

# Coactosin-Like Protein (COTL1) Promotes Glioblastoma (GBM) Growth in vitro and in vivo

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**Objective:** To assess the expression levels of COTL1 in human GBM tissues and evaluate the potential involvement of COTL1 in cancer progression.

**Methods:** Bioinformation analysis was performed to evaluate COTL1 mRNA levels in GBM tissues and normal tissues, according to the TCGA database, and explore the effects on prognosis. Immunohistochemical (IHC) assays were performed to evaluate COTL1 expression in human GBM tissues and the clinical pathological analysis was performed. Colony formation and MTT assays were performed to evaluate the effects of COTL1 on GBM cell proliferation. Immunoblot assays were performed to detect the expression level of COTL1, Ki67, and PCNA. A xenograft model was developed in mice to assess the effects of COTL1 on tumor growth in vivo.

**Results:** We found COTL1 had an obvious high expression in human GBM tissues. The expression of COTL1 was related to recurrence ( $P=0.006^{**}$ ) and prognosis of patients with GBM. Our data further demonstrated COTL1 promoted cell proliferation in vitro and contributed to tumor growth of GBM cells in mice.

**Conclusion:** We therefore identified a novel and promising therapeutic target for the treatment of GBM.

**Keywords:** coactosin-like protein, COTL1, glioblastoma), GBM, proliferation, recurrence, prognosis

## Introduction

Glioblastoma (GBM), as the most common form of malignant brain cancer, are genetically unstable, highly infiltrative, angiogenic, and resistant to chemotherapy.<sup>1,2</sup> In decades, the median survival of GBM is approximately 7–15 months from the time of diagnosis.<sup>3–5</sup> Surgical resection combined with radiotherapy and chemotherapy are the conventional therapy for GBM.<sup>6,7</sup> However, these therapies are efficacy limited due to high rates of recurrence, drug resistance, and devastating neurological deterioration.<sup>8,9</sup> Despite the advances in diagnosis and treatment of GBM, the patient prognosis has not been obviously improved. Targeted therapy showed a great prospect in the treatment of GBM. To combat this disease, novel therapeutic targets and approaches for the treatment of GBM are still needed.

Coactosin-like protein (COTL1), which belongs to the ADF/cofilin family, is an actin binding protein that could bind to actin filaments to mediate the actin cytoskeleton.<sup>10,11</sup> Additionally, COTL1 could suppress cofilin-induced actin depolymerization.<sup>12</sup> A previous study also demonstrated that COTL1 affected the migration of mouse neocortical neurons and was a potential regulator of T-cell activation.<sup>13</sup> COTL1 could compete with cofilin to promote lamellipodial protrusion.<sup>12</sup> In proinflammatory

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leukotriene biosynthesis, COTL1 increased 5-LO activity through interacting with 5-lipoxygenase (5-LO or ALOX5).<sup>14</sup> CLP/COTL1 was also reported to be involved in TGF $\beta$  signaling via TGF $\beta$  receptor 1 associated protein 1 (TGFBRAP1).

Notably, recent studies indicated the involvement of COTL1 in cancer progression. In myeloid cells, high COTL1 expression was observed.<sup>15</sup> Similarly, positively stained COTL1 was identified in most NSCLC tissues.<sup>16</sup> Additionally, COTL1 overexpression promoted cell proliferation in HCC827 cells suggesting COTL1 could act as a potential oncogene.<sup>17,18</sup> In breast cancer, COTL1 suppressed cancer growth by activating IL-24/PERP and inhibiting non-canonical TGF $\beta$  signaling.<sup>19</sup> Though there are wide effects of COTL1 in cancer progression, its possible role in GBM remains unclear.

Herein, we found COTL1 had an obvious high expression in human GBM tissues. The expression of COTL1 was related to clinical pathological features such as recurrence. Our data further suggested COTL1 promoted cell proliferation *in vitro* and contributed to tumor growth of GBM cells in mice. We therefore identified a novel and promising therapeutic target for the treatment of GBM.

## Materials and Methods

### Antibodies, Primers, and shRNA Plasmids

Anti-COTL1 (1:100 dilution for IHC, and 1:1,000 for Immunoblot, ab235833, Abcam, Cambridge, UK), anti- $\beta$ -actin (1:5,000 dilution, 60008-1-Ig, Proteintech, Chicago, IL), anti-Ki67 (1:1,000, ab16667, Abcam, Cambridge, UK), anti-PCNA (1:1,000, SAB2108448, Sigma-Aldrich, St. Louis, MO).

The quantitative PCR primers were listed as follows: COTL1: Forward, 5'-CCAAGATCGACAAAGAGGCTT-3' and Reverse, 5'-CGATGGTGGAGCCGTCATATTT-3'; GAPDH Forward: 5'-CGACCACTTTGTCAAGCT-3', Reverse, 5'-GGTTGAGCACAGGGTACTTTATT-3'. Pre-designed shRNA constructs targeting COTL1 were bought from Origene Co (Beijing, China). COTL1 shRNA sequence were as follows: sense, 5'-CCGTCATCTGGGTGACTTT TAAA-3'.

### Human Tissue Samples and Analysis

A total of 66 human GBM tissue and adjacent non-tumor tissues were collected from patients who underwent surgical resection in our hospital. Formal consent was obtained from all patients. Tissue specimens were frozen until use. Our

study was approved by the Ethics Committee of the Second People's Hospital of Lianyungang City. The clinicopathological characteristics of 66 patients with GBM were respectively obtained and analyzed.

To explore the COTL1 expression in human GBM tissues, immunohistochemical (IHC) assays were first conducted. Fixed tissues in 4% PFA at room temperature, embedded in paraffin blocks, were then cut into 5- $\mu$ m sections. Sections were antigen retrieved, blocked, and incubated with primary antibody targeting COTL1 for 2 hours and secondary antibody for 1 hour at room temperature. Slides were stained with DAB. Images were taken using a microscope (Olympus BX43).

The expression levels of COTL1 were scored as follows. The positive staining cells percentage was quantified as 0 for negative staining cells; 1 meant 10–50% positive staining, and 2 for more than 50% positive staining cells. The staining intensity was considered as 0 (negative staining), 1 (low level staining), and 2 (high level staining). The expression levels were quantified according to staining intensity score plus positive tumor cell staining score. Staining scores 0–2 were low expression, while 3–4 were considered high COTL1 expression.

### Cell Culture and Transfection

Human GBM cell line U251 and U87 cells were obtained from ATCC and maintained in ATCC-formulated Eagle's Minimum Essential Medium (Catalog No. 30–2003) supplied with 10% of fetal bovine serum (FBS, Gibco, Grand Island, CA) at 37°C in a 5% CO<sub>2</sub> incubator.

The transfection of COTL1 shRNA plasmids were conducted by Lipofectamine 3000 (Thermo Fisher Scientific, Inc.). COTL1 stable ablation was screened through puromycin successive addition.

### Quantitative PCR Assay

U251 and U87 cells were lysed for total RNAs extraction by Trizol reagent (Invitrogen, Carlsbad, CA). Subsequently, M-MLV reverse transcriptase were utilized to reverse transcribe RNA to cDNA. SYBR mixture (Takara, Kusatsu, Japan) was used to amplify genes. And targeted gene levels were normalized to GAPDH.

### Immunoblot Assays

Protein were extracted from cells or tumor tissues by lysis buffer (60 mM Tris-HCl, pH 6.8, 2% SDS, 20% glycerol,

0.25% bromophenol blue, 1.25% 2-mercaptoethanol, and protease inhibitor cocktail). Protein were isolated by SDS-PAGE, subsequently transferred onto PVDF membrane (Millipore, IPSN07852, USA). Then blocked with 5% BSA in TBST buffer and incubated with the indicated primary antibodies. After washing, it was incubated with the secondary antibodies. Each blot was analyzed with an ECL kit (GE Healthcare, RPN 2109, USA).

### Colony Formation Assay

Approximately 1,000 cells were placed into 6-well plates and maintained for 2 weeks and subsequently stained with 0.2% crystal violet and washed with PBS. Colony numbers in each well were analyzed.

### MTT Assay

Cells were plated into 96-well plates. After adherence, MTT was added to the cells. The stained cells were treated with 150  $\mu$ L DMSO. The OD value was measured at a 570 nm wavelength with a microplate reader.

### Tumor Growth Assays

Animal assay procedures involved in this study were approved by the Institutional Animal Care and Use Committee (IACUC) of the Second People's Hospital of Lianyungang City. Male nude BalB/c mice were bought from Beijing Vital River Laboratory Animal Technology Co., Ltd. (Beijing, China). To conduct tumor growth assay,  $1 \times 10^6$  U251 cells with or without stable COTL1 depletion were subcutaneously injected into nude mice. After 14 days, the tumor volume was measured every 3 days. According to the tumor volume, the tumor growth curve was displayed. After 29 days, the tumors were excised and photographed.

### Statistics

Statistical analysis was performed by Graph Pad software. Mean  $\pm$  standard deviation (SD) was displayed in the results. The correlation analysis between COTL1 level and clinical pathological features were obtained by  $\chi^2$  analysis. Students' *t*-test was used for statistical difference. \* Indicates  $P < 0.05$ , and  $P < 0.05$  was considered a significant difference.

## Results

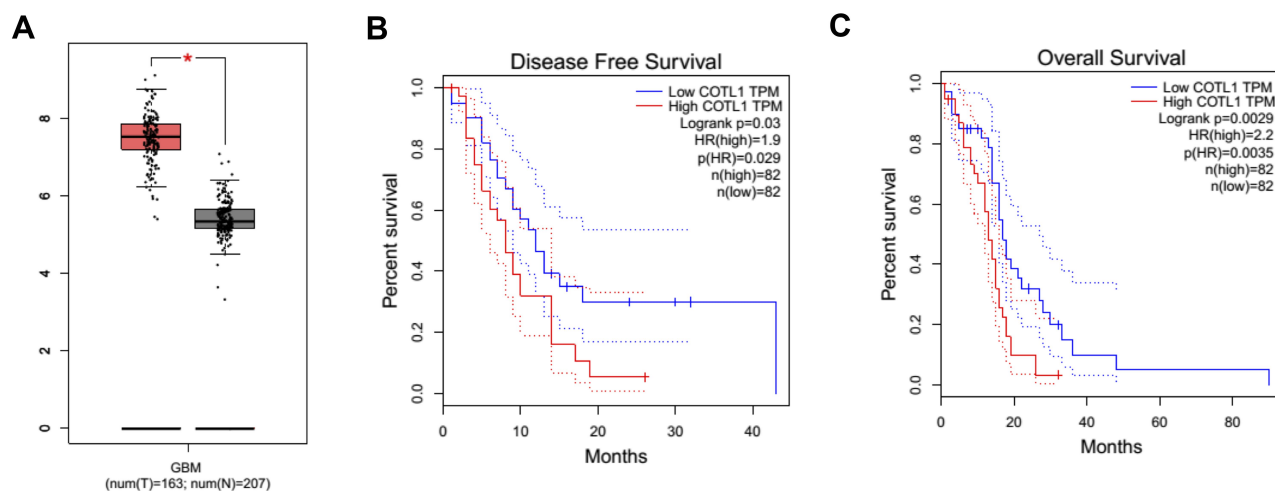
### Bioinformation Analysis Revealed COTL1 Expression Was Upregulated in Human GBM Tissues and Correlated with the Prognosis

Since the wide involvement of COTL1 in cancer progression, we assessed the expression of COTL1 in human GBM tissues. Though bioinformatic analysis, we found enhanced expression levels of COTL1 in human GBM patients in the TCGA database. The COTL1 mRNA levels in tumor tissues ( $n=163$ ) were significantly higher than non-tumor tissues ( $n=207$ ) (Figure 1A). Furthermore, we observed that COTL1 mRNA levels were correlated with the disease-free survival rate and overall survival rate ( $P=0.03$  and  $P=0.029$ , respectively, Figure 1B). Patients with high COTL1 expression in tumors had relatively lower disease-free survival rates and overall survival rates, suggesting the poor prognosis in the high COTL1 expression group. We therefore indicated that COTL1 was increased in human GBM tissues and correlated with the poor prognosis of GBM patients.

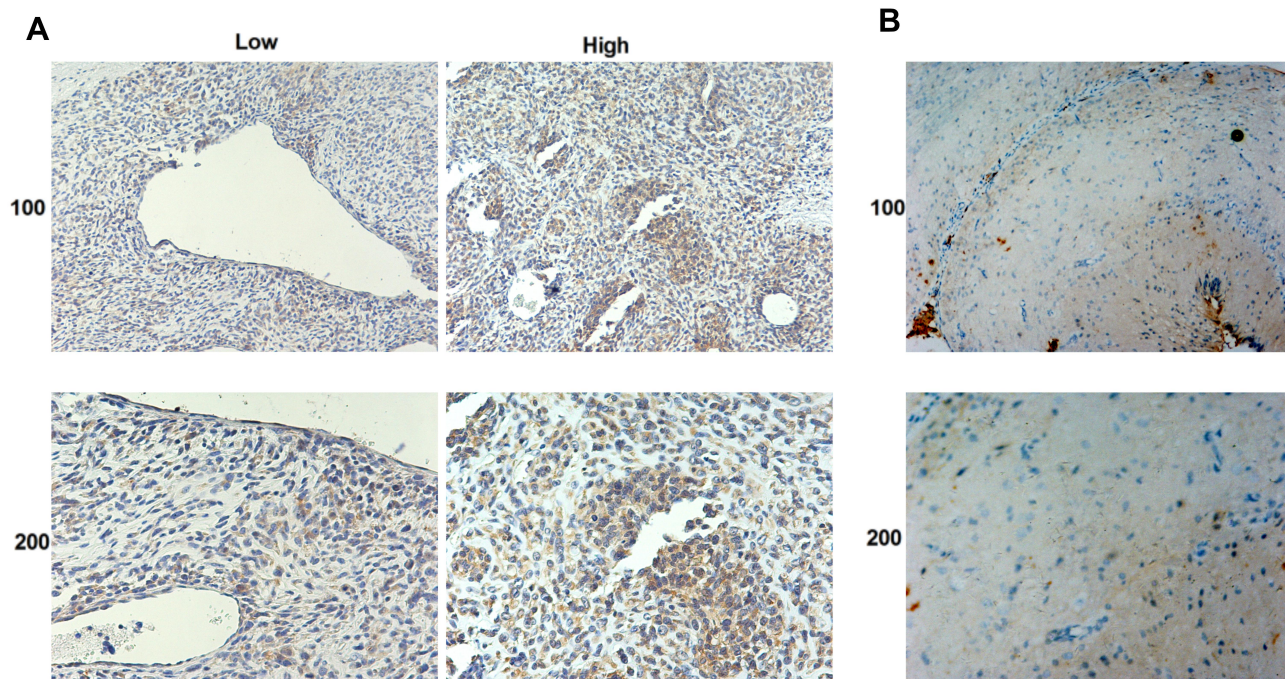
### COTL1 Was Upregulated in Human GBM Tissues and Associated with the Clinical Pathological Features of Patients with GBM

To further assess the expression levels of COTL1 in GBM patients, we performed IHC assays. As shown in Figure 2A and B, COTL1 staining intensity was obviously stronger in GBM tissues than adjacent non-tumor tissues (photograph shown in 100 $\times$  or 200 $\times$  magnification). Our results demonstrated high expression levels of COTL1 in human GBM tissues.

Then we further analyzed the relationship between COTL1 expression level and clinicopathological characteristics in 66 patients with GBM patients. According to the staining results, patients were divided into COTL1 high and low groups. Twenty-two patients exhibited low COTL1 expression and the remaining ( $n=44$ ) showed high expression of COTL1 (Table 1). We noticed that COTL1 expression was obviously correlated with recurrence ( $P=0.006^{**}$ , Table 1), whereas there was no obvious correlation between COTL1 expression and



**Figure 1** Bioinformatic analysis indicates that COTLI is enhanced in GBM patients and correlated with the prognosis. **(A)** COTLI expression level in GBM tissues and normal tissues was analyzed from bioinformatic analysis. (For tumor tissues and normal tissues,  $n=163$  and  $207$ , respectively, from TCGA dataset). **(B, C)** COTLI expression was correlated with the disease-free and overall survival rates of GBM patients in different numbers of cases. \*  $P<0.05$ .



**Figure 2** COTLI is highly expressed in human GBM tissues compared with normal tissues. COTLI expression level in GBM tissue samples **(A)** and normal tissues **(B)** was detected by IHC assays ( $100\times$  and  $200\times$  magnification, respectively).

clinical features such as patient age ( $P=0.212$ ), gender ( $P=0.278$ ), tumor lateralization ( $P=0.460$ ), and IDH1 mutations ( $P=0.712$ , Table 1). Therefore, we revealed that COTLI expression was correlated with the recurrence of GBM patients.

## COTLI is Effectively Downregulated in GBM Cells Transfected with COTLI shRNA Plasmids

Since the abnormal expression of COTLI was detected in GBM patients, we explored whether COTLI was involved

**Table 1** Relationships of COTL1 and Clinicopathological Characteristics in 66 Patients with Glioblastoma

Feature	All (n=66)	KIF15 Expression		$\chi^2$	P
		Low	High		
		(n=22)	(n=44)		
<b>Age (years)</b>					
< 55	40	11	29	1.555	0.212
≥ 55	26	11	15		
<b>Gender</b>				1.179	0.278
Male	42	12	30		
Female	24	10	14		
<b>Tumor lateralization</b>				0.545	0.460
Subtentorial	44	16	28		
Supratentorial	22	6	16		
<b>Recurrence</b>				7.661	0.006*
Yes	52	13	39		
No	14	9	5		
<b>IDH1 mutations</b>				0.136	0.712
No	44	14	30		
Yes	22	8	14		

in GBM progression. Human GBM cell line U251 and U87 cells were selected as the cell models of in vitro study on GBM. First, control or COTL1 shRNA plasmids were transfected into U251 and U87 cells to deplete the expression of COTL1. Through quantitative PCR assays, we found the COTL1 mRNA level decreased obviously after the transfection of its shRNA plasmids (Figure 3A). Similarly, COTL1 protein levels were also decreased, as shown in Immunoblot assays following the transfection of its shRNA plasmids (Figure 3B). Our data therefore confirmed COTL1 was effectively downregulated by the transfection of its shRNA plasmids.

### COTL1 Ablation Inhibited Cell Proliferation in vitro

To further explore the function of COTL1 in GBM cells, colony formation assays were then conducted. Both U251 and U87 cells transfected with control or COTL1 shRNA plasmids were seeded and maintained for 14 days to form colonies in a 6-well plate. We found COTL1 depletion resulted in a sharp reduction in colony numbers in both

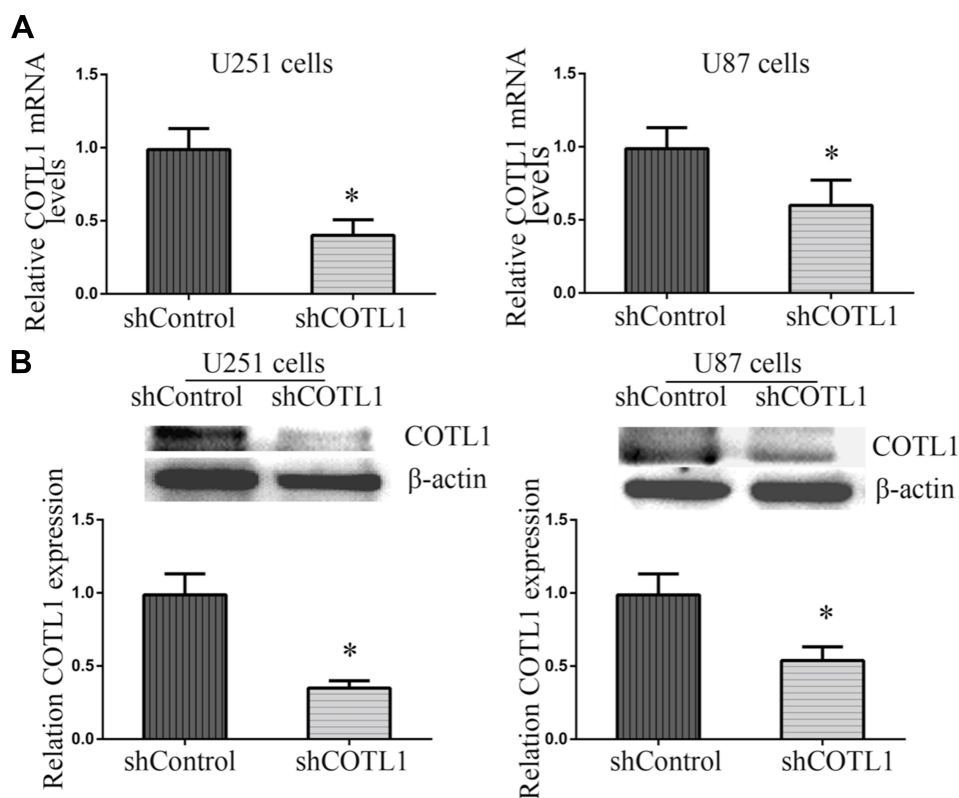
U251 and U87 cells (Figure 4A). In addition, we observed a decreased OD value at 570 nm wavelength through MTT assays in U251 and U87 cells transfected with COTL1 shRNA plasmids, which further proved the decreased proliferation ability (Figure 4B). Ki67 and PCNA were proliferate cell biomarkers reflecting the proliferation ability, and the expression of Ki67 and PCNA was also detected in U251 and U87 cells after transfection of control or COTL1 shRNA plasmids. Consistently, reduction of Ki67 and PCNA expression level in COTL1-depleted U251 and U87 cells were observed (Figure 4C and D), suggesting the depletion of COTL1 inhibited the proliferation of GBM cells.

### COTL1 Ablation Suppressed Tumor Growth of GBM Cells in vivo

As we found COTL1 contributed to cell proliferation in vitro, we therefore assessed that COTL1 might induce tumor formation in vivo. To confirm our assumption, we detected the tumor growth degree through a xenograft model. U251 cells were stably transfected with control or COTL1 shRNA lentivirus to alter COTL1 expression, and subsequently injected the control or COTL1 depleted U251 cells into BALB/c nude mice subcutaneously for 2 weeks, we monitored the tumor growth every 3 days until 29 days (n=6). Interestingly, the tumor volume in the COTL1 depletion group was significantly smaller than the control group (Figure 5A). Representative images of tumors in each group are displayed in Figure 5A. We then detected the expression levels of COTL1 and Ki67 in isolated tumors from control and COTL1 depletion mice through IHC assays. We found the expression of COTL1 and Ki67 in COTL1 depletion groups was obviously lower than that in the control group (Figure 5B and C), consistent with our in vitro data. Taken together, we confirmed COTL1 depletion tumor proliferation of GBM cells growth in vivo.

### Discussion

GBM is the most aggressive malignant tumor in the brain, with poor prognosis.<sup>20</sup> Neurological symptoms of GBM vary differently.<sup>21</sup> In decades, patient prognosis is still poor due to the limited therapies and high occurrence.<sup>22</sup> Median survival upon this treatment was 14 months (only four in the absence of treatment).<sup>23,24</sup> Therefore, revealing the molecular mechanisms related to GBM progression and founding promising therapeutic targets is still needed.



**Figure 3** COTL1 is downregulated in U87 and U251 cells after COTL1 shRNA transfection. Quantitative PCR analysis (**A**) and Immunoblot images (**B**) verified downregulation of COTL1 in U87 and U251 cells transfected with COTL1 shRNA plasmids. \*  $P < 0.05$ .

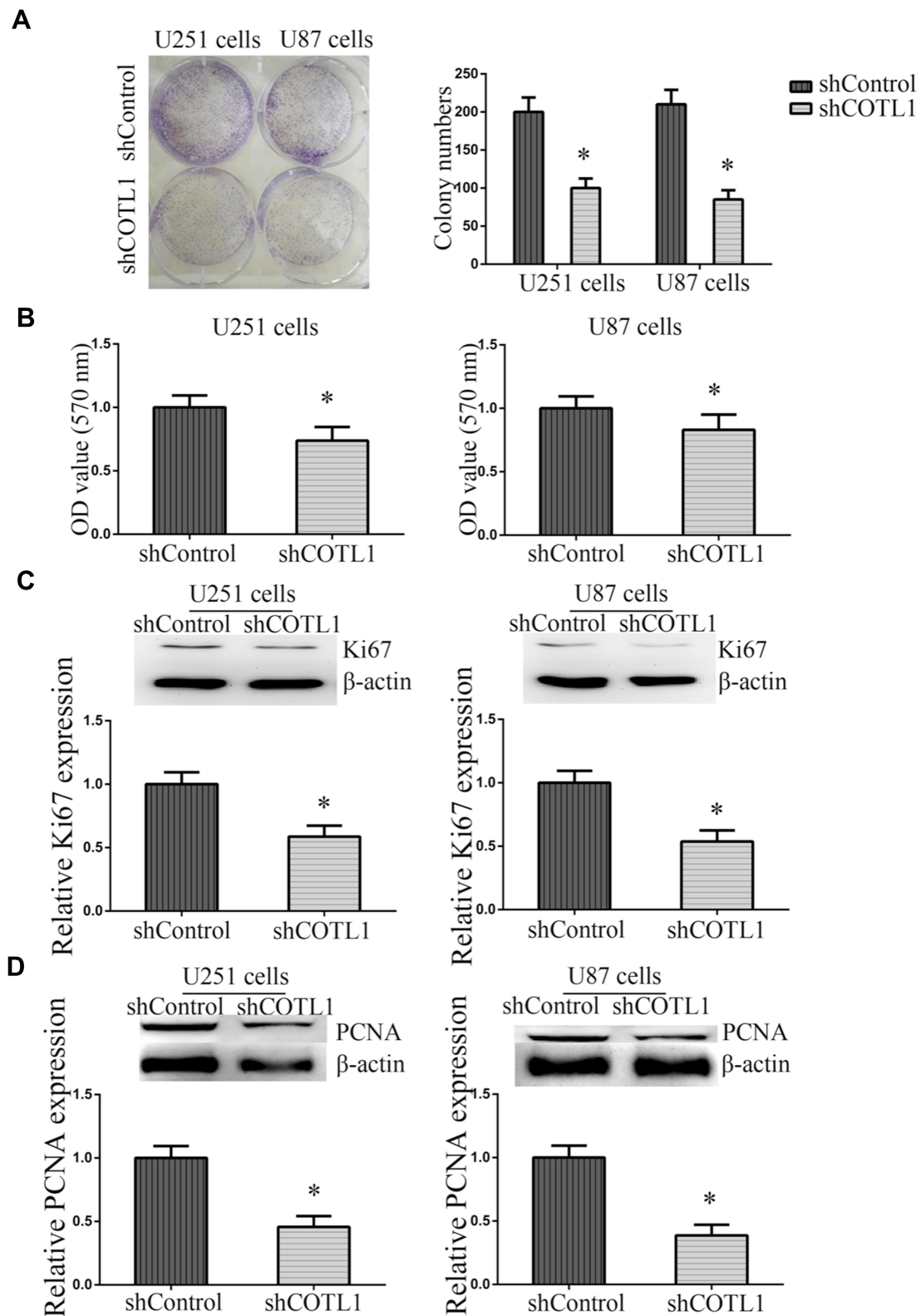
In this study, we observed obvious upregulation of COTL1, an actin binding protein, in human GBM tissues. We also noticed COTL1 expression level was associated with the clinical features such as recurrence of GBM patients through the clinical pathological analysis. Therefore, we thought COTL1 as a potential therapeutic target for the treatment of GBM.

Interestingly, a previous study identified COTL1 was up-regulated in small cell lung cancer (SCLC) tissues which was validated by Immunoblot analysis, Immunohistochemistry, and quantitative PCR assays.<sup>15</sup> In addition, most SCLC tissues (93%; 28/30) were COTL1-positive in immunohistochemistry, therefore COTL1 could be a potential biomarker in SCLC.<sup>15</sup> COTL1 was also overexpressed in pancreatic cancer tissues, compared to normal pancreatic tissues.<sup>25</sup> CLP/COTL1 is highly expressed in a rat epithelial breast cancer cell line (FE1.3) compared with its mesenchymal counterpart (FE1.2).<sup>19</sup> Knockdown of COTL1 in FE1.3 cells promoted cell proliferation, whereas its overexpression in FE1.2 cells inhibited proliferation and reduced tumor growth in xenograft assays.<sup>19</sup> Therefore, we speculated that COTL1 might be important in GBM progression. By conducting colony formation and MTT assays, we observed

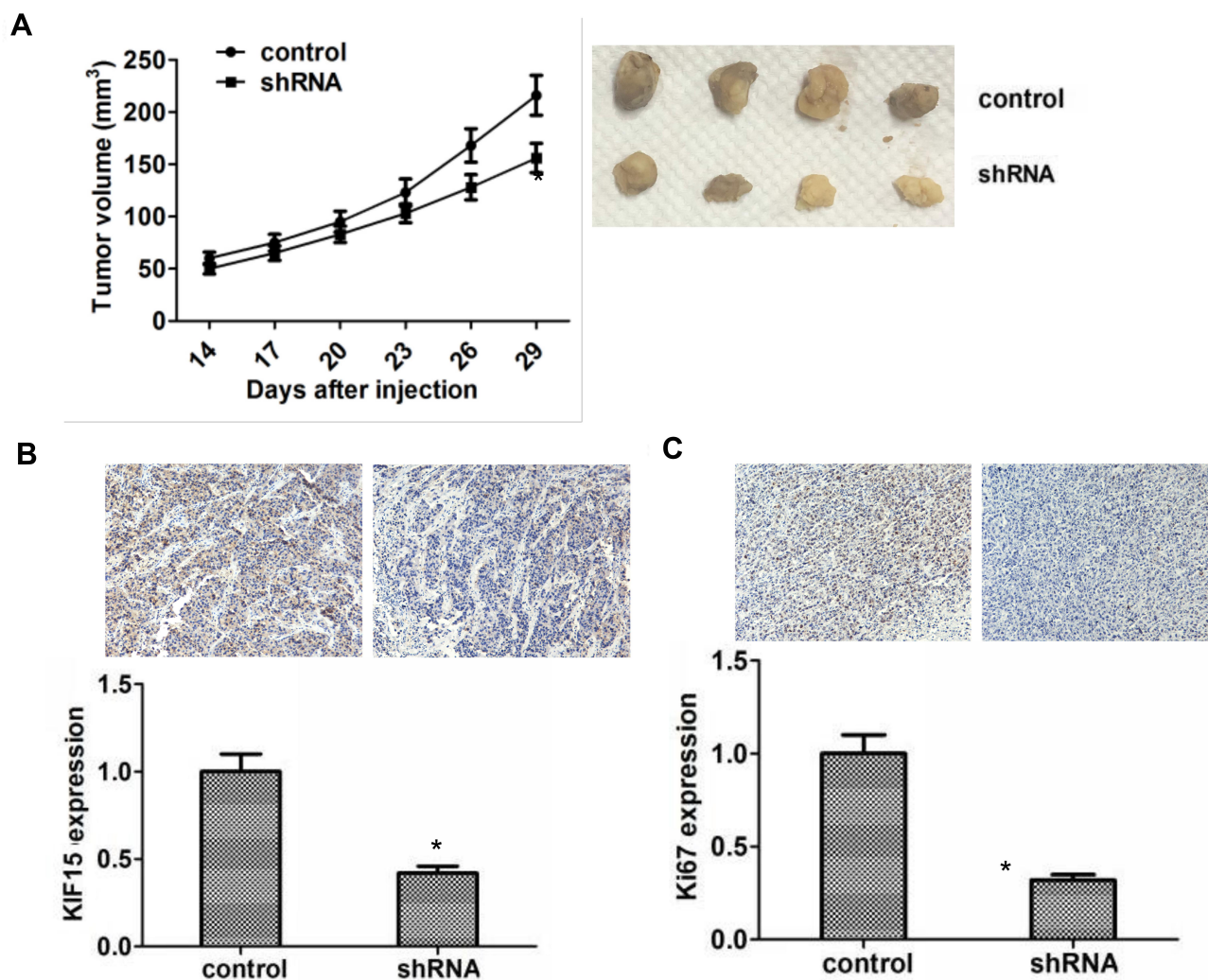
COTL1 inhibited GBM cell proliferation. COTL1 knock-down also reduced Ki67 and PCNA expression level in vitro and in mice. Our data therefore indicated COTL1 inhibited GBM cell proliferation.

COTL1, as an actin-binding protein, competes with cofilin for binding to F-actin. COTL1 protects F-actin from cofilin-mediated depolymerization.<sup>26</sup> CLP/COTL1 potentiated the growth suppressive effect of transforming growth factor- $\beta$ 1 (TGF $\beta$ 1), leading to downregulation of TGF $\beta$ -responsive genes vascular growth factor A/B (VEGFA/VEGFB), hypoxia inducing factor 1 $\alpha$  (HIF-1 $\alpha$ ), and thrombospondin 1 (TSP1), which mediate various hallmarks of cancer progression including angiogenesis, invasion, and metastasis.<sup>19</sup> In this study, we noticed COTL1 promoted the proliferation of GBM cells both in vitro and in mice, and whether COTL1 inhibited cell proliferation via affecting actin dynamics or TGF $\beta$ 1 requires further investigation.

COTL1 is involved in the regulation of neuronal migration and morphogenesis.<sup>17,18,27</sup> COTL1 overexpression suppressed the migration of neurons during mouse corticogenesis, and delayed neuronal migration in late-born neurons.<sup>11,27</sup> Its expression also disturbed neuron morphology.<sup>27</sup> These studies suggested that COTL1 could



**Figure 4** COTL1 depletion suppressed GBM cell proliferation in vitro. **(A)** Colony formation assays were performed to evaluate the proliferative ability of U87 and U251 cell transfected with control or COTL1 shRNA plasmids. **(B)** MTT assays were conducted to evaluate the proliferative ability of U87 and U251 cell transfected with control or COTL1 shRNA plasmids. **(C, D)** Ki67 **(C)** and PCNA **(D)** expression were detected to evaluate the effects on cell proliferation after COTL1 knockdown in U87 and U251 cells. \* $P < 0.05$ .



**Figure 5** COTL1 depletion inhibits tumor proliferation and growth of GBM cells in vivo. **(A)** Tumor growth curve of control or COTL1 stably depletion U87 cells were injected into nude mice, and after 14 days, tumor volume were evaluated every 3 days until 29 days (n=6) (left); Representative images of tumors from each group. **(B)** COTL1 expression level in tumor tissues were detected by IHC analysis. **(C)** Ki67 expression level in tumor tissues was detected through IHC assays. \* $P < 0.05$ .

affect the migration and invasion of cells, particularly cancer cells. We next should assess whether COTL1 affects the migration and invasion of GBM cells.

In conclusion, we here found the abnormal high expression of COTL1 in human GBM tissues. The expression of COTL1 was correlated with clinical pathological features and the prognosis of patients with GBM. Through the in vitro and animal assays, we found COTL1 promoted the proliferation of GBM cells. We therefore provide a novel and promising therapeutic target for the treatment of GBM.

## Ethics Statement

Our study was approved by the Ethics Committee of the Second People's Hospital of Lianyungang City. The

clinicopathological characteristics of 66 patients with GBM were respectively obtained and analyzed. All of the patients' consent was informed consent, and all of them were conducted in accordance with the Declaration of Helsinki. Animal assay procedures involved in this study were approved by Institutional Animal Care and Use Committee (IACUC) of the Second People's Hospital of Lianyungang City. Written confirmation has been given that all experiments were performed following the ethical guidelines of Second People's Hospital of Lianyungang City.

## Disclosure

The authors report no conflicts of interest in this work.



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