PABPC1 relevant bioinformatic profiling and prognostic value in gliomas

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Aim: We aimed at investigating molecular features and potential clinical value of *PABPC1* in gliomas.

Materials & methods: We assembled totally 1000 glioma samples with mRNA expression data from Chinese Glioma Genome Atlas and The Cancer Genome Atlas. We utilized R language as the main analysis tool. Gene Ontology was performed for functional analysis. **Results:** *PABPC1* was downregulated in gliomas with higher malignance and *PABPC1* may contribute as potential predictor of proneural subtype in gliomas. Higher expression of *PABPC1* was significantly related to better prognosis and related to biological process of translation. **Conclusion:** Our finding improves the understanding of *PABPC1* as a novel biomarker with potential therapeutic connotations.

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Gliomas represent the most prevalent and fatal brain tumor in adults [1–3]. According to the updated 2016 WHO classification system of CNS, with histology and molecular parameters, gliomas could be categorized as followed: lower grade gliomas (LGG) with isocitrate dehydrogenase (IDH) mutation with or without 1p/19q-codeletion, LGG with IDH-wildtype subtype, glioblastoma multiforme (GBM) with IDH mutation or not [4]. In order to improve diagnostic accuracy and treatment efficacy for the glioma patients, it is crucial to identify novel biomarkers and therapeutic targets.

RNA-binding proteins are versatile and can interact with many molecules. The poly adenosine tail of RNA can be bound by RNA poly(A) binding proteins (PABPs) specifically. PABPs are essential for initiation of translation and stabilization of mRNA [5–7]. In humans, PABPs include at least three functional proteins: PABP1, induced PABP (iPABP) and PABP3. Among them, PABP1 protein is encoded by the *PABPC1* gene [8]. In many cancers, overexpression of *PABPC1* promotes tumor progression and metastasis, such as esophageal cancer [9], gastric carcinoma [10], follicular thyroid cancer [11], bladder cancer [12] and so on. However, little is known about the genetic and epigenetic features of *PABPC1* in gliomas.

To explore the clinical and molecular characteristics of *PABPC1* in gliomas, we utilized the gene expression data from Chinese Glioma Genome Atlas (CGGA) dataset as training set and validated in The Cancer Genome Atlas (TCGA) dataset. We detected *PABPC1* expression was downregulated in gliomas with higher malignance and high expression of *PABPC1* in proneural subtype and showed a beneficial effect in patients with gliomas. This integrative study of *PABPC1* might provide a potential therapeutic target for glioma patients in future.

Materials & methods

Samples collected in this study

In CGGA dataset (<http://www.cgga.org.cn>), we collected 301 whole grade glioma samples with mRNA microarray data as training set. In TCGA dataset, we downloaded mRNA sequencing data of 699 glioma samples online

(<https://cancergenome.nih.gov/>) for validation. Thus, we obtained totally 1000 samples with mRNA expression data. Meanwhile, clinical follow-up and molecular information of these patients were collated.

IDH1/2 mutations

It was common to employ pyrosequencing technique to detect IDH mutation in CGGA [13], and IDH mutant status of TCGA patients downloaded online were mainly tested by pyrosequencing technique or whole exon sequencing technique.

TCGA subtype annotation

As for the TCGA subtype annotation, patients were divided into four subtypes (proneural–neural–classical–mesenchymal) using the published signatures and single-sample gene set enrichment analysis algorithm [14].

Immunohistochemical

Formalin-fixed, paraffin-embedded glioma specimens were cut (5 μ m section), deparaffinized, rehydrated before antigen repair in citrate buffer. After blocking endogenous peroxidase activity with ethanol containing 3% hydrogen peroxidase, we incubated sections in rabbit anti-PABP1 antibody (number 4992, dilution:1:50, Cell Signaling Technology) over night at 4°C. Diaminobenzidine was used as chromogens and slides were counterstained with hematoxylin before mounting. Each stained slide was scored by two independent neuropathologists. All experiments were performed with negative and positive control to ensure the quality of staining. Staining was scored using a four-point scale from 0–3: 0 = no staining, 1 < 10% neoplastic cells positive staining, 2 = 10–30% neoplastic cells positive staining, 3 > 30% neoplastic cells positive staining. We selected specimens from 6 glioma patients (3 of LGG, 3 of GBM) for immunohistochemical analysis. Five fields at 400 $\times$ magnification were analyzed per specimen. The *PABPC1* expression difference between two groups was tested by χ^2 test.

Gene ontology analysis

We filtered *PABPC1* significantly correlated genes (Pearson $|R| > 0.5$; $p < 0.05$) by the method of Pearson correlation analysis in TCGA dataset. Then *PABPC1* positively associated genes were chosen to perform gene ontology (GO) analysis in DAVID (<https://david.ncifcrf.gov/>) [15].

Statistical analysis

R language (version 3.5.1, <http://www.r-project.org>) was the main data analysis and mapping tool. Student's t-test was performed for *PABPC1* expression difference. For the comparison between categorical variables, we applied a two-tailed χ^2 test. The time interval from diagnosis to death or the last follow-up was defined as overall survival (OS) time. Based on median *PABPC1* expression, we divided patients into two groups, high- and low-*PABPC1* groups. Kaplan–Meier estimate was used in survival analysis with two-sided log-rank test. There was significant difference when $p\text{-value} \leq 0.05$.

Results

Patients

We selected 301 glioma patients of whole grade from CGGA as discovery cohort and 699 glioma patients of whole grades from TCGA for validation in our study (Table 1). Median age of patients in CGGA was 42 (from 13 to 70) and 47 (from 14 to 89) in TCGA. Male accounted for 60% in CGGA and 52% in TCGA. CGGA contained 122 grade II, 51 WHO grade III and 128 grade IV gliomas (GBMs). TCGA dataset included 223 grade II, 245 grade III and 168 grade IV gliomas. Molecular subtype of two datasets were shown in the table as well. We also collected data on genetic alteration. In CGGA, 135 (45%) tumors were detected with IDH mutation and 43 (14%) tumors harbored 1p/19q codeletion. In TCGA, 441 (63%) tumors exhibited IDH mutation and 172 (25%) showed 1p19q codeletion. Meanwhile, MGMT promoter methylation status of tumors was also available in two datasets. According to the updated 2016 WHO classification system of CNS [4], glioma patients in two databases were finally classified based on histologic and molecular data (Supplementary Table 1).

PABPC1 expression was downregulated in gliomas with higher malignance

In order to investigate the distribution characteristic of *PABPC1* expression, we compared the expression of *PABPC1* in gliomas of different grades, histopathology and IDH mutation status. In CGGA dataset, *PABPC1* showed the

Table 1. Baseline patient characteristics.

		CGGA (n = 301, %)	TCGA (n = 699, %)
Age	Median (range)	42(13–70)	47(14–89)
Gender	Male	180 (60)	366 (52)
	Female	121 (40)	268 (38)
	NA	0	65 (10)
KPS score	Preoperative KPS ≥ 80	173 (57)	324 (46)
	Preoperative KPS < 80	92 (31)	70 (10)
	NA	36 (12)	305 (44)
Pathological type	A	80 (27)	170 (24)
	O	32 (11)	180 (26)
	OA	61 (20)	118 (17)
	GBM	128 (43)	166 (24)
	NA	0	65 (9)
Molecular subtype	Neural	81 (27)	115 (16)
	Proneural	86 (29)	250 (36)
	Mesenchymal	111 (37)	103 (15)
	Classical	23 (8)	92 (13)
	NA	0	139 (20)
Grade	2	122 (41)	223 (32)
	3	51 (17)	245 (35)
	4	128 (43)	166 (24)
	NA	0	65 (9)
IDH mutation	Mutant	135 (45)	441 (63)
	Wild	162 (54)	246 (35)
	NA	4 (1)	12 (2)
1p/19q status	Codeletion	43 (14)	172 (25)
	Noncodeletion	258 (86)	520 (74)
	NA	0 (0)	7 (1)
MGMT promoter methylation	Methylated	91 (30)	492 (70)
	Not methylated	90 (30)	168 (24)
	NA	120 (40)	37 (5)

CGGA: Chinese Glioma Genome Atlas; GBM: Glioblastoma multiforme; IDH: Isocitrate dehydrogenase; TCGA: The Cancer Genome Atlas.

lowest expression in glioblastoma (GBM; [Figure 1A](#)). The result was validated in TCGA ([Figure 1C](#)). Next, we divided patients into IDH-mutant groups and IDH-wildtype and found that *PABPC1* was poorly expressed in IDH-wildtype groups compared with IDH-mutant groups across different grades ([Figure 1B & D](#)). We also divided patients into groups according to 2016 WHO classification and found that *PABPC1* was poorly expressed in malignant molecular phenotypes (IDH-wildtype or 1p/19q-intact, [Supplementary Figure 1A & B](#)). To further clarify the relationship between *PABPC1* and glioma grade at the protein expression level, we selected specimens from six glioma patients (3 of LGG, 3 of GBM, 5 fields at 400 × magnification were analyzed per specimen) for immunohistochemical analysis. Two representative stained sections were showed in [Supplementary Figure 1C & D](#). Consistent with the results above, the expression of *PABPC1* was lower in GBM ($p = 0.00281 \chi^2$ test). Thus, both in RNA and protein expression level, *PABPC1* expression was downregulated in gliomas with higher malignance.

PABPC1 was a potential marker for proneural molecular subtype

To depict the correlation between *PABPC1* and molecular subtype, we further explored *PABPC1* expression in different TCGA molecular subtype. In [Figure 2A & B](#), our result showed that *PABPC1* was highly expressed in proneural subtype in both datasets. We were inspired that *PABPC1* might be a potential biomarker for proneural subtype. Hence, we drew the receiver operating characteristic curve for *PABPC1* expression and proneural subtype. In CGGA, the area under the receiver operating characteristic curve was 0.786, and at the optimal cutoff point (0.268), the sensitivity and specificity were 65.1 and 82.8%, respectively ([Figure 2C](#)). In TCGA, the area under

Figure 1. The expression level of PABPC1 in different grades and IDH status. (A & C) The expression difference of PABPC1 in grade II, grade III and GBM of CGGA and TCGA datasets. **(B & D)** The expression difference of PABPC1 in IDH-mutant and IDH-wildtype across all grades of CGGA and TCGA datasets.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

CGGA: Chinese Glioma Genome Atlas; GBM: Glioblastoma multiforme; IDH: Isocitrate dehydrogenase; ns: Non-significant; OS: Overall survival; TCGA: The Cancer Genome Atlas.

the receiver operating characteristic curve was 0.875, and at the optimal cutoff point (13.281), the sensitivity and specificity were 84.4 and 77.1%, respectively (Figure 2D). It revealed that PABPC1 was a potential marker for proneural subtype.

PABPC1 showed significant prognostic power

To explore the prognostic value of PABPC1, we performed the Kaplan–Meier survival analysis. The patients were divided into two groups, high and low PABPC1 groups, based on the median expression level. It showed that glioma patients of high PABPC1 expression group had a significantly longer OS than PABPC1 low expression group in training dataset (Figure 3A; $p = 0.0022$). Next, we explored the prognostic value of PABPC1 in different

Figure 2. *PABPC1* expression in molecular subtypes and predictive value for proneural subtype. (A & B) *PABPC1* was significantly increased in proneural subtype. (C & D) ROC curves exhibited highly sensitivity in predicting proneural subtype. **** $p < 0.0001$.

ROC: Receiver operating characteristic; TCGA: The Cancer Genome Atlas.

grade gliomas and found that the OS difference was significant in WHO grade III ($p = 0.029$; Figure 3C) and GBM ($p = 0.045$; Figure 3D), except for grade II ($p = 0.43$; Figure 3B).

The 2016 WHO guideline classified gliomas into five subtypes based on histopathology and IDH status and 1p19q codeletion [4]. Since five glioma subtypes had different characteristics and prognosis [16], we further evaluated the prognostic value of *PABPC1* in five subgroups of patients. For LGG, survival time of high *PABPC1* group was obviously longer than that of low *PABPC1* group in LGG-IDHmut-codel ($p = 0.041$; Figure 3E), LGG-IDHmut-

Figure 3. The *PABPC1* survival curves of all gliomas in Chinese Glioma Genome Atlas cohorts. Kaplan–Meier survival analysis showed that high expression of *PABPC1* conferred a significantly better prognosis in all grade gliomas (A), grade III (C) and GBM (D) patients, except for grade II (B). Kaplan–Meier survival curves for LGG patients with IDH mutant and 1p/19q codeletion (E), IDH-mutant but not 1p/19q codeletion (F), IDH-wildtype (G). Kaplan–Meier survival curves also show the prognostic value of GBM patients with IDH-wildtype (H) and IDH-mutant (I) in the CGGA cohort. p-value is the result of a log-rank test between the two groups shown in each panel. CGGA: Chinese Glioma Genome Atlas; Codel: Codeletion; GBM: Glioblastoma multiforme; IDH: Isocitrate dehydrogenase; LGG: Lower-grade glioma; OS: Overall survival.

Figure 4. *PABPC1* was closely related to translation in gliomas. GO analysis showed *PABPC1* was significantly associated with biological function of translation, cytoplasmic translation, formation of translation preinitiation complex in two datasets. GO: Gene Ontology; IDH: Isocitrate dehydrogenase; MGMT: O6-methylguanine-DNA methyltransferase promoter; TCGA: The Cancer Genome Atlas.

noncode (p = 0.028; Figure 3F) and LGG-IDH-wild (p = 0.041; Figure 3G). There were similar differences in prognosis between two groups for GBM-IDHwt (p = 0.046; Figure 3H) and GBM-IDHmut (p = 0.046; Figure 3I).

We also performed the survival analysis in TCGA dataset and obtained similar results though no statistical significance was detected in LGG-IDH-wild and GBM-IDHmut (Supplementary Figure 2). Therefore, *PABPC1* was a positively prognosis predictor in gliomas, and higher expression of the *PABPC1* indicated excellent survival.

Functional annotation of *PABPC1*

To better understand the underlying biological function of *PABPC1*, we filtered genes that were significantly correlated with *PABPC1* in TCGA dataset (correlation $|R| > 0.5$; p < 0.05) utilizing Pearson correlation analysis. As a result, 187 positively correlated genes and 116 negatively correlated genes met the criteria, respectively (Supplementary Table 2). We chose the positive genes (187 genes) for GO Analysis and detected enrichment in biological function of translation (False Discovery Rate [FDR] = 1.48E-23, Benjamini = 6.45E-24), cytoplasmic translation (FDR = 9.91E-05, Benjamini = 2.16E-05), formation of translation preinitiation complex (FDR = 0.001539, Benjamini = 2.24E-04) (Figure 4A & B & Supplementary Figure 3), which was consistent with previous research [17–20].

Discussion

Gliomas are associated with high disability and mortality rate, which seriously endanger human health and quality of life. Standards surgical resection with radiochemotherapy fail to improve survival of glioma patients substantially [2,21]. Hence, new diagnostic and treatment strategies are urgently needed. New biomarkers are currently being developed for identifying cancer risk, determining prognosis, detecting recurrence and predicting responses to specific drugs [22,23]. It is in urgent need to identify more biomarkers and establish new molecular classification systems for further precision medicine.

In glioma patients, many prognosis biomarkers have been reported, such as IDH mutation, MGMTp methylation, 1p/19q codeletion, EGFR and so on [24]. And PD-L1 [25], TIM-3 [26], DCTD [27], pHH3 [28] and FGFR3 [29] have been demonstrated as biomarker in our previous study.

We have noticed that control of mRNA stability and translation plays a crucial role in various biology processes, such as cell growth and neuronal plasticity [30,31]. mRNA-binding proteins (mRBPs) play a key role in maintaining mRNA stability and controlling transport and translation [32]. Hundreds of such mRBPs have been discovered and

studied over the years [33]. Previous studies both *in vivo* and *in vitro* have confirmed that *PABPC1* control cell proliferation [34–37], promotes cell migration and spreading [38], which is closely related to the malignant phenotype of cancer.

At present, there are few reports on the characteristics and significance of *PABPC1* in gliomas. We enrolled totally 1000 glioma patients with transcriptome data from CGGA and TCGA dataset in this study. We found that *PABPC1* was upregulated in beneficial pathological type such as low grade, IDH1/2 mutation and 1p/19q co-deletion. Moreover, *PABPC1* was preferentially expressed in proneural subtype. These results indicated that *PABPC1* expression was related to beneficial biological process. These beneficial biological processes might contribute to tumor stability and therapy sensitivity.

GO analysis of positively related genes gave us a real insight into the biological functions of *PABPC1*. We found that *PABPC1* was significantly related to translation. Translation refers to the cellular metabolic process of protein formation, using mRNA to form specific polypeptide chain. Changes in translation can seriously affect gene expression and dysregulation of translation have been documented in several disorders, including cancer [39,40]. Meanwhile, the relationship between translation and many well-established cancer genes (e.g., PIK3CA, MYC, PTEN) has been deeply revealed [39,41]. For example, MYC hyperactivation increased translation of m7GpppN cap (eIF4F)-dependent mRNAs, resulting in chromosomal instability and cancer development [42]. Therefore, the role of translation function in cancer cannot be underestimated and the mechanism of *PABPC1*-regulating translation needs deeper investigation in gliomas.

For prognosis analysis, survival curve showed that high-*PABPC1* expression predicted significantly better OS in glioma either in whole grade gliomas, grade II, grade III or GBM. These results indicated that *PABPC1* was a beneficial molecular prognosis marker with potential important therapeutic implications in gliomas. Due to the important role of *PABPC1* in translation and gene stabilization, the mechanism of the downregulation of this gene in glioma patients with poor prognosis needs to be clarified.

Nowadays, traditional cytotoxic agents no longer meet the requirements of modern precision medicine in glioma and an amount of selective, mechanism-based agents come forth. Our understanding of the gliomagenesis has improved, resulting in new treatment options like targeted therapy. This study will provide new insights for targeted therapy of gliomas.

Conclusion

We first summarized the molecular features and potential clinical value of *PABPC1* in gliomas. *PABPC1* is a favorable biomarker for gliomas and predicts better survival for patients of glioma. Our finding improves the understanding of *PABPC1* as a novel therapeutic target for gliomas.

Summary points

- Gliomas represent the most prevalent and fatal brain tumor in adults. In order to improve diagnostic accuracy and treatment efficacy for the glioma patients, it is crucial to identify novel biomarkers and therapeutic targets.
- Little is known about the genetic and epigenetic features of *PABPC1* in gliomas.
- To explore the clinical and molecular characteristics of *PABPC1* in gliomas, we utilized the gene expression data from Chinese Glioma Genome Atlas dataset as training set and validated in The Cancer Genome Atlas dataset.
- We detected *PABPC1* expression was downregulated in gliomas with higher malignance.
- *PABPC1* was a potential marker for proneural molecular subtype.
- *PABPC1* was a positively prognosis predictor in gliomas, and higher expression of the *PABPC1* indicated excellent survival.
- Functional annotation revealed that *PABPC1* was related to biological process of translation.
- Our finding improves the understanding of *PABPC1* as a novel biomarker with potential therapeutic connotations.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2019-0268

Financial & competing interests disclosure

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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