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Budding uninhibited by benzimidazoles 1 promotes cell proliferation, invasion, and epithelial-mesenchymal transition via the Wnt/β-catenin signaling in glioblastoma

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ABSTRACT

The pathogenesis and progression of GBM (glioblastoma), as one of the most frequently occurring malignancies of the central nervous system, are regulated by several genes. BUB1 (budding uninhibited by benzimidazoles 1) is a mitotic checkpoint that plays an important role in chromosome segregation as well as in various tumors. However, its role in glioma is unknown. The current study discovered prominently elevated BUB1 in glioma and a significant relationship between BUB1 expression, a high World Health Organization grade, and a poor prognosis in glioma patients. Moreover, BUB1 triggered EMT (epithelial-mesenchymal transition) apart from promoting glioma cell proliferation, migration, and infiltration. Besides, BUB1 promoted EMT by activating the Wnt/β-catenin axis. As implied by our study, BUB1 probably has the potential as a target for GBM management.

1. Introduction

Among tumors of the central nervous system, glioblastoma (GBM) is the most frequently occurring and hostile one [1]. Despite ongoing advancements in treatment strategies such as surgery, radiotherapy, chemotherapy, and immunotherapy, its median life expectancy remains less than 15 months, and its five-year survival rate is less than 5% [2,3]. Therefore, finding new potential therapeutic targets to prolong patient survival is essential.

EMT (epithelial-mesenchymal transition) refers to the epithelial cell conversion into mesenchymal cells, during which the adhesion capacity between tumor cells is lost, and epithelial polarity disappears, ultimately enhancing the invasion and migration of cells. EMT is a mechanism of tumor cell invasion, metastasis, and recurrence [4,5]. Studies have shown that the inhibition of EMT can reduce the probability of tumor cell metastasis [6]. The Wnt/β-catenin signaling pathway is mainly involved in the pathogenesis, progression, deterioration, and metastasis of multiple types of human cancers [7]. Previous research has linked abnormal activation of the canonical Wnt/β-catenin signaling to decreased survival in GBM patients [8], emphasizing the need further to investigate the role of Wnt signaling in GBM progression.

A serine/threonine kinase called BUB1 (budding uninhibited by benzimidazoles 1) exerts a pivotal function in the chromosomal

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segregation as a mitotic checkpoint. According to prior research, the role of BUB1 in carcinoma development and management is crucial [9]. BUB1 expression is linked to a poor clinical prognosis in breast cancer patients. BUB1 knockdown reduced the cancer stem-cell potential of MDA-MB-231 breast carcinoma cells [10]. BUB1 was overexpressed among myeloma patients, and compared to patients with early-stage myeloma, the expression of BUB1 in patients with advanced-stage myeloma was significantly higher. Knockdown of BUB1 in cells derived from human myeloma leads to less frequent errors of chromosomal segregation in the mitotic cells [11]. Besides, BUB1 promotes tumor cell proliferation by activating SMAD family member 2 in hepatic carcinoma [12].

Although the effects and regulatory mechanisms of BUB1 have been studied in other tumors, its role in GBM has received little attention. This study aimed to measure BUB1 expression and investigate its biological significance in GBM. These findings could point to a potential therapeutic target for GBM.

2. Materials and methods

2.1. Cell culture

We procured GBM cell lines (U87 and U251) from the American Type Culture Collection (VA, USA). All cells were cultured in DMEM (Dulbecco's modified Eagle's medium; Gibco, USA) with 10% FBS and 1% streptomycin/penicillin (Gibco, USA) in a humidified incubator under 37 °C and 5% CO_2 conditions.

2.2. Lentiviral transfection and establishing stable cell lines

ShRNA (short-hairpin RNA)-encoding LVs (lentiviral vectors) against BUB1 (LV-shBUB1), as well as corresponding blank vectors (LV-control/LV-shNC), were all from GenePharma Biotech (Shanghai, China). Infectious lentiviruses were used to infect cells for 16 h before changing the medium. Puromycin (5 μg/mL; Sigma German) was used to select stable cells after 7 days.

2.3. Cell Counting Kit-8 (CCK-8) assay

The proliferative potential of cells was examined utilizing a CCK-8 kit (MCE, China) by following the manufacturer's instructions. Each well of 96-well microplates was seeded with 1,000 cells and supplied with 10 μL of CCK-8 buffer. The absorbance values of cells from day 1 to day 5 were analyzed per the manufacturer's instructions. After 2 h of incubation following the aforementioned procedure, the 450-nm absorbance per well was determined.

2.4. Colony formation assay

About 500 GBM cells were seeded per well of 6-well microplates and subjected to10-d cultivation in DMEM. After a 10-min immobilization with formaldehyde (4%), the colonies were stained for 15 min with 1% crystal violet (Beyotime, China), followed by counting and analysis.

2.5. Wound healing analysis

About 1×10^6 GBM cells were seeded per well of a 6-well microplate, cultured overnight, and then scratched using a 200-μL pipette tip. Following twice washing with PBS (phosphate-buffered saline), the cells were incubated using 1% FBS-involving DMEM. At 0 and 12 h, wound closure was photographed using an inverted microscope. Wound closure space was measured via Image J, while wound closure rate was computed by comparing it with negative controls' results. Cell mobility = ((Scratch width at 0 h - Scratch width after culture)/Scratch width at 0 h) × 100%.

2.6. Transwell assays

The capacity of cell invasion was examined utilizing Transwell chambers (Millipore, USA). First, 1:8 dilution of Matrigel (150 μL; BD Biosciences, USA) was coated onto the chambers. The upper chamber was seeded with 1×10^5 cells in FBS-absent DMEM (100 μL), while 25% FBS-involving DMEM (600 μL) was added to the lower chamber. This was followed by a 24-h incubation of cells under 37 °C conditions. Later, the culture medium in the upper chamber was discarded, and the Transwell chambers were washed with PBS twice. Following a 10-min immobilization with formaldehyde (4%), the cells were subjected to 15-min Giemsa staining. Counting of migrated and invaded cells were accomplished in 5 random fields of view at 400X. The experimentation was triplicated.

2.7. Quantitative real-time PCR

The TRIzol reagent (Invitrogen, China) was used to extract total RNA, and complementary DNA (cDNA) was synthesized from RNA templates. For BUB1, the PCR primers were as follows: forward, 5′-TGGGAAAGATACATACAGTGGGT-3′; reverse, 5′-AGGGGATGACAGGGTTCCAAT-3′. The gene expression level was determined using a real-time detection system and the SYBR Green PCR mix (Qiagen, USA) (ABI, USA). The endogenous control was glyceraldehyde 3-phosphate dehydrogenase (GAPDH).

2.8. Protein extraction and western blotting

Radioimmunoprecipitation assay (RIPA) lysis buffer was adopted for total protein extraction from the GBM cells, which involved phenylmethylsulfonyl fluoride and a cocktail. According to the manufacturer's protocol, the protein concentration was determined using bicinchoninic acid assay kits (Beyotime, China). Protein samples were isolated using SDS-PAGE electrophoresis (10% gel), then transferred to PVDF (polyvinylidene fluoride) membranes. The next step was a 1-h blockage of membranes with 5% skimmed milk-involving TBS (tris-buffered saline) at ambient temperature and a subsequent overnight incubation at 4 °C using primary antibodies. The antibodies used are as follows: BUB1 (Abways, USA), E-cadherin, N-cadherin (Abways, USA), vimentin (Abways, USA), E-cadherin (Abways, USA), glycogen synthase kinase-3β (GSK-3β) (Abways, USA), and glyceraldehyde-3-phosphate dehydrogenase (Beyotime, China). After washing with TBS with Tween 20 thrice, a further 1-h incubation of membranes was accomplished using a secondary antibody at ambient temperature. The membranes were then washed three times more. Finally, the membranes were exposed to chemiluminescent reagents using an image analyzer (Bio-Rad, CA, USA) (Millipore, MA, USA).

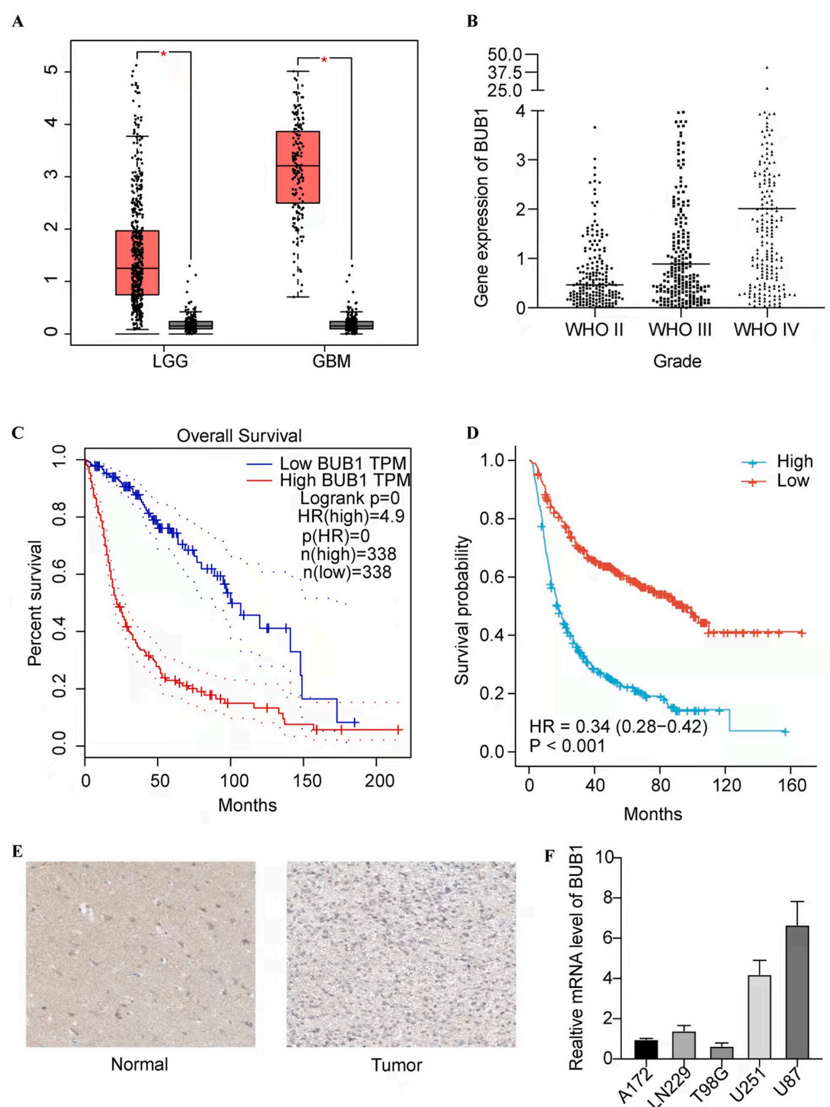

Fig. 1. In the GBM (glioblastoma) tissues, BUB1 (budding uninhibited by benzimidazoles 1) was up-regulated, which was linked to a poor outcome. (A) Compared to the normal cerebral tissues, BUB1 was upregulated in the glioma (low-grade) and GBM tissues, according to the GEPIA (Gene Expression Profiling Interactive Analysis) database-based analysis. (B) The World Health Organization grade was linked to the BUB1 expression. (C–D) Overall survival plots for the glioma patients either highly or lowly expressing BUB1 (GEPIA and Chinese Glioma Genome Atlas databases). (E) Compared to the normal tissues, up-regulation of BUB1 was noted in the GBM tissues. (F) RT-PCR (real-time polymerase chain reaction) findings of BUB1 levels in the GBM (A172, LN229, T98G, U87, and U251) cells.

2.9. Statistical analysis

The Shapiro-Wilk test was used to test the normality of the data. Normally distributed data were shown as the means ±SDs. Analysis of data and computation of *P*-values were accomplished via GraphPad Prism 7.0. The two-sided unpaired Student's *t*-test or one-way ANOVA were used to determine the statistical difference between two or multiple groups. Experiments were all triplicated, and P values < 0.05 were regarded as statistically significant.

3. Results

3.1. BUB1 was overexpressed in glioma and was associated with a poor prognosis

To determine the critical role of BUB1 in glioma, the BUB1 level analysis was accomplished by utilizing the GEPIA (Gene Expression Profiling Interactive Analysis) database. BUB1 expression was increased in low-grade glioma and GBM tissues, and BUB1 expression in GBM was upregulated in LGG (Fig. 1A). According to CGGA (Chinese Glioma Genome Atlas) database data, there was a positive relationship between glioma grade and BUB1 level (Fig. 1B). Then, survival analysis was accomplished by exploiting the GEPIA and CGGA databases, revealing that the overall life expectancy of glioma patients with higher BUB1 expression was shorter (Fig. 1C and D). Based on the Human Platelet Antigen database (www. protinaltas.org), the BUB1 expression in tumor tissue was significantly higher than that in non-tumor tissue (Fig. 1E). Furthermore, we compared BUB1 expression levels in glioma cell lines A172, LN229, T98G, U251, and U87, and found that BUB1 was expressed in U87 and U251 (Fig. 1F).

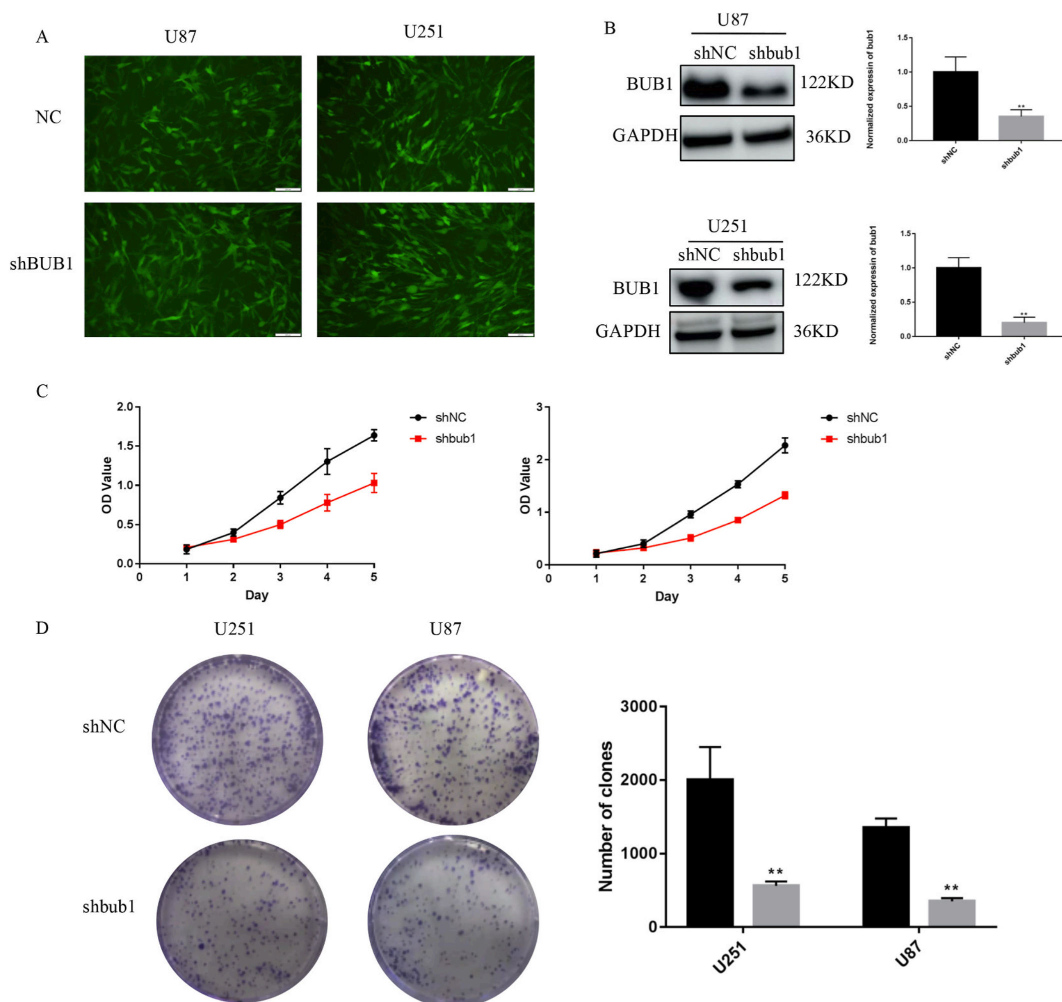

Fig. 2. BUB1 facilitated the in-vitro carcinoma proliferation in GBM cells. (A) Short-hairpin RNA against BUB1 was effectively transfected into U87 and U251 cells. (B) BUB1 knockdown in the U87 and U251 cell lines. (C) The viability of transfected U87 and U251 cells was determined using the Cell Counting Kit-8 assay. (D) Cloning capacity assessment of the transfected U87 and U251 cells was accomplished via the colony formation assay (**P < 0.01).

3.2. Effects of BUB1 depletion on the cell proliferation and colony formation of GBM cells

Given the tight linkage of high BUB1 expression to the poor outcome of glioma, especially in GBM, the functionality of BUB1 in the GBM cells was assessed. Transfection of the U87 and U251 cells with shBUB1 was accomplished, with a transfection efficiency of up to 90%. Western blot was employed to validate the knockdown efficiency (Fig. 2A and B). Subsequently, CCK-8 combined with colony formation assays were adopted to examine the proliferation ability of U87 and U251 cells. As expected, significant cell growth suppression was observed in the knockdown group compared to the control group in both U87 and U251 cells, and BUB1 depletion significantly suppressed U87 and U251 cell proliferation (Fig. 2C). Furthermore, we also investigated the role of BUB1 in cell colony formation; the result showed that U87-shBUB1 and U251-shBUB1 cells had a markedly lower number of colonies than the control shRNA-transfected cells (1892 ± 345 vs. 541 ± 109 for U251 and 1421 ± 232 vs. 278 ± 69 for U87; Fig. 2D). Therefore, we confirmed the pivotal regulatory function of BUB1 in the proliferation and colony formation of glioma cells.

3.3. Effects of BUB1 on the migration and invasion of the GBM cells

In order to explore the potential functional role of BUB1 in GBM, wound-healing and transwell assay were performed. Compared to the negative control groups, the BUB1-knockdown groups exhibited prominently weaker cellular migration ($P = 0.008$ for U87; $P = 0.009$ for U251, compared to the shNC group; Fig. 3A and B). Furthermore, glioma cells exhibited lower invasive ability in the Transwell assay after BUB1 knockdown in U87 and U251. The numbers of invasive cells for U87-shNC and U87-shBUB1 are 98.33 ± 20.21, 33.67 ± 8.85, and the P value was 0.0069, whereas the numbers of invasive cells for U251-shNC and U251-shBUB1 are 56.67 ± 9.61, 15.33 ± 3.51, and the P value was 0.0022 (Fig. 3C). As implied by these findings, BUB1 enhanced the capacities of U87 and U251

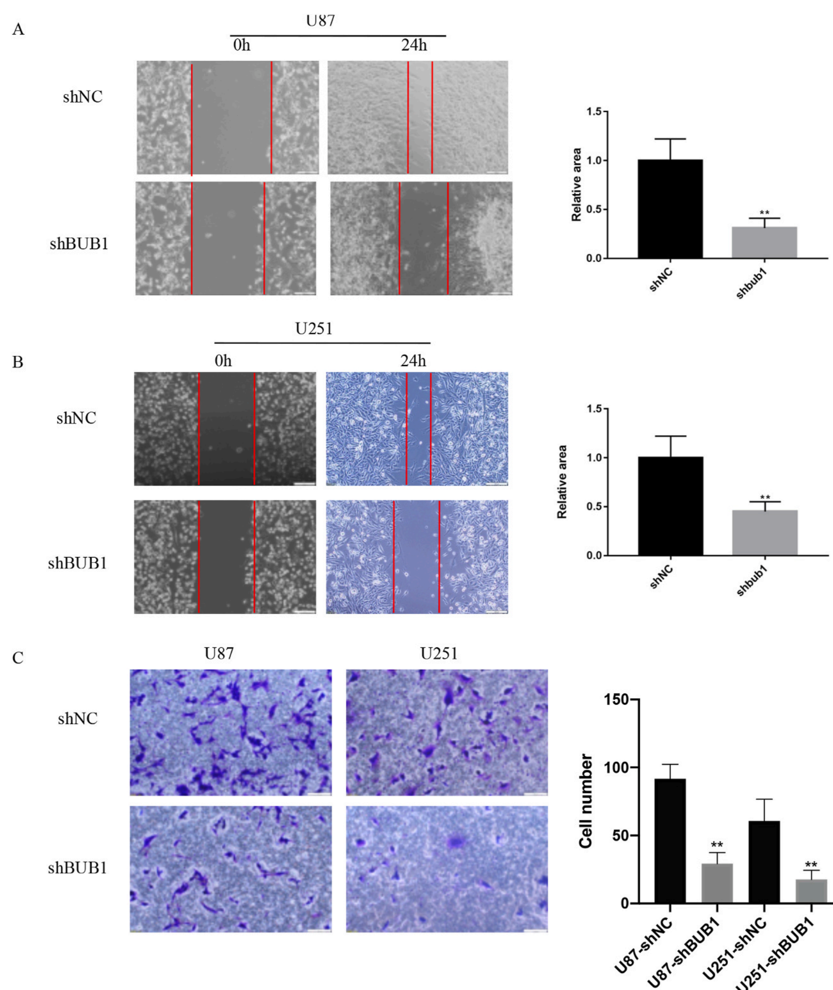

Fig. 3. Budding uninhibited by benzimidazoles 1 (BUB1) knockdown suppressed the abilities of GBM cell invasion and migration in vivo. (A–B) The wound healing assay was used to test the migration abilities of transfected U87 and U251 cells. (C)The capacities of transfected U87 and U251 cell invasion were assayed with Transwell chambers. (**$P < 0.01$).

cell invasion and migration.

3.4. BUB1 modulated the expression of EMT-related proteins

Although major studies of EMT have been limited to epithelial tumors, there is growing evidence that EMT-related processes play a similar role in gliomas. EMT is closely involved in carcinoma cell migration and infiltration. We examined the expression of EMT markers to verify if BUB1 facilitates cell migration and infiltration via EMT. The Western blot analysis revealed that the epithelial marker E-cadherin was upregulated in the BUB1-down-expressed glioma cells, whereas the mesenchymal markers N-cadherin and vimentin were downregulated. These data showed that BUB1 modulated the migration and invasion of glioma cells via EMT (Fig. 4A).

3.5. BUB1 activated the Wnt/β-catenin signaling pathway

According to prior research, the EMT in GBM is facilitated through the initiation of the Wnt/β-catenin axis [13]. As further determination of the potential signaling pathways modulated by BUB1 was necessary, we investigated whether BUB1 modulated the Wnt/β-catenin axis in U87 and U251 cells. As demonstrated by Western blot results, the GSK-3β and β-catenin levels were lower for the BUB1-downregulated glioma cells (Fig. 4B).

4. Discussion

Our findings shed light on the underlying mechanism of BUB1-regulated EMT in GBM. BUB1 was overexpressed in GMB and was linked to tumor grade and patient survival. BUB1 regulates glioma cell EMT via the Wnt/β-catenin axis.

A growing body of evidence suggests that BUB1 plays an important role in the progression of several types of cancer [9–12]. In this study, we successfully identified BUB1 as an oncogene in GBM using bioinformatics. According to The Cancer Genome Atlas and CGGA database-based analyses, we found a prominent correlation of the BUB1 expression with the glioma grade, whereas its negative association with the total survival rate among glioma patients. Subsequently, Human Protein Atlas further confirmed its expression in the tissues of patients with GBM and revealed its high levels in the U87 and U251 cells. Suggestively, BUB1 exerts a functional effect on glioma pathogenesis. As a cell cycle regulator, BUB1 functions crucially in mitosis by encoding serine/threonine protein kinases, phosphorylating the mitotic checkpoint members, and eliciting spindle checkpoints [14,15]. Although studies have shown that BUB1 is overexpressed in various carcinomas, including gastric, ovarian [16,17], and low-grade breast carcinomas, its high expression is associated with a favorable outcome [18].

Next, we evaluated the function of BUB1 in GBM cells. The results showed that the downregulation of BUB1 pronouncedly repressed cell proliferation, migration, and infiltration of GBM cells. Given the complicated function of EMT in carcinoma metastasis and recurrence through the facilitation of cellular migration/invasion or probable other pathways [19], we further investigate the effect of BUB1 on EMT. Knockdown of BUB1 repressed the expressions of N-cadherin and vimentin genes and EMT regulatory proteins in U87 and U251 cells, whereas it facilitated the E-cadherin gene expression to regulate EMT. These data elucidate the underlying molecular mechanisms of the BUB1-modulated EMT process, suggesting that the management of glioma may be improved by targeting BUB1.

Previous studies have shown that BUB1 may affect glioma cells by regulating EMT through the Wnt/β-catenin axis initiation.

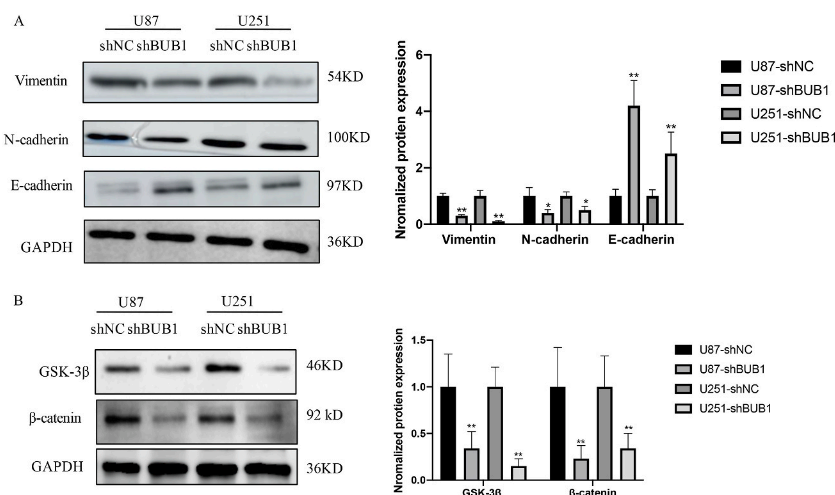

Fig. 4. In GBM cells, the short-hairpin RNAs against BUB1 inhibited the EMT (epithelial-mesenchymal transition) through blockage of the Wnt/β-catenin axis. (A) Western blot results of EMT-associated proteins (e.g., E-cadherin, N-cadherin, and vimentin) in the transfected U87 and U251 cells. (B) The Western blot assay for Wnt/β-catenin-related proteins glycogen synthase kinase-3β and β-catenin (*$P < 0.05$, **$P < 0.01$).

Activation anomaly of a Wnt/β-catenin signal promotes EMT in many tumors, including GBM [20,21]. Most β-catenin proteins are attached to the cell membrane and are rarely found in the cytoplasm under normal conditions. When a Wnt/β-catenin signal activation error occurs, β-catenin degradation is suppressed. Subsequently, the β-catenin up-regulates the EMT-associated genes (e.g. N-cadherin, vimentin, and slug genes) after entry into the carcinoma cell nucleus, thereby achieving the EMT mediation [22]. Western blot revealed the ability of shBUB1 to repress the GSK-3β and β-catenin gene expressions, showing agreement with the wound healing and Transwell assay findings.

The combination of bioinformatics analysis and cell transfection technique allowed us to detect not only the aberrant expression of BUB1 in GBM but also investigate its effect *in vitro*. Another strength of the current study was to investigate the involvement of Wnt signaling, which provided insight into a potential target axis in GBM treatment. The study's limitations should be acknowledged and addressed in future research. To begin, the clinical data were obtained from databases rather than being validated using samples collected from our own patients. Second, we only looked into the Wnt pathway's role in the progression and EMT of GBM caused by BUB1, and we did not look into other pathways that might be involved. Therefore, more research is needed to address these limitations.

To summarize, we identified BUB1, a tumor-related gene in GBM, may function as an oncogene by promoting tumor proliferation, infiltration, and EMT through abnormal Wnt/β-catenin axis initiation, which offers new insights and probable therapeutic targets for gliomas.

Declarations

Author contribution statement

Zhang Jinshi: Wenjin Wei: Qinglin Zhong: Kaiming Feng: Ruijin yang: Qiuhua Jiang: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

No data was used for the research described in the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e16996.

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