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ORIGINAL ARTICLE

Identification of N^6-methyladenosine-related lncRNAs for patients with primary glioblastoma

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Abstract

To investigate the m^{6}a-related long non-coding RNAs (lncRNAs) that may be exploited as potential biomarkers in primary glioblastoma (pGBM), a cohort of 268 glioma samples from GSE16011 dataset was included for discovery. The Chinese Glioma Genome Atlas (CGGA) microarray and RNA sequencing databases were used for validation. Bioinformatic analyses were performed using the R software. The m^{6}a-lncRNA co-expression networks were constructed, and four m^{6}a-related lncRNAs (MIR9-3HG, LINC00900, MIR155HG, and LINC00515) were identified in pGBM patients on the univariate Cox regression analysis. Patients in the low-risk group had longer overall survival (OS) and progression-free survival (PFS) than those in the high-risk group ($P = 0.0025$, $P = 0.0070$). Moreover, the high-risk group displayed older age, isocitrate dehydrogenase (IDH) wild-type, classical and mesenchymal TCGA subtype, and G3 CGGA subtype. Distinct m^{6}a status was identified according to histologic grade and two groups (low-risk and high-risk). Functional annotation showed that differentially expressed genes between the two groups were enriched in immune response, apoptosis, cell adhesion, negative regulation of transcription, negative regulation of RNA metabolic process, and regulation of RNA metabolic process. We profiled the m^{6}a status in glioma and identified four m^{6}a-related prognostic lncRNAs for pGBMs.

Keywords N^6-Methyladenosine · lncRNAs · Glioblastoma · RNA microarray · RNA sequencing

Introduction

Primary glioblastoma (pGBM) is a common malignant brain tumor, and the median overall survival (OS) is approximately 14.4 months [1]. It reported that N^6-methyladenosine (m^{6}a) is a chemical modification present in multiple RNA species [2]. Many studies have revealed its essential roles in physiological processes. METTL14 is highly expressed in normal hematopoietic stem cells, and it can promote self-renewal of leukemia stem cells and plays an oncogenic role in the development and maintenance of acute myeloid leukemia (AML) [3]. Moreover, WTAP has also been reported to be upregulated in AML [4]. Inhibition of FTO could suppress the growth and self-renewal of glioblastoma stem cell (GSC) and prolongs the lifespan of glioblastoma stem cell-grafted mice [5]. Knockdown FTO could effectively inhibit cell proliferation and invasion in lung squamous cell carcinoma [6]. Overexpression of ALKBH5 could promote the proliferation and tumorigenesis of GSCs [7]. It was reported that YTHDC1 could recognize m^{6}a on XIST and promote X chromosome silencing [8]. YTHDF1 was correlated with the survival and pathology stage in hepatocellular carcinoma [9]. Dysregulation of long non-coding RNAs (lncRNAs) may contribute to glioma pathogenesis [10–13]. HOXA11-AS and MALAT1 were involved in cell cycle progression and were closely associated with poor prognosis [14, 15]. It indicated that lncRNA GAS5 expressions are negatively correlated with YTHDF3 in tumors, and YTHDF3 could facilitate m^{6}a-modified lncRNA GAS5 degradation [16]. m^{6}a can regulate the expression of lncRNA RP11, then trigger the

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dissemination of tumor cells [17]. m^6a eraser ALKBH5 can demethylate KCNK15-AS1 and regulate KCNK15-AS1-mediated cell motility [18]. Therefore, aberrant expressions of m^6a-related lncRNAs may have prognostic value for pGBM patients.

We used the GSE16011 (training set), Chinese Glioma Genome Atlas (CGGA) microarray, and CGGA RNA sequencing (validated sets) databases to explore the prognostic value of m^6a-related lncRNAs.

Methods

Patients and datasets

The GSE16011 was downloaded from the Gene Expression Omnibus (GEO). All CGGA data used in this study were available from CGGA website (http://www.cgga.org.cn). The grade 1 samples were excluded to avoid data bias. A total of 757 patients (GSE16011: LGG 109, pGBM 159; CGGA microarray: LGG 152, pGBM 109; CGGA sequencing: LGG 141, pGBM 87) were included in our study. In addition, patients with clinical information were used in the survival analysis. All patients were diagnosed histologically by two neuropathologists according to 2007 WHO classification guidelines. Informed consent was undertaken from the patients, and our study was approved by the Ethics Committee of Beijing Tiantan Hospital. The clinical information was downloaded from each website.

lncRNA profile mining

We identified the lncRNA profiles by using an established lncRNA mining method [19, 20]. Some lncRNA-specific probes were fortuitously represented on the gene microarrays, so we could achieve the lncRNA profiling by analyzing these existing data. For example, lncRNA expression signatures may be determined by mining the Affymetrix gene expression microarray data [21, 22]. The platform of GSE16011 was the Affymetrix GeneChip Human Genome U133 Plus 2.0 Array. Only lncRNAs were retained based on their Refseq IDs or Ensembl IDs. A total of 1248 lncRNAs (1901 probes) were screened from the GSE16011 dataset. The functions of m^6a on RNA are determined by the interaction between its methyltransferases, demethylases, and m^6a readers [2]. Finally, 493 m^6a-related lncRNAs (694 probes) were identified by constructing m^6a-lncRNA co-expression networks (Cor value 0.4; $P \leq 0.001$).

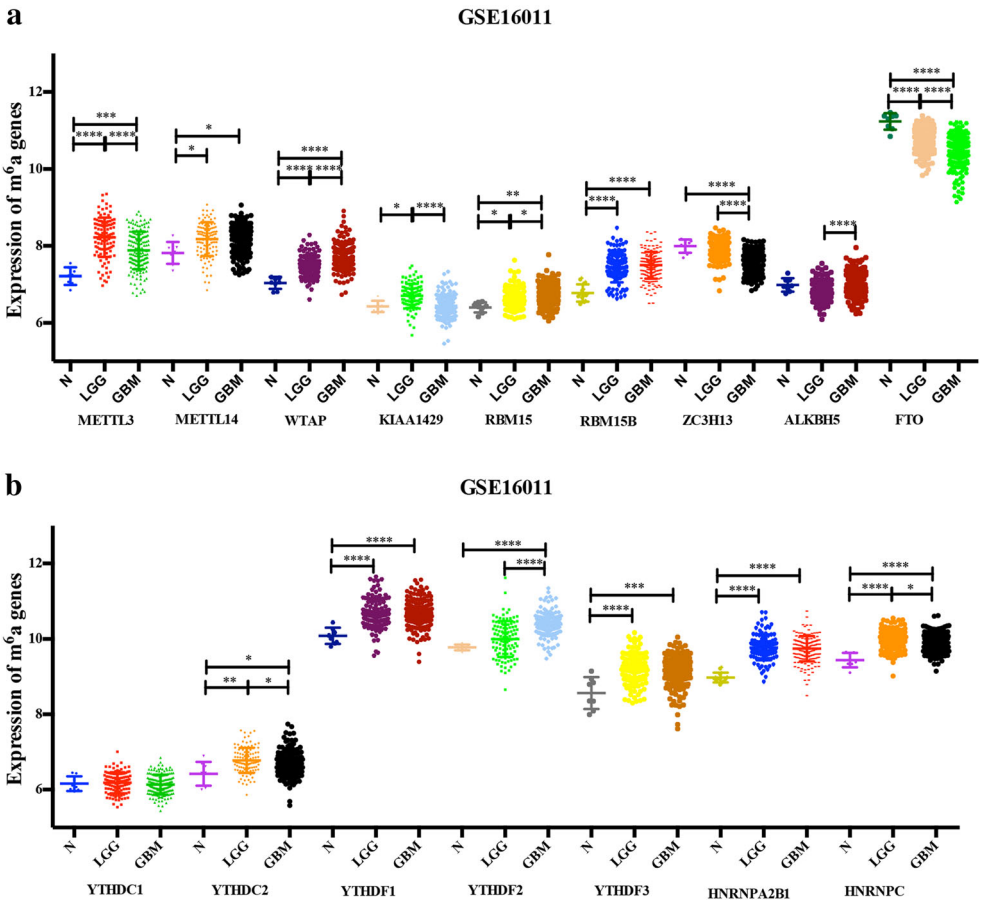

Fig. 1 The m^6a-related genes were dysregulated in gliomas from GSE16011 dataset. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$. **a**, **b** The expression of 16 m^6a-related genes

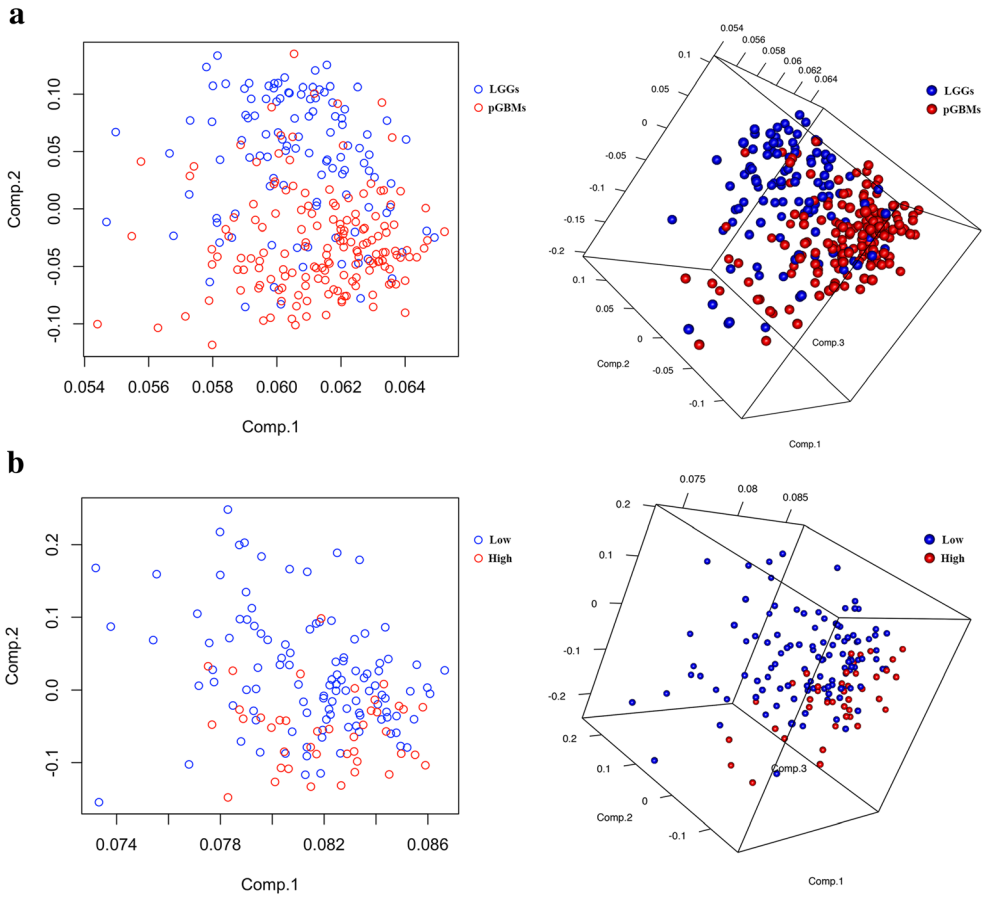

Fig. 2 Distinct m^{6}a status was identified according to histologic grade, low-risk and high-risk groups. **a** LGG and pGBMs displayed different m^{6}a status. **b** Low-risk and high-risk groups displayed different m^{6}a status

Statistical analysis

The risk score was determined as previously reported [23–25]. Briefly, the risk score was assigned according to a linear combination of the expression level of lncRNAs weighted by the regression coefficient [20, 26, 27].

The prognostic m^{6}a-related lncRNAs were identified using univariate Cox regression analysis and ranked ascendingly by *P* values. Low-risk and high-risk groups were divided using the median risk score. The multivariate Cox regression analysis was performed by the SPSS software (version 22; SPSS Inc., Chicago, IL, USA), and the principal component analysis (PCA) was performed by the R software (version 3.2.3). GraphPad Prism 6 (GraphPad Software Inc., La Jolla, CA, USA) was used to display the Kaplan-Meier curve. DAVID database (https://david.ncifcrf.gov/) was used for functional annotation between two groups. A two-sided *P* value of < 0.05 was considered statistically significant. The *P* value has been corrected by false discovery rate (FDR).

Table 1 Top four m^{6}a-related lncRNAs identified from Cox regression analysis

Probes	Symbol	HR	Low95	High95	*P* value	*β* value
238603_at	MIR9-3HG	0.81	0.72	0.92	8.80E−04	−0.21
239675_at	LINC00900	1.48	1.17	1.87	1.22E−03	0.39
235936_at	MIR9-3HG	0.59	0.42	0.84	3.05E−03	−0.52
229437_at	MIR155HG	1.17	1.05	1.30	4.88E−03	0.16
1556414_at	LINC00515	0.62	0.43	0.89	1.05E−02	−0.48

Results

The m^{6}a-related genes were dysregulated in gliomas

A total of 16 m^{6}a-related genes were identified from the three datasets, and we analyzed these data to explore the expression patterns of m^{6}a genes in gliomas. As shown in Fig. 1, fourteen m^{6}a-related genes (METTL3, METTL14, WTAP, KIAA1429, RBM15, RBM15B, ZC3H13, FTO, YTHDC2, YTHDF1, YTHDF2, YTHDF3, HNRNPA2B1, and HNRNPC) were differentially expressed in gliomas comparing with normal brain tissues. Of these genes, METTL3, METTL14, WTAP, RBM15, RBM15B, YTHDC2, YTHDF1, YTHDF2, YTHDF3, HNRNPA2B1, and HNRNPC were upregulated, while ZC3H13 and FTO were downregulated in gliomas (Fig. 1). WTAP, RBM15, ALKBH5, and YTHDF2 were significantly upregulated, while METTL3, KIAA1429, ZC3H13, FTO, YTHDC2, and

HNRNPC were significantly downregulated in GBMs comparing with LGGs. We further validated these findings in additional datasets (Fig. s-1).

Identification of m^{6}a-related lncRNAs in patients with pGBM

A total of 1248 (1901 probes) lncRNAs were identified from GSE16011 by using lncRNA expression profile mining [19, 20, 28]. We identified m^{6}a-related lncRNAs by constructing m^{6}a-lncRNA co-expression networks, and 494 lncRNAs (694 probes) were identified (Cor value 0.4, $P \leq 0.001$). Based on these m^{6}a-related lncRNA expression profiles, we conducted a principal component analysis (PCA) to investigate the difference between LGGs and pGBMs. It showed that LGGs and pGBMs were generally distributed in different directions (Fig. 2a).

We collected 341 pGBM (GSE16011 150, CGGA microarray 108, CGGA RNA sequencing 83) patients from three datasets. The top five prognostic probes ($P \leq 0.01$) are listed in Table 1. The m^{6}a-related lncRNAs were MIR9-3HG, LINC00900, MIR155HG, and LINC00515. A five m^{6}a-related-lncRNA signature was developed using a risk score method [23–25, 29]. Based on the median risk score, we divided the pGBMs into two groups (low-risk and high-risk groups). Patients in the high-risk group showed shorter overall survival (OS) than the low-risk group (median OS 7.80 vs. 11.04 months; $P = 0.0025$; Fig. 3a). These findings were further validated in two additional datasets (CGGA microarray, CGGA RNA sequencing) using the same β value, which showed similar results, respectively. Moreover, patients in the low-risk group showed longer progression-free survival (PFS) than the high-risk group (median PFS 406 vs. 271 days; $P = 0.0070$; Fig. 3b). Furthermore, two groups divided based on the median risk score displayed different m^{6}a status (Fig. 2b).

Associations between the m^{6}a-related lncRNAs and clinicopathologic features

We assessed the expression of the m^{6}a-related lncRNAs in different grades. The results showed that LINC00900 and MIR155HG were increased with tumor grades, while MIR9-3HG and LINC00515 were decreased in three datasets (Fig. 4a). The expressions of LINC00900 and MIR155HG in the high-risk group were higher than those in the low-risk group, while MIR9-3HG and LINC00515 were lower in three datasets (Fig. 4b).

The clinicopathologic features were collected from the three databases. The patients in the high-risk group showed the features of older age, isocitrate dehydrogenase (IDH) wild-type, classical and mesenchymal TCGA subtype, and G3 CGGA subtype (Fig. 5a). These findings were further validated in two additional databases. The risk score was an independent factor based on the univariate and multivariate Cox regression analyses ($P = 0.017$, HR = 1.338) (Table s-1).

Functional annotation of the m^{6}a-related lncRNAs

Functional annotation of the m^{6}a-related lncRNAs was explored between two groups. The co-expressed genes were screened with the absolute value of Pearson correlation

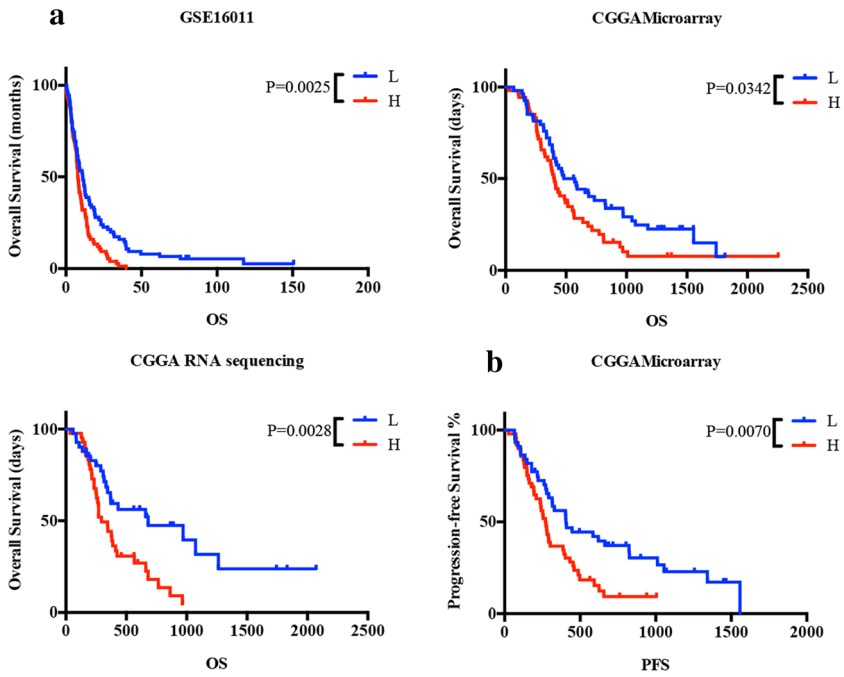

Fig. 3 Kaplan-Meier curves of OS and PFS among pGBM patients from different groups in three datasets. **a** The OS among pGBMs in different groups stratified by the signature in three datasets. **b** The PFS among pGBMs in different groups stratified by the signature in CGGA microarray dataset

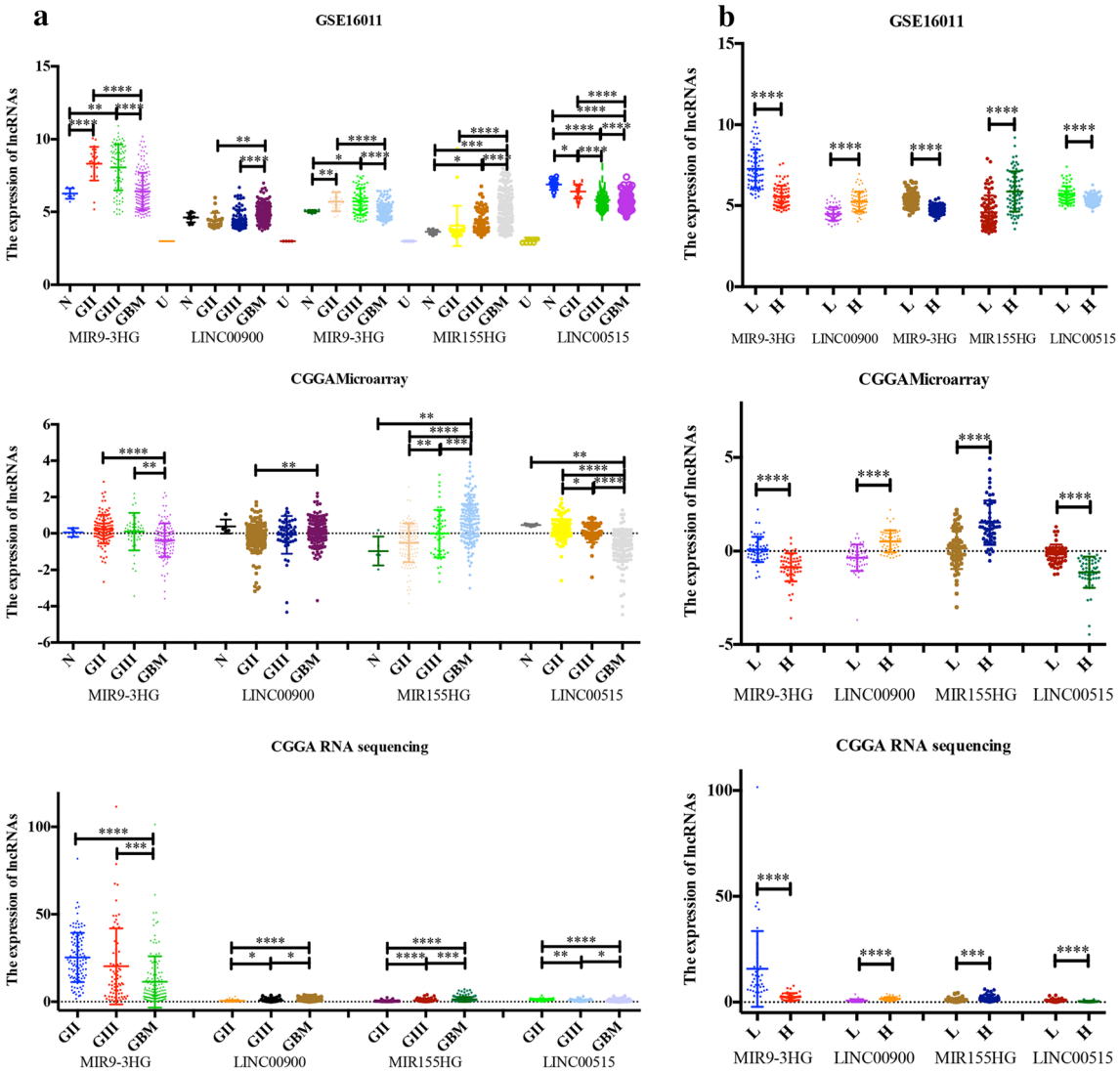

Fig. 4 Expression of four m^{6}a-related lncRNAs in different grades and groups. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$. **a** The expression of four m^{6}a-related lncRNAs in different grades. **b** The expression of four m^{6}a-related lncRNAs in different groups

coefficient 0.5. Finally, we identified 1495 (895 positive, 600 negative) genes with co-expression networks in GSE16011. The biological process (BP) analysis was conducted using DAVID (The Database for Annotation, Visualization and Integrated Discovery). The results showed that differentially expressed genes between the two groups were enriched in immune response, apoptosis, cell adhesion, negative regulation of transcription, negative regulation of RNA metabolic process, and regulation of RNA metabolic process (Fig. 5b).

Discussion

A total of 355 pGBM patients were collected to explore the prognosis of m^{6}a-related lncRNAs in three datasets (GSE16011, CGGA microarray, and CGGA RNA sequencing). We identified 494 lncRNAs (694 probes) according to the lncRNA-m^{6}a co-expression networks. On the univariate Cox regression analysis, four m^{6}a-related prognostic lncRNAs were screened. Using a risk score method, we created a risk score that could divide pGBMs into low- and high-risk groups based on the median value. The OS and PFS in the low-risk group were longer than those in high-risk group (Fig. 3). The multivariate Cox regression analysis showed that the risk score was an independent factor.

Mounting evidence suggests that m^{6}a has critical roles in cancer pathogenesis. The effect of m^{6}a on the mechanisms and functions of lncRNA methylation is unclear. Recently, it was reported that ALKBH5 could demethylate KCNK15-AS1 and regulate KCNK15-AS1-mediated cell migration and invasion [18]. The lncRNA XIST is highly methylated with at least 78 m^{6}a residues. Knockdown of RBM15, RBM15B, or METTL3 impairs XIST-mediated gene silencing [8]. Moreover, lncRNA FOXM1-AS could facilitate the interaction of ALKBH5 with FOXM1 nascent transcripts and

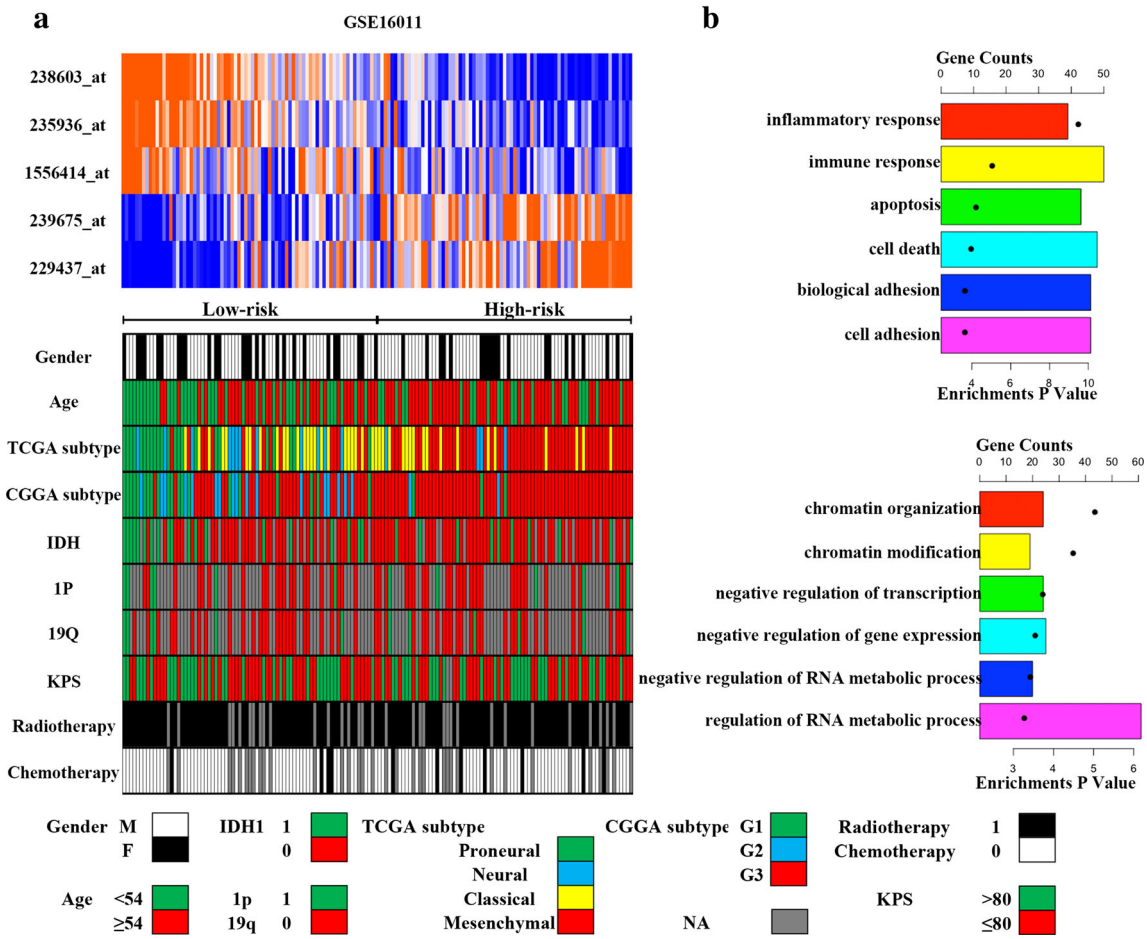

Fig. 5 Distribution of lncRNA expression, clinicopathologic features, and functional annotation in GSE16011 dataset. **a** Heatmap of four m^{6}a-related lncRNAs expression and clinicopathologic features in low-risk and high-risk groups. Rows represent corresponding genes, while columns indicate corresponding patients. **b** BP analysis of the differentially expressed genes in low-risk and high-risk groups

contribute to GSC maintenance [7]. The m^{6}a may influence lncRNA splicing that might alter cancer progression [30].

Four m^{6}a-related prognostic lncRNAs were identified in our study. MIR9-3HG and LINC00515 were protective genes, while LINC00900 and MIR155HG were risky genes. It was reported that MIR9-3HG could maintain neural stem cells in undifferentiated state by regulating NR2E1 [31] that plays an oncogenic role in prostate carcinogenesis [32]. MIR155HG is involved in colorectal cancer progression [33] and significantly correlated with the overall analysis of patients with kidney renal clear cell carcinoma [34]. Moreover, MIR155HG is upregulated in mesenchymal GBMs and blocking MIR155HG/miR-155 axis could inhibit mesenchymal transition in glioma [35, 36]. LINC00515 could enhance the autophagy and chemoresistance of melphalan-resistant myeloma by inhibiting miR-140-5p [37]. It showed that the expression of LINC00515 was decreased in cisplatin-resistant ovarian cancer cells [38].

Our study focuses on the m^{6}a-related lncRNAs, and there are some limitations in our study. Our findings were explored based on bioinformatics analysis and needed to be further validated with additional datasets. The four lncRNAs may provide clues for discovering the mechanisms and functions of m^{6}a for pGBM patients. Moreover, experimental research should be carried out on these lncRNAs.

In conclusion, the m^{6}a-lncRNA co-expression networks were constructed and we identified four m^{6}a-related prognostic lncRNAs for pGBMs. The expression of m^{6}a status was significantly different between LGGs and pGBMs. Moreover, pGBM patients divided based on the median risk score also displayed a feature of different m^{6}a status.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by the Beijing Tiantan Hospital institutional review board (IRB).

Informed consent Informed consent was obtained from each patient involved in our research.

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