze the TRIM5 expression (Tumor or Normal) from TCGA. Besides, data of 4 clinicopathological features including age, gender, grade and histological type were also extracted from TCGA.

1.2 Survival analysis

To explore associations between TRIM5 expression and glioma patient OS, TRIM5 expression level and clinical data of glioma were downloaded from TCGA. Then, package edgeR and R Limma package were used to transform the information. After excluding patients with incomplete information, we performed OS analysis by using R package.

1.3 Clinical correlation and Cox risk analyses

The relevant clinical and survival information of LGG and GBM patients was obtained from TCGA database. We eliminated patients without complete clinical data and acquired 668 patients (508 LGG and 160 GBM) for analyses. As for clinical correlation analysis, LGG and GBM patients were divided into high and low TRIM5 groups (grouped according to the median value), with 334 cases in each group.

1.4 Network analysis

To identify the possible interaction networks of TRIM5, we conducted co-expression analysis via Oncomine database with tumor type limited to “brain”.

Protein-protein interaction (PPI) analysis of TRIM5 was performed using STRING (https://string-db.org/) database[15]. In addition, KEGG pathway enrichment analysis was conducted by GSEA 4.0.3 software with 1 000 permutations[16]. Normal P value < 0.05 and false discovery rate (FDR) < 0.05 was the filter.

1.5 Immune infiltration analysis

CIBERSORT (https://cibersort.stanford.edu/) online tool is a deconvolution algorithm utilized to explore the correlation between gene expression and tumor-infiltrating immune cells (TIICs)[17]. We uploaded the standard TRIM5 expression data of 703 samples from TCGA to CIBERSORT algorithm running, and then selected samples with P < 0.05 to the final study cohort. Subsequently, the CIBERSORT obtained the proportion of TIICs in the high- and low-TRIM5 groups. In addition, TIMER (http://timer.cistrome.org/)[18] was utilized to report the correlation between immune infiltration and TRIM5 level in glioma. The analyzed immune cells include B cells, CD4+, Dendritic cells, CD8+ T cells, Macrophages and Neutrophils. Kaplan-Meier curves were downloaded from TIMER to analyze the relationship between immune infiltration or TRIM5 level and OS of LGG and GBM patients respectively.

1.6 Statistical analysis

The statistical analyses were conducted using R software 3.6.3 and GraphPad Prism 8.0.1. Student's t-test or ANOVA were utilized to assess the TRIM5 difference between glioma tissues and normal tissues. The relationship between TRIM5 level and clinicopathological features was compared by chi-square tests. Survive analyses were evaluated by the Kaplan-Meier with the log-rank test and Cox regression analysis. P < 0.05 was considered significant.

2 Results

2.1 High expression of TRIM5 in glioma

We found TRIM5 was elevated in central nervous system (CNS) and brain tumors compared with normal tissues via Oncomine (Fig. 1a). For verification, we conducted meta-analysis of TRIM5 expression in 4 analyses in Oncomine database (Fig. 1b). Compared with normal brain tissues, the TRIM5 level was statistically increased in GBM or Astrocytoma tissues (P < 0.001, Fig.

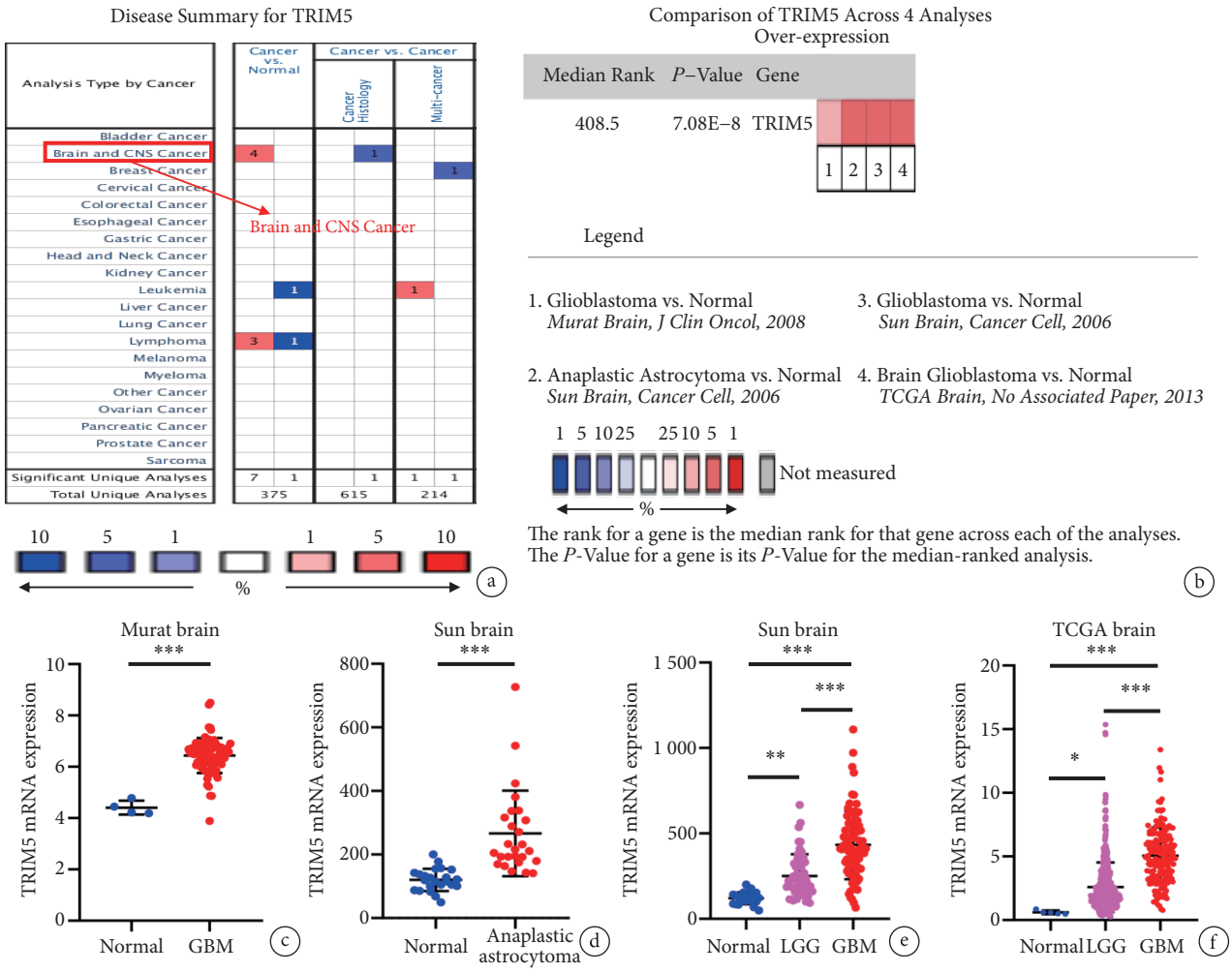

Fig.1 Elevated TRIM5 expression in glioma a. TRIM5 expression between cancer and normal tissues of Brain and CNS cancer in Oncomine; b. meta-analysis of TRIM5 expression in 4 analyses; c-f. TRIM5 expression in Murat Brain, Sun Brain and TCGA Brain

1c and 1d). Compared with LGG tissues, the TRIM5 expression was significantly higher in GBM tissues based on Sun Brain and TCGA Brain ($P < 0.001$, Fig. 1e and 1f). In order to further verify the above results, we observed that TRIM5 was increased in numerous cancers including LGG and GBM by using GEPIA tool (Fig. 2a). As expected, TRIM5 expression in LGG and GBM was notably higher than that in normal control (Fig. 2b). These results demonstrated that TRIM5 was upregulated in glioma and might be an indicator to predict the malignancy of glioma.

2.2 Relationship between TRIM5 level and prognosis in glioma

We performed Kaplan-Meier to analyze the influence of TRIM5 in OS of glioma patients (LGG+GBM), which showed that high TRIM5 expression would lead to a worse outcome ($P < 0.001$, Fig. 3a). Besides, subgroup analysis indicated that higher TIRM5 was risk factor for 1-year, 3-year and 5-year OS in glioma patients (all $P < 0.001$, Fig. 3b–3d). Subsequently, we performed prognostic analysis in LGG and GBM patients respectively, the results revealed that increased TRIM5 predicted poor OS in patients with LGG (all $P < 0.001$, Fig. 3e–3h), while was not correlated to prognosis of GBM patients (all $P > 0.05$, Fig. 3i–3l).

2.3 Clinical correlation and Cox analyses based on TCGA

We performed the correlation analyses between TRIM5 level and clinicopathological characteristics in glioma patients by TCGA (LGG+GBM). As shown in

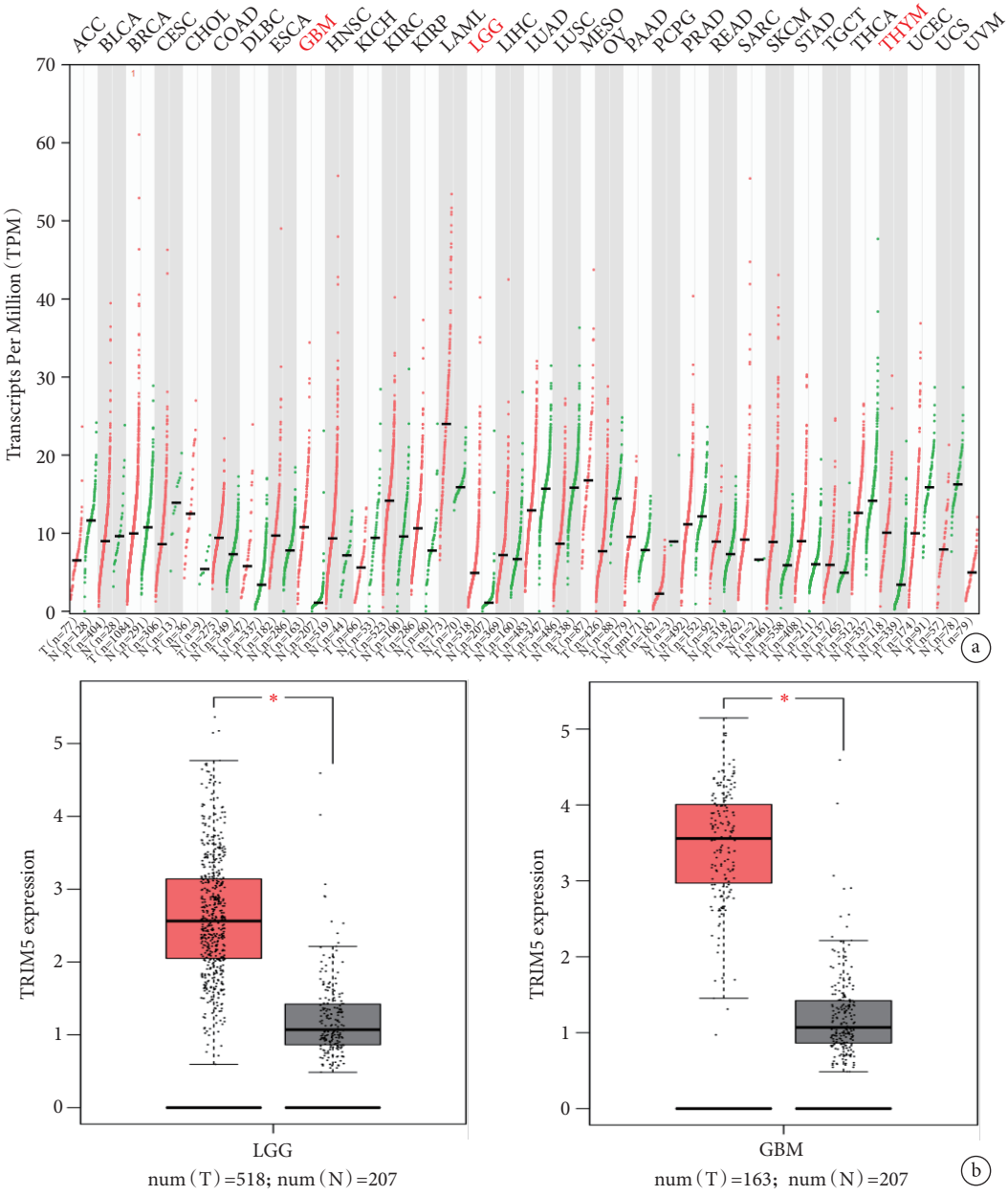

Fig.2 TRIM5 expression based on GEPIA database a. TRIM5 was notably increased in variety tumors; b. TRIM5 expression in LGG and GBM compared with normal control. *, $P < 0.05$

Tab. 1, high TRIM5 expression was significantly correlated to older age (χ^2 = 44.310, P < 0.001), higher grade (χ^2 = 130.100, P < 0.001) and more malignant histological type (χ^2 = 125.500, P < 0.001). Above results illustrated that TRIM5 contributed to predict glioma progression.

To further confirm the prognostic role of TRIM5, univariate and multivariate Cox analyses were employed (LGG and GBM patients). As shown in Tab. 2, TRIM5 expression was a risk factor (HR = 1.481, 95% CI = 1.201–1.824, P = 0.000) for glioma OS. Besides, age (HR = 1.047, 95% CI = 1.035–1.060, P < 0.000) and grade (HR = 3.110, 95% CI = 2.300–4.206, P < 0.000) were both risk factors. Next, we continued to perform analyses in LGG patients and the results showed that TRIM5 expression (HR = 1.816, 95% CI = 1.419–2.322, P < 0.000) could be acted as an independent prognostic factor. In addition, age (HR = 1.064, 95% CI = 1.047–1.082, P < 0.000), grade (HR = 1.915, 95% CI = 1.219 –3.009, P =0.005) and histological type (HR = 0.709, 95% CI = 0.566–0.890, P = 0.003) were all risk factors for LGG patients OS (Tab. 3).

2.4 The network interactions with TRIM5

To explore the possible molecular mechanisms of TRIM5, we predicted some co-expressed genes with TRIM5 in glioma by Oncomine database. We found strong correlation between NMI, TRIM22 and DDX60 etc. with TRIM5 with the correlation score > 0.7 (Fig. 4a). STRING indicated that IRF3, IRF7, OAS1, OAS2, OAS3, OASL, GBP1, PML, BTBD1 and BTBD2 were contacted with TRIM5 (Fig. 4b). Lastly, KEGG pathway enrichment of TRIM5 showed that highly expressed TRIM5 was mainly enriched in “pathways in cancer”, “apoptosis”, and some immune-related pathways (Fig. 5). The specific information of the enrichment pathways is shown in Tab. 4.

2.5 Correlation analyses between TRIM5 and TIICs

According to the above results, TRIM5 may play an

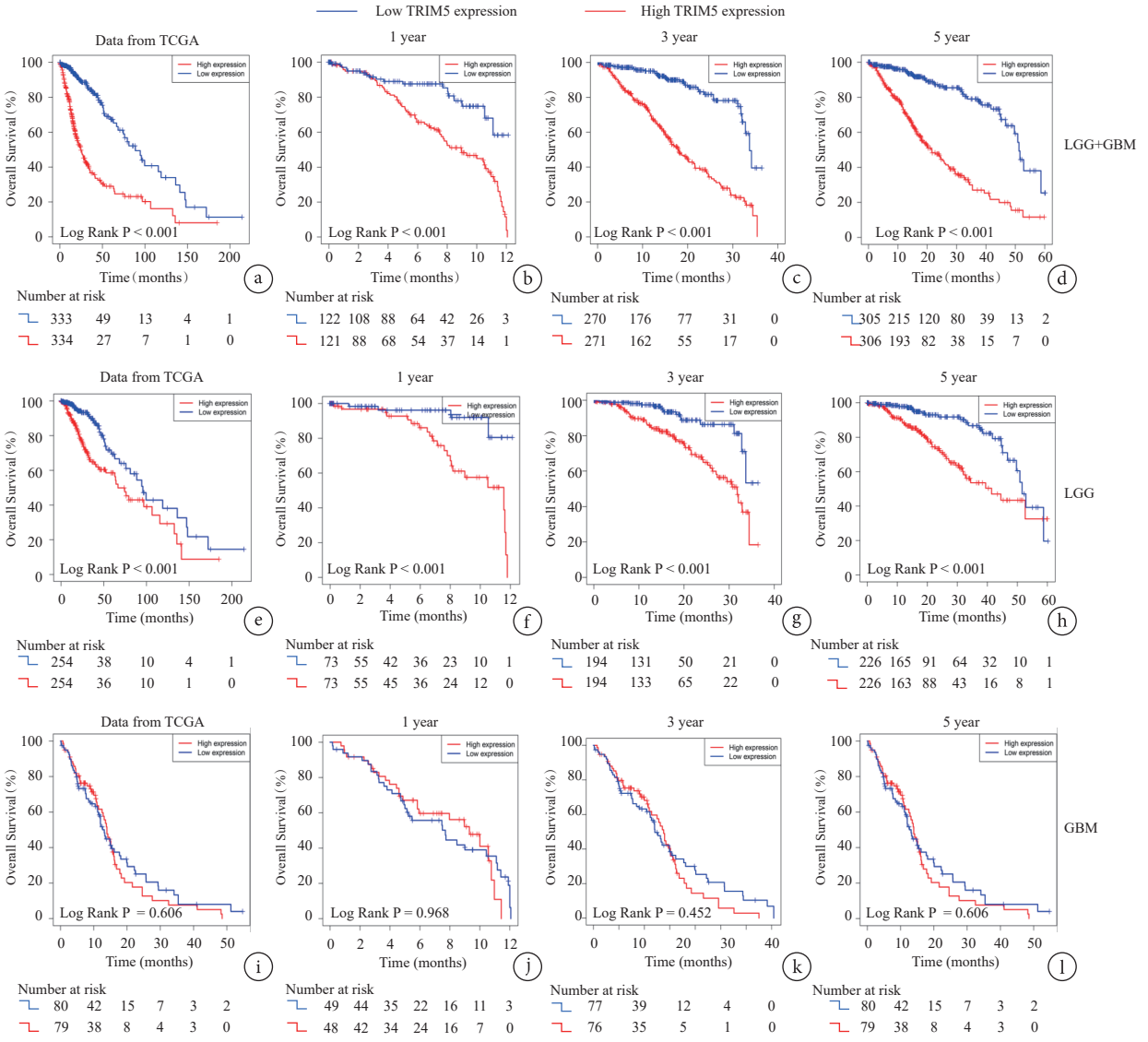

Fig.3 TRIM5 upregulation was associated with poor prognosis in glioma on TCGA database a–d. OS of LGG+GBM patients; e–h. OS of LGG patients; i–l. OS of GBM patients

Tab.1　Correlations between TRIM5 expression and clinicopathological characteristics in glioma patients (LGG+GBM)

Parameters	Cases (*n*=668)	TRIM5 expression		χ^2	*P* value
		Low (*n*=334)	High (*n*=334)		
Age/year				44.310	**<0.001**
⩽51	406	245 (73.35%)	161 (48.20%)		
>51	262	89 (26.65%)	173 (51.80%)		
Gender				2.930	1.711
Female	283	152 (45.51%)	131 (39.22%)		
Male	385	181 (54.19%)	204 (61.08%)		
Grade				130.100	**<0.001**
G2	247	170 (50.90%)	77 (23.05%)		
G3	262	145 (43.41%)	117 (35.03%)		
G4	159	19 (5.69%)	140 (41.92%)		
Histological				125.500	**<0.001**
Astrocytoma	192	107 (32.03%)	85 (25.45%)		
Oligoastrocytoma	317	208 (62.28%)	109 (32.63%)		
GBM	159	19 (5.69%)	140 (41.92%)		

Positive results were highlighted in bold

Tab.2　Univariate and multivariate Cox analyses of OS in LGG+GBM patients

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	1.073	1.061–1.084	**<0.000**	1.047	1.035–1.060	**<0.000**
Gender	1.124	0.858–1.471	0.396			
Grade	4.702	3.784–5.843	**<0.000**	3.110	2.300–4.206	**<0.000**
Histological type	1.971	1.698–2.288	**<0.000**	0.886	0.754–1.041	0.140
TRIM5 expression	2.808	2.342–3.366	**<0.000**	1.481	1.201–1.824	**0.000**

Positive results were highlighted in bold

Tab.3　Univariate and multivariate Cox analyses of OS in LGG patients

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	1.065	1.048–1.081	**<0.000**	1.064	1.047–1.082	**<0.000**
Gender	1.060	0.726–1.548	0.762			
Grade	3.120	2.061–4.723	**<0.000**	1.915	1.219–3.009	**0.005**
Histological type	0.749	0.601–0.934	**0.010**	0.709	0.566–0.890	**0.003**
TRIM5 expression	2.400	1.839–3.132	**<0.000**	1.816	1.419–2.322	**<0.000**

Positive results were highlighted in bold

immune-related role in glioma. And tumor-infiltrating lymphocytes were widely believed to be the predictors of OS in cancer patients[19]. Therefore, we then used CIBERSORT algorithm to calculate the proportion of 22 immune cells in the low and high TRIM5 expression groups. As shown in Fig. 6a, gamma delta T cells, activated NK cells, Monocytes, activated mast cells and Eosinophils were decreased (all $P < 0.05$) in high TRIM5 level group, while M0 and M1 Macrophages and resting mast cells were increased (all $P < 0.05$) compared with low TRIM5 level group. Moreover, we compared the correlations between 22 immune cell types (Fig. 6b). The heat map showed a strong negative correlation between M0 Macrophages and Monocytes ($r = -0.76$), and moderate negative correlation between M2 Macrophages and activated mast cells ($r = -0.53$), as well as resting NK cells and activated NK cells ($r = -0.48$). We also observed that TRIM5 was positively correlated with B cells ($r = 0.205$, $P = 6.50e{-}06$), CD4 + T cells ($r = 0.312$, $P = 2.81e{-}12$), Dendritic cells ($r = 0.433$, $P = 2.55e{-}23$), Macrophages ($r = 0.421$, $P = 5.86e{-}22$) and Neutrophils ($r = 0.418$, $P = 1.15e{-}21$) in LGG, and CD4 + T cells ($r = 0.297$, $P = 4.22e{-}04$), Dendritic cells ($r = 0.353$, $P = 2.31e{-}05$) and Macrophages ($r = 0.19$, $P = 2.60e{-}02$) in GBM by using TIMER (Fig. 7). These results showed that TRIM5 might influence the immune infiltration of glioma patients.

3　Discussion

Glioma is one of the most common tumors of brain. Surgery is the general treatment for glioma, but postoperative chemoradiotherapy is often needed because of the invasive growth characteristics of glial cells[20-21]. GBM is the most malignant glioma with a

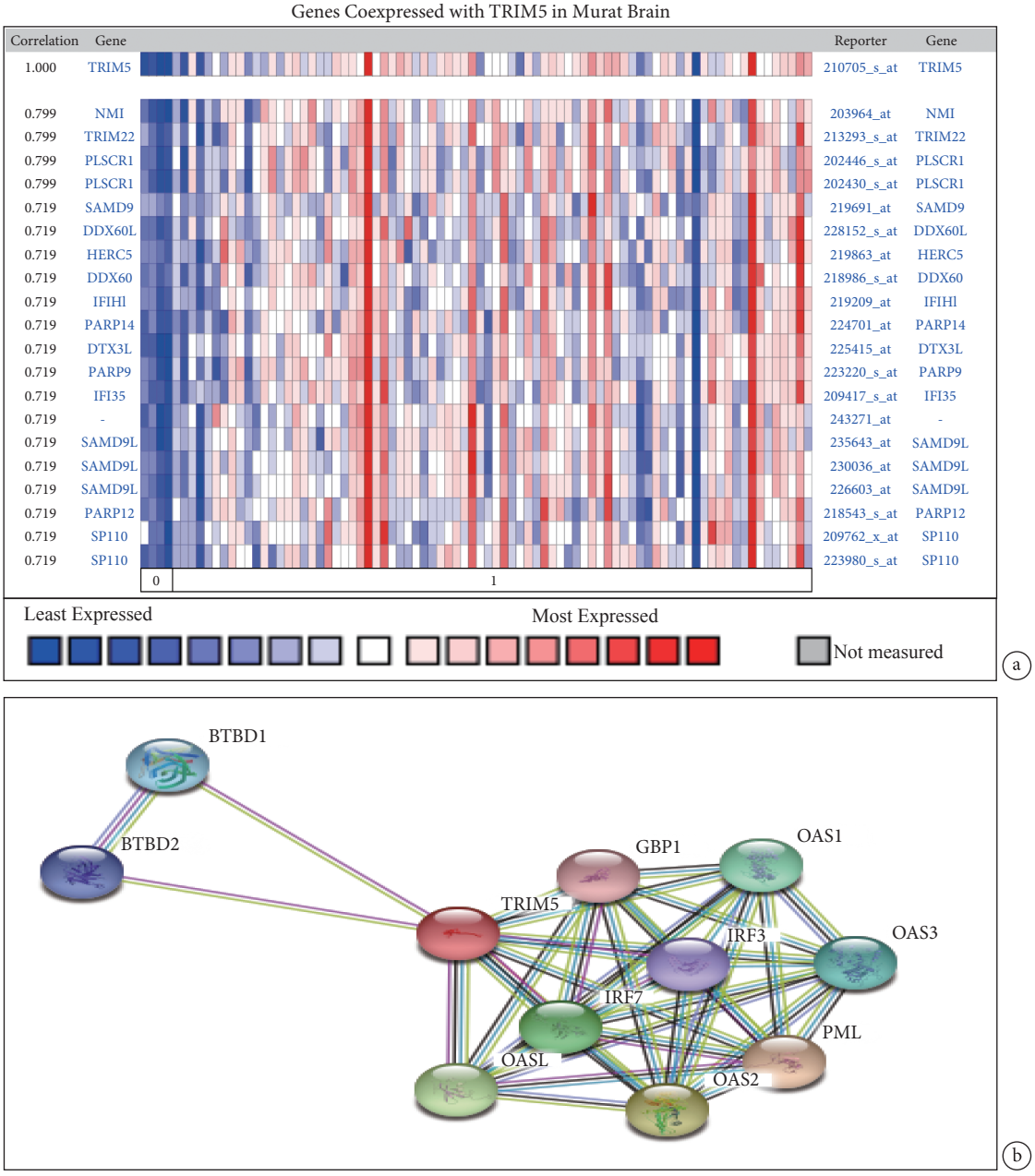

Fig.4 The potential interaction networks prediction of TRIM5 a. transcriptome prediction of TRIM5 in glioma in Oncomine database; b. TRIM5 protein interaction networks in STRING

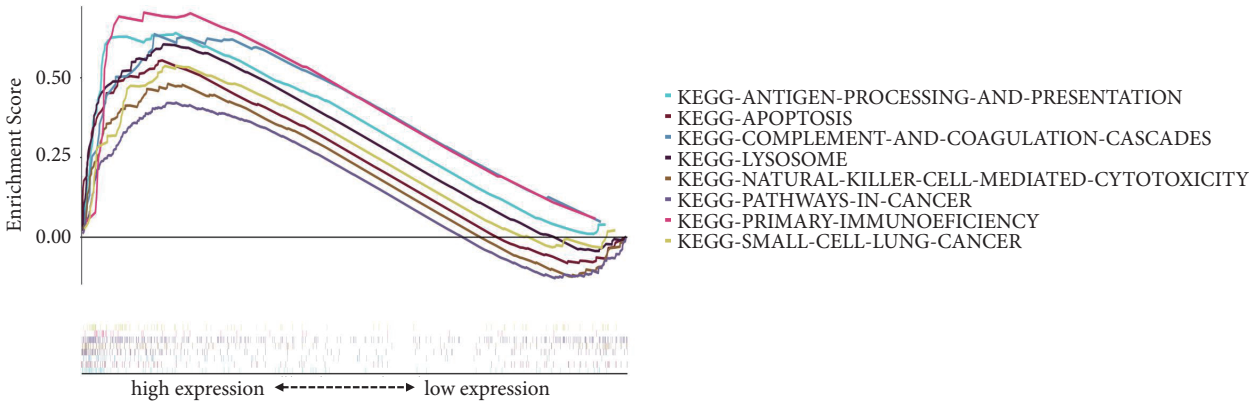

Fig.5 Enrichment plots from GSEA analysis

Tab.4　Results of part KEGG enrichment analyses

Gene set name	NES	NOM *p*-val	FDR q-val
KEGG_PATHWAYS_IN_CANCER	1.705	0.002	0.045
KEGG_SMALL_CELL_LUNG_CANCER	1.864	0.002	0.026
KEGG_APOPTOSIS	2.021	0.002	0.033
KEGG_LYSOSOME	1.958	0.004	0.025
KEGG_ANTIGEN_PROCESSING_AND_PRESENTATION	1.965	0.002	0.047
KEGG_COMPLEMENT_AND_COAGULATION_CASCADES	1.926	0.000	0.022
KEGG_NATURAL_KILLER_CELL_MEDIATED_CYTOTOXICITY	1.745	0.032	0.038
KEGG_PRIMARY_IMMUNODEFICIENCY	1.882	0.006	0.028

Abbreviations: NES, normalized enrichment score

median lifetime of 12-16 months and a poor prognosis because of tumor recurrence and resistance[22-23]. Therefore, biomarkers for early diagnosis of glioma can provide guidance for treatment and prognosis of patients.

Over the past few years, there have been many reports on the functions of TIRM5 in autophagy[24-26]. As

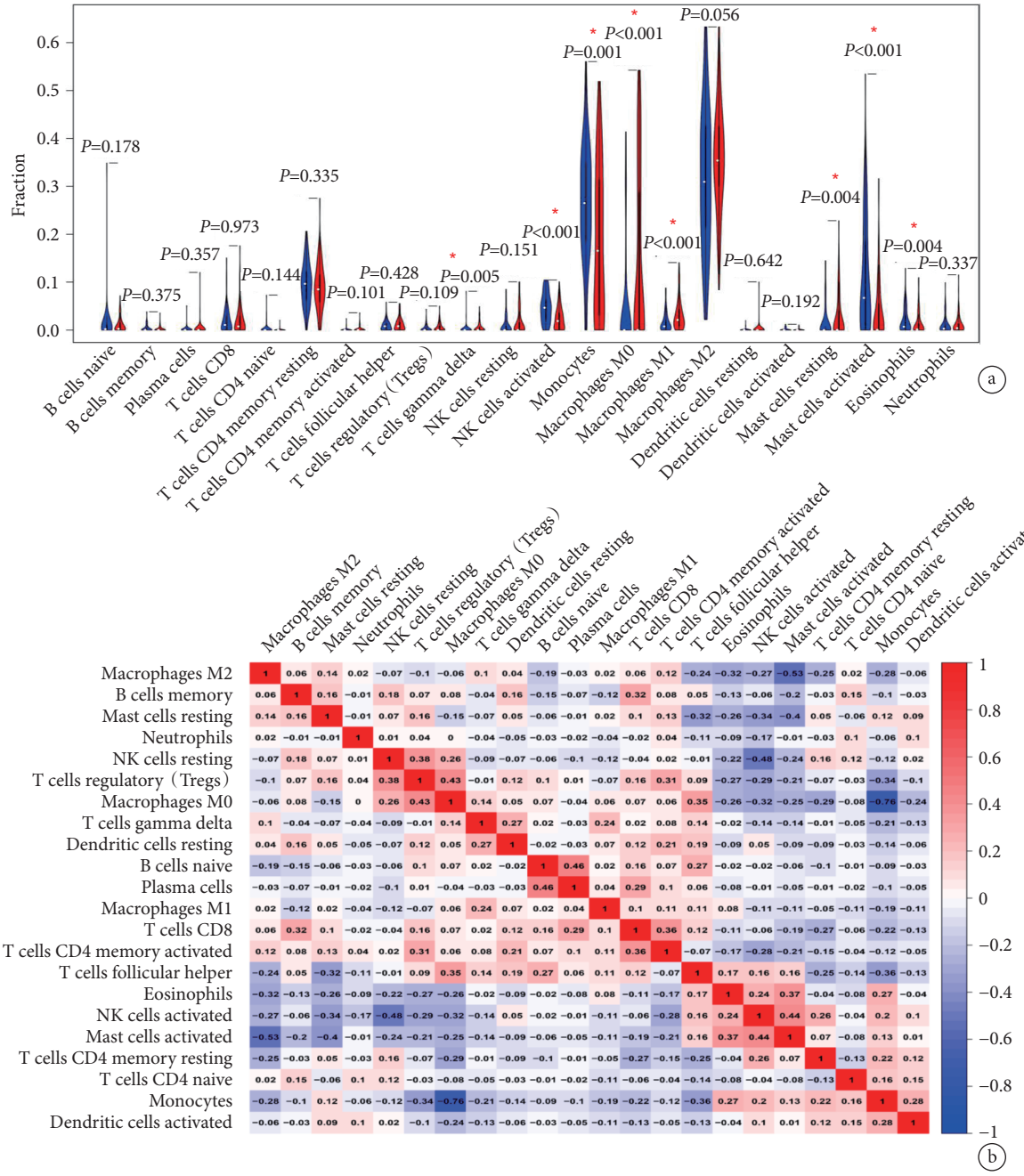

Fig.6　The proportion of 22 immune cells effected by TRIM5 expression　a. the ratio of 22 immune cells in glioma in low (blue) and high (red) TRIM5 expression groups, * $P < 0.05$; b. heat map of 22 immune cells in glioma samples

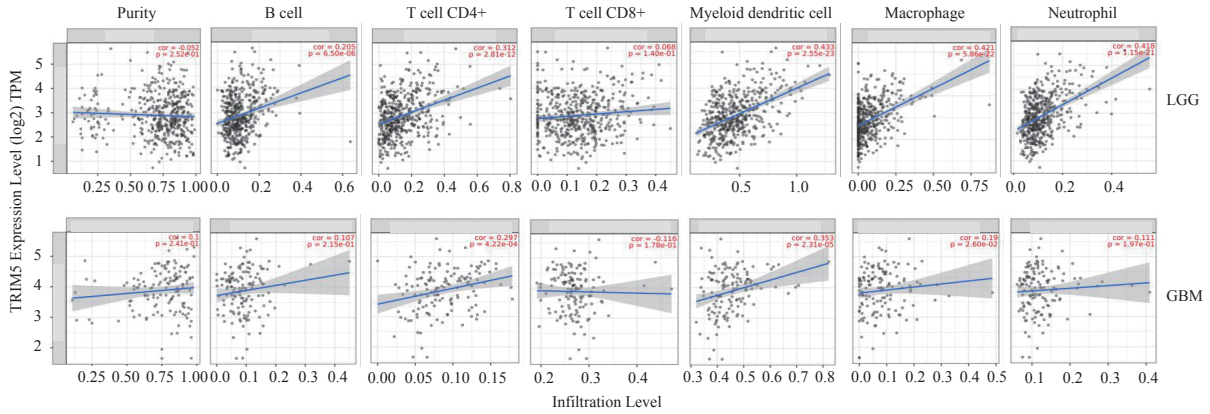

Fig.7 Correlation analyses between TRIM5 and immune infiltration

an autophagic receptor, TRIM5 protects cells from HIV-1 infection by autophagically degrading the retrovirus capsid[7]. Previous study has shown that autophagy was a regulator of homeostasis and survival and had a dual role in cancers[27]. One side, autophagy deficiency could lead to oxidative stress and genome instability which can cause tumorigenesis and progression[28-30]. On the other hand, the upregulation of autophagy can help the tumor cells growth and survival[31-33]. Activation of autophagy has been found in many malignant brain tumors, while autophagy induction in GBM is controversial[34]. In addition, numerous genes involved in autophagy, such as SH3GLB1, LAMP2, ULK1, SQSTM1/p62 and MAPK8IP1, have been found to participate in the diagnosis and prognosis of glioma[34-35]. However, the expression and prognostic role of TRIM5 in glioma are still unknown. In this study, we elucidated the potential function of TRIM5 in glioma and found that TRIM5 was upregulated in glioma tissues by Oncomine, GEPIA and TCGA databases. Meanwhile, TRIM5 was higher in GBM samples than that in LGG. Therefore, we speculate that TRIM5 may be a useful biomarker to distinguish the malignancy degree of glioma.

We further explored the prognostic value of TRIM5 in glioma. Obviously, patients with high TRIM5 expression level had shortened OS. Further, the increased expression of TRIM5 decreased the 1-year, 3-year and 5-year OS in glioma patients (LGG+GBM) and LGG patients without influencing GBM patients. In line with the previous study, diagnosis age, histological type and grade were risk factors for OS of LGG patients[36]. In our study, we also found that TRIM5 was an independent prognostic factor for glioma patients. Besides, the clinical correlation analysis also showed that TRIM5 was positively correlated with stage and histological type, which again confirmed the idea that TRIM5 could act as an indicator biomarker to distinguish degree of glioma malignancy. Nonetheless, more research is needed to determine whether TRIM5 prediction is appropriate for GBM patients. And, the relationship between TRIM5 and existing glioma prognostic biomarkers (such as IDH 1/2 and 1p/19q co-deletion) will be further explored.

And then we look for the molecular pathways that TRIM5 might be involved in. The STRING database revealed that TRIM5 may interact with IRF3, IRF7, OAS1, OAS2, OAS3, OASL, GBP1, PML, BTBD1 and BTBD2 proteins. Previous study illustrated that IRF3 and IRF7 were two transcription factors participating in virus induction and IFN production[37]. In addition, IRF3 and IRF7 deficiency can lead to the lack of innate immune response caused by IFNα and IFNβ absence after viral infection[38]. Human 2'-5'- oligoadenylate synthetase (OAS) proteins have been found to contribute to the antiviral property via inducing apoptosis of infection cells[39]. In the KEGG analysis, TRIM5 upregulation was concentrated in apoptosis pathway, cancer-related molecular pathways and immune-related signaling pathways. In view of the characteristics of TRIM5 and the above predicted results, we speculated that TRIM5 could play a role in glioma by immune-related mechanisms.

To verify the above assumption, we used the CIBERSORT and TIMER database for analysis. As expected, CIBERSORT analysis revealed that activated NK cells, activated mast cells and Monocytes (all $P < 0.05$) were notably reduced in the group with high TRIM5 level, whereas M0 and M1 Macrophages (all $P < 0.001$) were remarked increased. And, strongly negative correlation existed between M0 macrophages and monocytes ($r = -0.76$). Moreover, our finding showed that TRIM5 expression was associated with B cells, CD4+ T cells, Dendritic cells, Macrophages and Neutrophils in LGG, and CD4+ T cells, Dendritic cells and Macrophages in GBM. NK cells are innate lymphocytes that can rapidly secrete cytokines such as IFNγ or TNFα to cancer cells, thereby inhibiting angiogenesis and carcinogenesis[40-41]. In recurrent malignant glioma patients, autologous NK cells injection therapy was partially effective with no severe neurological toxicity[42]. From our results, we can infer that increased TRIM5 inhibits the infiltration and immune response of NK cells in glioma. Macrophages are recognized as myeloid-derived suppressor cells (MDSCs), which have the ability to induce strong

immunosuppressive[43]. Previous study has shown that blocking monocytes transformation into MDSCs can produce more robust anti-tumor response in patients with non-immunosuppressed GBM[44]. Consistent with above results, we revealed that the high expression of TRIM5 could reduce the proportion of Monocytes and increase the proportion of Macrophages, resulting in a poor prognosis in glioma patients, which may be related to immunosuppression. Mast cells participated in innate and specific immunity, which can suppress the stemness of glioma cells, providing a feasibility for anti-tumor immune response[45]. Our study also showed the reduction of activated mast cells proportion in high TRIM5 expression glioma. These data confirm that TRIM5 may be an auxiliary biomarker in immunotherapy of glioma. However, the molecular mechanism by which TRIM5 affects immune infiltration in glioma remains poor understood and need to be further explored.

In conclusion, we demonstrated that elevated TRIM5 was correlated with the increase of malignancy in glioma and could act as an effective prognostic biomarker for glioma patients. Moreover, this is the first report to identify the correlation between TRIM5 expression and immune cells infiltration. These data may provide a theoretical basis for the prognosis and treatment of patients with glioma, and further exploration of the deep mechanism of TRIM5 in glioma immune infiltration and clinical validation are of great significance.

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Conflict of interest

The authors declare no potential conflicts of interest.

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