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Cell division cycle associated 7 like predicts unfavorable prognosis and promotes invasion in glioma

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ABSTRACT

Background: Cell division cycle associated 7 like (CDCA7L) belongs to the JPO protein family, which is recently identified as a target gene of c-Myc and is frequently dysregulated in multiple cancers. This study aimed to explore the clinicpathological value and biological role of CDCA7L in glioma.

Methods: CDCA7L expression in glioma patients was determined using the Oncomine database, and the prognostic role of CDCA7L expression was assessed in a retrospective cohort study. Moreover, the relationship of CDCA7L expression with the clinicopathological characteristics in glioma patients, including age, gender, tumor size, cystic change, Karnofsky performance scale (KPS) score, tumor location, extent of resection, WHO grade, adjuvant therapy and tumor recurrence, was analyzed in this study. In addition, the CDCA7L small interfering (si) RNA was constructed and transfected into the glioma U251 cells, so as to examine the role of CDCA7L in glioma patients. Besides, the changes in U251 cell invasion after transfection with CDCA7L siRNA were also monitored through Transwell assay.

Results: Our results suggested that CDCA7L expression was up-regulated in different glioma types, including glioblastoma, oligodendroglioma, diffuse astrocytoma and anaplastic astrocytoma. Moreover, the current retrospective cohort study indicated that high CDCA7L expression was associated with tumor size, WHO grade, adjuvant therapy and recurrence, as well as the poor overall survival (OS) and recurrence-free survival (RFS) in glioma patients. Lastly, CDCA7L expression was knocked down using CDCA7L siRNA, which could block the invasion abilities of glioma U251 cells.

Conclusions: CDCA7L is highly expressed in human glioma tissues and a high CDCA7L expression level predicts the dismal prognosis for glioma patients. Moreover, CDCA7L can promote glioma invasion, which can serve as an independent potential prognostic biomarker for glioma patients.

1. Introduction

Glioma is the most common central nervous system malignant tumor in adults, which is characterized by the frequent recurrence, rapid progression, aggressiveness and poor prognosis [1]. Particularly, patients with glioblastoma (GBM) are associated with the median survival time of less than one year [2]. Notably, the prognosis for glioma patients remains dismal despite of the various existing treatment options, including surgery, radiotherapy and chemotherapy [3]. To date, few useful biomarkers are available for monitoring the burden and response of glioma to treatment. Therefore, early diagnosis and prognostic evaluation of glioma are critical for the early treatment initiation and the resultant improved survival of patients.

Cell division cycle-associated 7-like protein (CDCA7L) is suggested as a target gene of c-Myc, which can interact with c-Myc [4]. Activation of the C-Myc oncogene is a crucial event in the pathogenesis of a large number of human malignant tumors, including glioma [4–7]. Moreover, CDCA7L has been reported to be deregulated in several cancer types, which may be a potentially important target in cancer and always indicates dismal prognosis [4,8]. Thus, CDCA7L may probably

Abbreviations: CDCA7L, cell division cycle associated 7 like; GBM, glioblastoma; DMEM, Dulbecco's modified Eagle's medium; siRNA, small interfering RNA; qRT-PCR, quantitative real-time polymerase chain reaction; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; MMP, matrix metallopeptidase; PBS, phosphate-buffered saline; OS, overall survival; RFS, recurrence-free survival; KPS, Karnofsky performance scale; GTR, gross total resection; PR, partial resection; WHO, World Health Organization

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play an important role in tumor progression. However, the functional role of CDCA7L in the prognostic effects and tumorigenesis of glioma has not been fully elucidated yet.

To the best of our knowledge, this was the first study examining the prognostic value and functional role of CDCA7L in glioma. Findings in this study suggested that CDCA7L expression was up-regulated in glioma tissues. Subsequently, the clinical significance and function of CDCA7L expression in human glioma would also be explored.

2. Materials and methods

2.1. Bioinformatics analysis through the oncomine databases

Differences in the CDCA7L mRNA expression between glioma and the matched normal tissues (Sun Brain) were collected from the Oncomine database (https://www.oncomine.org). Typically, the filtering conditions were restricted as follows: gene: CDCA7L; analysis type: brain and CNS cancer vs. normal analysis; data type: mRNA; fold change > 2; gene rank: top 10%; and p-value < 0.0001.

2.2. Patients and tissue samples

From 2012–2017, one hundred and thirty-six glioma patients undergoing an initial surgery at the First Affiliated Hospital of Xinxiang Medical University were enrolled into this study. Additionally, ten normal brain tissues (NBTs) were obtained through epileptic resections. All patients were diagnosed with glioma in the pathology department of the hospital. Each patient had provided the informed consent to participate in this study, and the use of samples for research was approved by the Medical Ethics Committee of the First Affiliated Hospital of Xinxiang Medical University. All samples were immediately frozen and stored in liquid nitrogen, and all patients were naive to any therapy before resection.

2.3. Cell lines

Human glioma cell line U251 cells were purchased from Shanghai Cell Bank (Shanghai, China) and cultured in Dulbecco's modified Eagle's medium (DMEM; Gibco, Carlsbad, CA, USA) supplemented with 10% fetal bovine serum (FBS, Invitrogen, Carlsbad, CA, USA) at 37 °C with 5% CO_2.

2.4. Quantitative real-time polymerase chain reaction (qRT-PCR) assay

Total RNA was extracted from glioma tissues and cells using the Trizol reagent according to the manufacturer's protocol (Invitrogen, Shanghai, China). The CDCA7L mRNA expression levels were detected through RT-qPCR using the one-step RT-PCR kit (Takara Bio, Inc., Otsu, Japan) in accordance with the manufacturer's protocol. Besides, the CDCA7L primers were obtained from Genechem Co. Ltd. (Shanghai, China), with glyceraldehyde 3-phosphate dehydrogenase (GAPDH) as an internal control. Specifically, the primers used were shown as follows: CDCA7L: forward, 5′-TTGGCGACTCGCTACCAGAT-3′, and reverse: 5′-AATGAAAGCGCACATCCTGC-3′; and GAPDH: forward, 5′-GGAGTCAACGGATTTGGTCGTAT-3′, and reverse: 5′-AGCCTTCTCC ATGGTGGTGAAGAC-3′. Additionally, the CDCA7L mRNA expression levels were quantified using the $2^{-\Delta\Delta CT}$ method and normalized using the GAPDH mRNA expression level.

2.5. Transfection of glioma U251 cells

The CDCA7L small interfering RNA (siRNA) and negative control siRNA (NC siRNA) were purchased from Shanghai Genechem Biotechnology Co., Ltd. Typically, a total of 5×10^5 U251 cells/well that achieved 60% confluence were plated in a 6-well plate and infected with CDCA7L siRNA or NC siRNA. The efficiency of CDCA7L siRNA transfection was validated through RT-qPCR and Western blotting.

2.6. Western blotting

The tissues and cells were harvested following the manufacturer's instructions, and the protein concentration was determined using a BCA Protein Assay Kit (Pierce, Rockford, IL, USA). Afterwards, equal amounts of total protein under each treatment were separated using 12.5% SDS-PAGE, which were then transferred onto the PVDF membranes. The first antibodies were purchased from Abcam (Shanghai) Trading Co., Ltd., including rabbit anti-CDCA7L (Dilution: 1/2000, ab70637), anti-Matrix metallopeptidase 9 (MMP-9) (Dilution: 1/1500, ab73734), and anti-GAPDH antibody (1:2500, ab9485); while the horseradish peroxidase-conjugated goat anti-rabbit IgG (Shanghai Genechem Co., Ltd.) was used as a secondary antibody. Meanwhile, GAPDH was used as an internal control to normalize the CDCA7L expression levels.

2.7. Transwell invasion assay

The invasion assay was performed using a Transwell chamber (Millipore, Billerica, MA, USA). In brief, the transfected cells were seeded in the upper chamber with serum-free medium (1×10^5 cells), while the lower chamber contained DMEM supplemented with 10% FBS and was coated with Matrigel. Additionally, cells were fixed and stained with hematoxylin and eosin (HE) after infection with CDCA7L siRNA or NC siRNA. Cell number was counted and expressed as the average number of cells/field of view. The experiments were performed in triplicate.

2.8. Statistical analysis

In this study, the Statistical Product and Service Solutions (SPSS) 22.0 software (SPSS Inc., Chicago, IL, USA) was used for data processing and statistical analysis.

Measurement data were expressed as means ± standard deviations (SD), and analyzed by Student's *t*-test between two groups and by analysis of variance among groups. Enumeration data were analyzed through chi-square test. The survival was assessed by Kaplan–Meier analysis and differences in the survival rate were evaluated through log-rank test. The multivariate and univariate analyses of survival data were performed using Cox regression analysis. A p-value of < 0.05 was considered as statistically significant.

3. Results

3.1. CDCA7L was overexpressed in human glioma tissues

To determine whether CDCA7L was differentially expressed between glioma tissues and the matched normal tissues, CDCA7L mRNA expression was examined through analyzing the Oncomine database. A total of five analyses met the inclusion criteria, and the Sun Brain's Statistics was selected due to the most research subjects. Our analysis revealed that, compared with normal brain tissues, CDCA7L mRNA expression was markedly up-regulated in different glioma types, including glioblastoma (t = 9.980, P < 0.0001, Fig. 1A), oligodendroglioma (t = 3.987, P < 0.0001, Fig. 1B), diffuse astrocytoma (t = 2.383, P = 0.014, Fig. 1C) and anaplastic astrocytoma (t = 3.359, P = 0.001, Fig. 1D)

3.2. CDCA7L was upregulated in human glioma tissues

Subsequently, the CDCA7L expression levels in one hundred and thirty-six glioma samples and normal brain tissues were determined using qRT-PCR assay. Typically, the clinicopathological characteristics of glioma patients were summarized in Table 1. As shown in Fig. 2, the

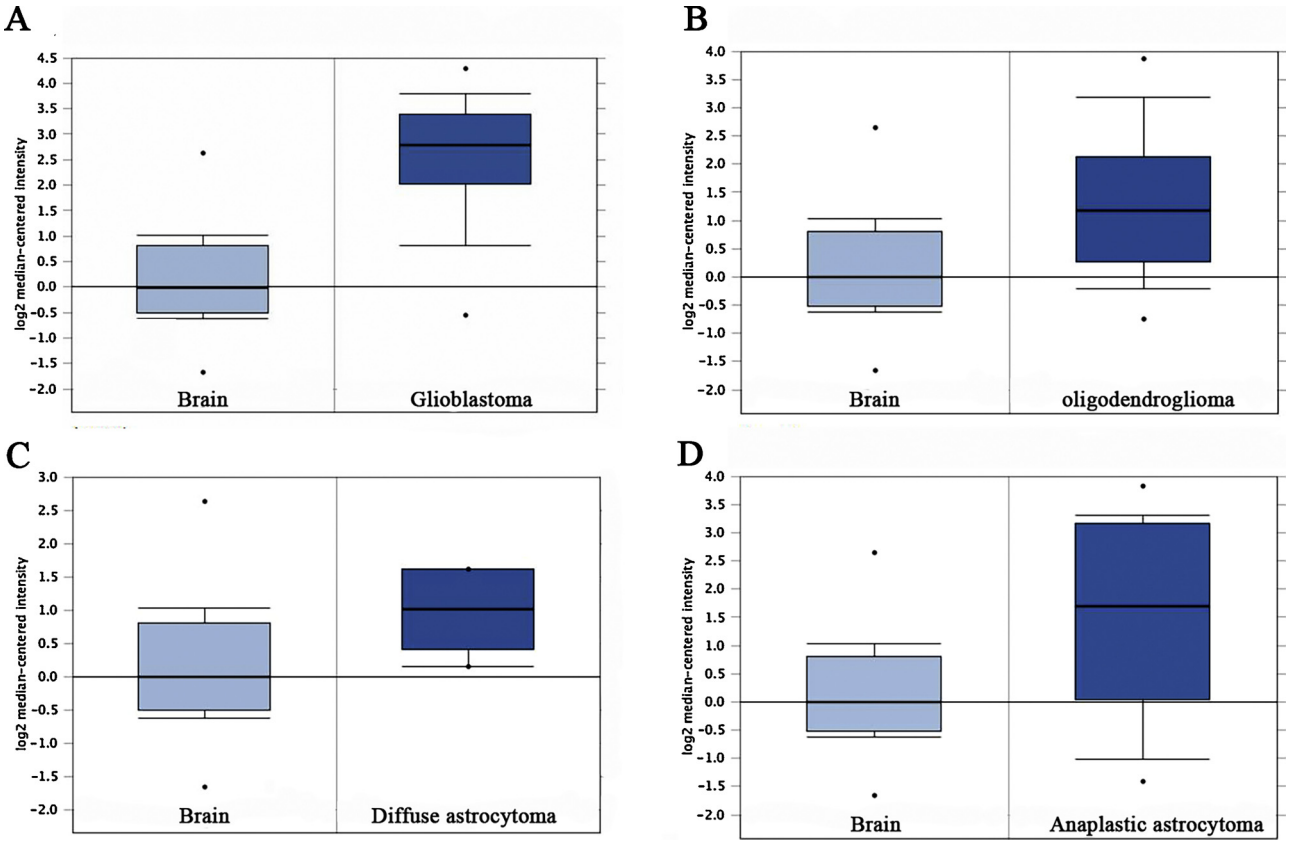

Fig. 1. CDCA7L is overexpressed in glioma tissues. The CDCA7L mRNA expression levels are markedly up-regulated in glioblastoma (A), oligodendroglioma (B), diffuse astrocytoma (C) and anaplastic astrocytoma (D) compared with those in normal brain tissues. Data are collected and analyzed via the Oncomine database.

results indicated that the CDCA7L mRNA levels in glioma tissues were evidently higher than those in normal brain tissues. These results indicated that CDCA7L might be involved in glioma progression.

3.3. Association of CDCA7L expression with clinicopathological characteristics of glioma

For statistical analysis, glioma patients were divided into the high CDCA7L expression group (n = 68) and low CDCA7L expression group (n = 68) based on the median value of CDCA7L expression level. Then, the association of CDCA7L expression with the clinicopathological characteristics in glioma patients was explored. As shown in Table 2, the CDCA7L expression level was dramatically associated with the tumor size ($P < 0.0001$), WHO grade ($P < 0.0001$), adjuvant therapy ($P = 0.016$) and recurrence ($P = 0.024$). However, no associations were observed between CDCA7L expression and age, gender, cystic change, Karnofsky performance scale (KPS) score, tumor location as well as extent of resection ($P > 0.05$). In addition, Spearman analysis of correlation between CDCA7L and clinicopathological characteristics revealed that CDCA7L expression was markedly correlated with tumor size ($P < 0.0001$), WHO grade ($P < 0.0001$), adjuvant therapy ($P = 0.016$) and recurrence ($P = 0.024$), as displayed in Table 3.

3.4. High CDCA7L expression was associated with poor prognosis for glioma

To explore the prognostic value of CDCA7L expression in glioma, Kaplan-Meier analysis and log-rank test were further performed in this study. The results showed that glioma patients with high CDCA7L expression had shorter OS (Fig. 3A, $P < 0.0001$) and recurrence-free survival (RFS) (Fig. 3D, $P < 0.0001$) than those with low CDCA7L expression. In addition, Kaplan-Meier survival analysis of CDCA7L expression was conducted in a subset of glioma patients with different WHO grades. The results confirmed that, high CDCA7L expression indicated poor OS (Fig. 3B–C, $P < 0.0001$) and RFS (Fig. 3E–F, $P < 0.001$), either in low-grade and high-grade glioma patients.

Subsequently, all clinical data were collected and analyzed by multivariate and univariate Cox regression. The findings demonstrated that CDCA7L expression was an independent prognostic factor affecting the OS (Table 4) and RFS (Table 5) of glioma patients ($P < 0.05$).

3.5. Inhibition of CDCA7L expression by CDCA7L siRNA in human glioma U251 cells

To explore the role of CDCA7L in glioma, CDCA7L siRNA and NC siRNA were transfected into human glioma U251 cells, and the knockdown effects were analyzed by qRT-PCR and western blotting, respectively. After transfection, the CDCA7L mRNA (Fig. 4A) and protein (Fig. 4B) levels in U251 cells of CDCA7L siRNA group were evidently lower than those of NC siRNA group.

3.6. Downregulation of CDCA7L expression markedly inhibited glioma U251 cell invasion

After transfection with CDCA7L siRNA or NC siRNA, the invasion abilities of the transfected cells were examined. As shown in Fig. 5, downregulating CDCA7L expression would reduce the number of invading glioma U251 cells by about 50% compared with that in NC siRNA group upon Transwell assays ($t = 5.073$, $P = 0.001$).

3.7. Inhibition of MMP-9 expression by CDCA7L siRNA in human glioma U251 cells

Furthermore, U87 cells were transfected with CDCA7L siRNA or NC

Table 1
Clinicopathological characteristics of patient samples and expression of CDCA7L in glioma.

Characteristics	No of cases (%)
Age (years)	
< 45	63 (46.3)
≥ 45	73 (53.7)
Gender	
Female	69 (50.7)
Male	67 (49.3)
Tumor size	
< 5	74 (54.4)
≥ 5	62 (45.6)
Cystic change	
Absence	80 (58.8)
Presence	56 (41.2)
KPS score	
≥ 80	74 (54.4)
< 80	62 (45.6)
Tumor location	
Infratentorial	57 (41.9)
Supratentorial	79 (58.1)
Extent of resection	
GTR	77 (56.6)
PR	59 (43.3)
WHO Grade	
I/II	51 (37.5)
III/IV	85 (62.5)
Adjuvant therapy	
Absence	72 (52.9)
Presence	64 (47.1)
Recurrence	
Absence	57 (41.9)
Presence	79 (58.1)
Status	
Live	65 (47.8)
Death	71 (52.2)
Expression of CDCA7L	
Low expression	68 (50.0)
High expression	68 (50.0)

Abbreviations: KPS, Karnofsky performance scale; GTR, gross total resection; PR, partial resection; WHO, World Health Organization.

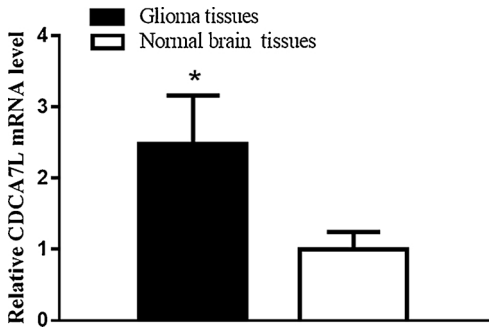

Fig. 2. The CDCA7L expression levels in glioma tissues are outstandingly higher than those in normal brain tissues. *p < 0.05 means vs normal brain tissues.

siRNA, and the MMP-9 protein expression levels were determined by Western blotting. The results demonstrated that the MMP-9 protein levels were dramatically down-regulated after transfection with CDCA7L siRNA compared with that after transfection with NC siRNA (Fig. 6).

4. Discussion

As a transcriptional regulator, c-Myc can promote tumor development through regulating a variety of target genes; however, the biological role of these target genes in the development of GBM remains unclear yet. CDCA7L belongs to the JPO protein family, which is recently identified as a target gene of c-Myc [9,10]. CDCA7L can complement the c-Myc transformation-defective mutant W135E and potentiate the Myc-mediated transformation [11].

High CDCA7L expression has been identified in several type cancers, and CDCA7L may be critical for cancer progression, which may also serve as a potential treatment target for cancer. In addition, CDCA7L has been shown to induce colony formation and contribute to the MYC-mediated transformation of medulloblastoma cells, suggesting that CDCA7L may potentially play an important role in the development of

Table 2
Correlation between CDCA7L expression and clinicopathologic characteristics of glioma patients.

Characteristics	CDCA7L expression		P value
	low, no. cases	high, no. cases	
Age (years)			
< 45	29	34	0.390
≥ 45	39	34	
Gender			
Female	31	38	0.230
Male	37	30	
Tumor size			
< 5	48	26	0.000
≥ 5	20	42	
Cystic change			
Absence	43	37	0.296
Presence	25	31	
KPS score			
≥ 80	40	34	0.302
< 80	28	34	
Tumor location			
Infratentorial	32	25	0.224
Supratentorial	36	43	
Extent of resection			
GTR	41	36	0.387
PR	27	32	
WHO Grade			
I/II	39	12	0.000
III/IV	29	56	
Adjuvant therapy			
Absence	43	29	0.016
Presence	25	39	
Recurrence			
Absence	35	22	0.024
Presence	33	46	
Status			
Live	43	22	0.000
Death	25	46	

Abbreviations: KPS, Karnofsky performance scale; GTR, gross total resection; PR, partial resection; WHO, World Health Organization.

Table 3
Spearman analysis of correlation between CDCA7L and clinicopathological.

Variables	CDCA7L expression level	
	Spearman correlation	p-Value
Age	−0.074	0.394
Gender	−0.103	0.233
Tumor size	0.325	0.000
Cystic change	0.09	0.299
KPS score	0.089	0.305
Tumor location	0.104	0.227
Extent of resection	0.074	0.391
WHO Grade	0.41	0.000
Adjuvant therapy	0.206	0.016
Recurrence	0.194	0.024
Status	0.309	0.000

Abbreviations: KPS, Karnofsky performance scale; WHO, World Health Organization.

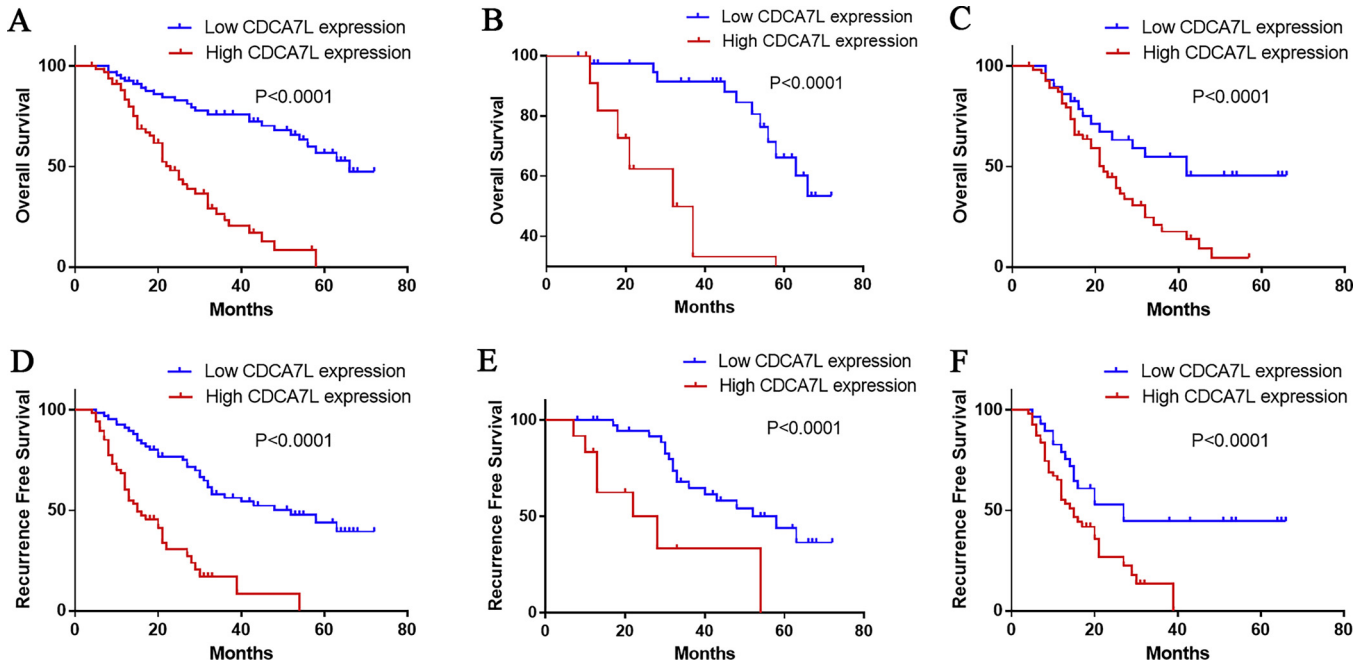

Fig. 3. Kaplan-Meier curves showing the survival of glioma patients with different CDCA7L expression levels. A–C. OS curves stratified by CDCA7L expression in total (A), low-grade (B) and high-grade (C) glioma patients. D–F. RFS curves stratified by CDCA7L expression in total (D), low-grade (E) and high-grade (F) glioma patients.

Table 4
Univariate and multivariate analyses for overall survival in glioma patients.

Variable	Univariate analysis			Multivariate analysis		
	p-value	HR	95% CI	p-value	HR	95% CI
Age (< 45 vs. ≥45)	0.459	0.839	0.526-1.336	0.495	0.842	0.514-1.380
Gender (Female vs. Male)	0.845	1.048	0.657-1.672	0.414	1.247	0.734-2.120
Tumor size (< 5 vs. ≥5 cm)	0.000	2.975	1.842-4.804	0.023	1.939	1.096-3.429
Cystic change	0.000	2.433	1.507-3.929	0.000	2.722	1.568-4.724
KPS score	0.003	2.069	1.283-3.336	0.729	1.105	0.629-1.939
Tumor location	0.037	1.648	1.033-2.744	0.117	1.512	0.901-2.536
Extent of resection	0.065	1.551	0.973-2.472	0.762	1.082	0.649-1.804
WHO Grade	0.000	3.495	2.010-6.078	0.011	2.46	1.234-4.901
Adjuvant therapy	0.083	1.516	0.947-2.427	0.335	1.292	0.767-2.178
Expression of CDCA7L	0.000	4.797	2.788-8.254	0.002	2.984	1.496-5.951

Table 5
Univariate and multivariate analyses for Recurrence-free survival in glioma patients.

Variable	Univariate analysis			Multivariate analysis		
	p-value	HR	95% CI	p-value	HR	95% CI
Age(years)	0.728	0.924	0.593-1.439	0.421	0.824	0.515-1.319
Gender	0.408	1.207	0.773-1.886	0.149	1.443	0.877-2.373
Tumor size	0.000	3.189	2.017-5.041	0.001	2.338	1.386-3.944
Cystic change	0.007	1.867	1.188-2.934	0.055	1.637	0.989-2.709
KPS score	0.007	1.858	1.188-2.907	0.744	1.09	0.651-1.823
Tumor location	0.021	1.731	1.086-2.759	0.046	1.634	1.009-2.646
Extent of resection	0.116	1.426	0.916-2.218	0.756	1.081	0.663-1.726
WHO Grade	0.000	2.514	1.549-4.082	0.021	2.023	1.112-3.678
Adjuvant therapy	0.266	1.285	0.826-2.001	0.68	1.113	0.670-1.849
Expression of CDCA7L	0.000	3.969	2.405-6.551	0.006	2.344	1.282-4.286

medulloblastoma [4]. Tian et al. had reported that CDCA7L could activate the extracellular signal-regulated kinase 1/2 signaling pathway and regulate the cell cycle, thereby promoting hepatic carcinoma progression [8]. Such evidence suggests that CDCA7L may play a key role in cancer progression. However, the role of CDCA7L in the progression and prognosis of glioma patients has not been well clarified yet.

In the current study, the clinical significance and function of CDCA7L in glioma patients were first explored. Firstly, the public expression profiles and clinical data of glioma patients from oncomine database were used, and the results demonstrated that CDCA7L expression levels were outstandingly up-regulated in four types of glioma tissues compared with normal brain tissues. Secondly, similar to

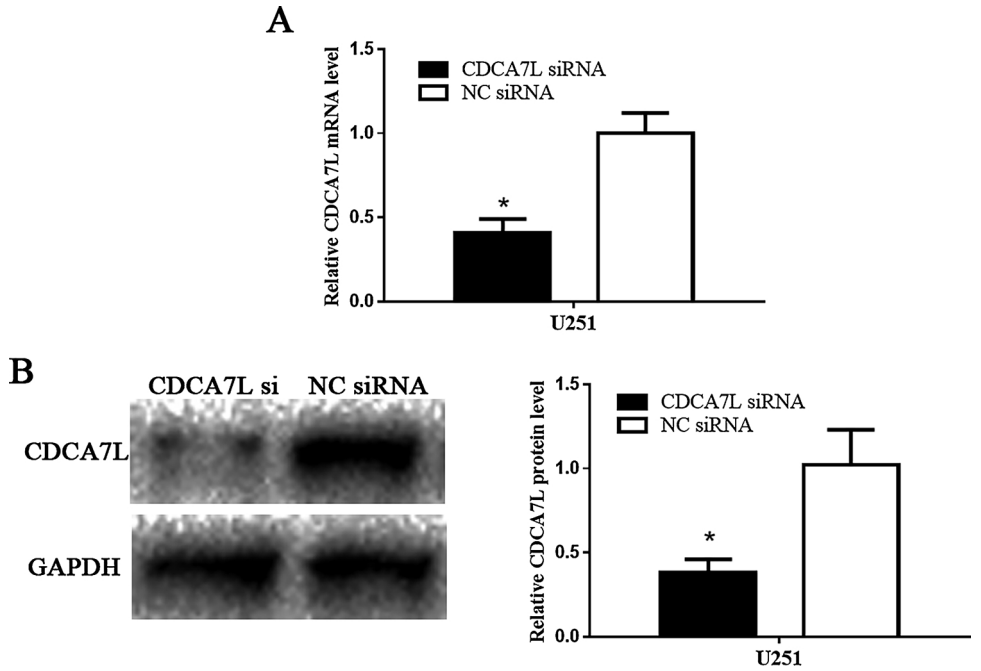

Fig. 4. CDCA7L siRNA is constructed, which can inhibit the CDCA7L expression levels in glioma cells. The knockdown efficiency of CDCA7L is assessed by qRT-PCR (A) and Western blotting assays (B). *p < 0.05 means vs the NC siRNA group.

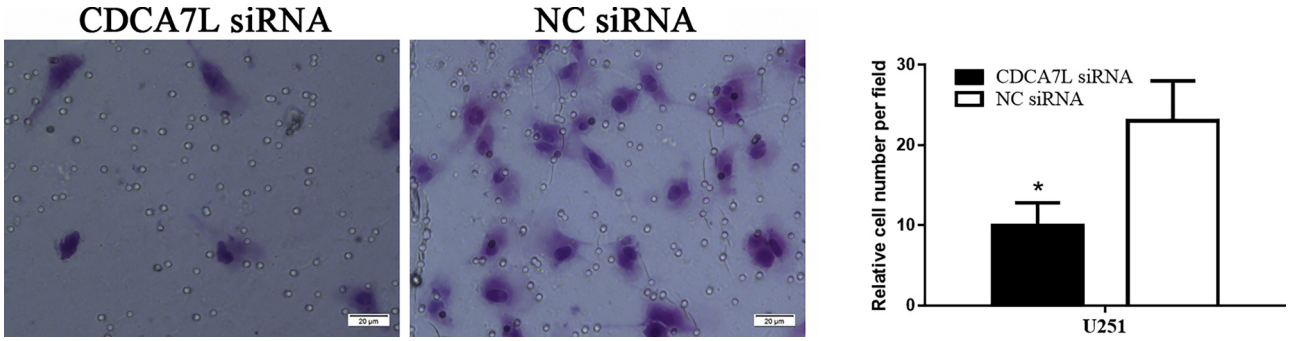

Fig. 5. CDCA7L modulates the invasion abilities of glioma U251 cells. Knockdown of CDCA7L expression would markedly suppress the invasion abilities of glioma U251 cells. *p < 0.05 means vs the NC siRNA group.

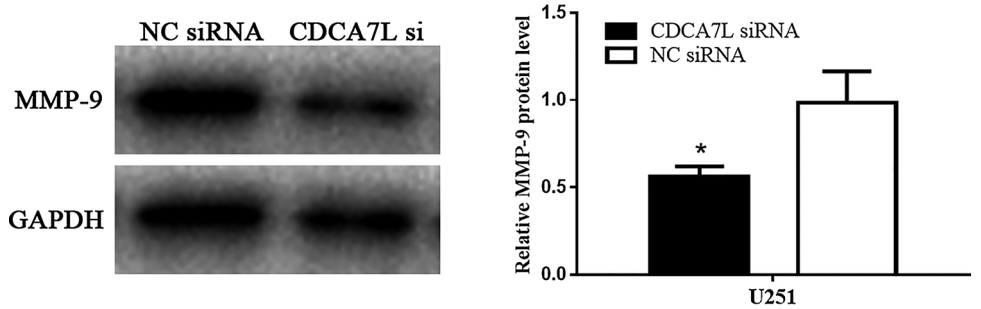

Fig. 6. CDCA7L modulates the MMP-9 expression levels in glioma U251cells. *p < 0.05 means vs the NC siRNA group.

previous results, our findings suggested that CDCA7L was highly expressed in human glioma tissues compared with normal brain tissues. Thirdly, statistical assays indicated that the CDCA7L expression level was dramatically associated with tumor size, WHO grade, adjuvant therapy and recurrence. In addition, Kaplan-Meier analysis revealed that glioma patients with high CDCA7L expression levels had shorter OS and RFS. Further multivariate and univariate survival analyses confirmed that CDCA7L could potentially serve as an independent prognostic biomarker for glioma patients.

In addition, to detect the function of CDCA7L in glioma cells, CDCA7L siRNA was constructed and transfected into the glioma U251 cells, which could down-regulate the CDCA7L gene expression levels in U251 cells in vitro. The results indicated that knockdown of CDCA7L expression could evidently inhibit the invasion abilities of glioma U251 cells. Nevertheless, further validation and functional evaluation are required to assess the role of CDCA7L in other glioma cell lines and explore the explicit mechanism underlying this association.

5. Conclusions

In conclusion, our findings indicate that CDCA7L plays a crucial role in the progression and prognosis of human glioma. CDCA7L is highly expressed in human glioma tissues, and the high CDCA7L expression predicts dismal prognosis for glioma patients. Besides, downregulation of CDCA7L expression by CDCA7L siRNA would inhibit the invasion abilities of glioma U251 cells. Taken together, CDCA7L may potentially serve as an independent prognostic biomarker for glioma patients.

Conflict of interest

The authors have no conflict of interest to declare.

Informed consent

All patients provided written informed consent according to the local ethics committee regulations.

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Research involving human participants and/or animals/ethical approval

This study was reviewed and approved by the Ethics committee of the First Affiliated Hospital of Xinxiang Medical University.

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