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β-Catenin is involved in Bex2 down-regulation induced glioma cell invasion/migration inhibition

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ABSTRACT

Previously, we found that brain expressed X-linked gene 2 (Bex2) regulates the invasion/migration ability of glioma cells. However, the mechanism of this effect remains unknown. In current study, we reported that Bex2 down-regulation inhibited glioma cell migration and invasion by decreasing the nucleus and cytoplasm protein level of β-catenin. We found that the protein levels of Bex2 and β-catenin were up-regulated and showed direct correlation in glioma tissues. Bex2 down-regulation significantly decreased β-catenin protein levels but not its mRNA levels. Furthermore, the decreased protein level of β-catenin was located in the nucleus and cytoplasm but not in the cell membrane. Further study found that the effects of Bex2 down-regulation on the invasion and migration of glioma cell could be reversed by β-catenin over-expression. Taken together, Bex2 affects the invasion and migration ability of glioma cells by regulating β-catenin.

1. Introduction

Glioblastoma is a kind of highly aggressive and incurable tumor with a median survival time of 12 months in China [1] in our currently available treatment. These tumors are one of the most lethal tumors because the tumor cells invade extensively into the nearby normal brain tissues leading to recurrence of the tumor [2]. However, the mechanisms of invasion are largely unknown.

The brain expressed X-linked (Bex) gene family is an X-chromosome-linked gene family and its known members include Bex1, Bex2, Bex3, Bex4, Bex5, and Bex6 [3,4]. In 2002, Yang et al. [5] identified Bex2 by the high-throughput sequencing of the embryonic-cerebral cDNA library. Recently, Bex2 was found to be involved in some cancer progression. For example, Bex2 is up-regulated in a subset of primary breast cancers and mediates apoptosis induced by nerve growth factor/nuclear factor-kappa B inhibition in breast cancer cell lines [6]. Furthermore, Bex2 not only may regulate mitochondrial apoptosis and the G1 cell cycle but also has a functional interplay with c-Jun/JNK and p65/RelA and participates in a feedback loop with ErbB2 in breast cancer [7–9]. However, studies about the effect of Bex2 on in glioma development showed contrast results [10,11]. Findings in our laboratory showed that Bex2 is highly expressed in glioma tissues and Bex2 down-regulation inhibits glioma cell growth by regulating JNK/c-Jun signaling and p65/RelA [12]. Furthermore, we firstly reported that Bex2 down-regulation inhibits glioma cell invasion and migration and impacts the expression of MMP-2 and N-Cadherin [13]. However, the mechanism of this effect was largely unknown.

As we know, the process where glioma cells escape from the initial tumor site and migrate into the surrounding brain parenchyma is involved in a diverse array of biological incidents [14–16]. One important process is reorganization of the cytoskeleton, assembly and disassembly of cell–cell adhesions [17,18]. Studies have demonstrated the cadherin/catenin complex is the main regulator for intercellular adhesion [18–20]. One important component of cadherin/catenin complex is β-catenin, who connects extracellular adhesion molecules and intracytoplasmic cytoskeleton, such as actin, and plays a critical role in maintaining the normal morphological structure of epithelial cells, as well as intercellular connections [21,22]. In addition, most of the invasion/migration-related proteins, such as matrix metalloprotein (MMP), CD44 and

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fibronectin are regulated by β-catenin-mediated Tcf/Lef transcription factors in the Wnt signal pathway [23–27]. In the Wnt pathway, free β-catenin in cytoplasm is imported into the nucleus and binds to Tcf/Lef transcription factors, thus impacting the transcription of invasion/migration-related genes, including MMP-2 [28] and eventually affecting the invasion/migration ability of glioma cell [29].

In this study, we explore the mechanism of the effect of Bex2 on glioma cell migration/invasion. We found that the inhibition effect of Bex2 down-regulation on glioma cell migration/invasion was mediated by decreasing the protein level of β-catenin.

2. Material and methods

2.1. Glioma and nontumorous human brain tissues

All tissue samples were collected from the Affiliated Hospital of Xuzhou Medical College during 2010–2012 (Xuzhou, China). The gliomas ($n = 33$) were histologically diagnosed by the Department of Pathology at the Affiliated Hospital of Xuzhou Medical College based on the World Health Organization grading system [30]. As controls, human nontumorous brain tissues ($n = 17$, mostly from the cortex) were obtained from patients with decompressive surgery after physical injuries to the brain. These specimens were collected from the patients registered at the above-mentioned hospital, and written informed consent was obtained from the patients. This study was approved by the ethics committee of the hospital.

2.2. Cell culture and reagent

Human U251 and U87 cell lines were purchased from Shanghai Cell Bank of the Chinese Academy of Sciences (Shanghai, China). Cells were cultured in 5% CO_2 and 95% humidified atmosphere air at 37 °C in DMEM/F-12 (Gibco, Carlsbad, CA, USA), supplemented with 10% FBS (Evergreen Biological Engineering Co., Ltd., Hangzhou, China).

2.3. Transient transfection of β-catenin, β-catenin small interfering RNA and Bex2 small interfering RNA

Transfection of Bex2 siRNA, β-catenin and its siRNA were performed using the Lipofectamine™ 2000 transfection reagent (Invitrogen) according to the manufacturer's instructions. The β-catenin plasmid was purchased from Addgene (Plasmid #16518, Addgene Inc., Cambridge, MA, USA). The sequence of Bex2-si472 (Shanghai GenePharma Co.) targeting human Bex2 are 5′-CAAGGAUGAGA GAGGAGAATT-3′. The sequence of β-catenin siRNA (Shanghai GenePharma Co.) targeting human β-catenin are 5′-CAUGCAGAAU ACAAAUGAUTT-3′. SiNC: 5′-UUCUCCGAACGUGUCACGUTT-3′. All of the transfections were performed three times independently.

2.4. Reverse transcription-polymerase chain reaction

The extraction of total RNA from cells was achieved using the TRIzol Reagent (Tiangen Biotech Co.). First-strand cDNA was synthesized using the Reverse Transcription Reagents (TaKaRa RNA PCR Kit (AMV) Ver. 3.0) according to the manufacturer's instructions. Primers (Sangon Biotech Co.) for Bex2 were as follows: sense: 5′-CGGAATTCATGGAGTCCAAAGAGGAACG-3′ and antisense: 5′-CGGGATCCGTGGGCATAAGGCAAAACTCATCG-3′. The primers for β-actin were: sense: 5′-CTGGGACGACATGGAGAAAA-3′ and antisense: 5′-AAGGAAGGCTGGAAGAGTGC-3′. The primers for β-catenin were: sense: 5′-AGGAAGCTTCCAGACACGC-3′ and antisense: 5′-CGCACTGCCATTTTAGCTCC-3′. The relative band intensities were determined using Image J software.

2.5. Wound healing assay

Twenty-four hours after transfection, monolayers were scratched with a plastic pipette tip and washed twice with PBS to move away dead cells and hatched in serum-free media. At the designated time (0, 24 and 48 h after scratching), five randomly selected fields were acquired under an inverted microscope (Olympus IX71, Tokyo, Japan). In each field, the amount of cells across the wound was quantified and the experiment was performed at least three times. The mean number of cells of the control group was described as 100% and the mean number of other groups was normalized by means of the control group, respectively.

2.6. Transwell invasion assays

Cell invasion assay using a transwell system was performed as described previously [19]. Filters were precoated with matrigel (BD Biosciences, Franklin Lakes, NJ, USA). Approximately 5×10^4 cells in serum-free media were added to the top chamber and the bottom chamber was filled with DMEM containing 10% FBS. After 24 h of incubation, the cells on the upper surface were gently removed with a cotton swab and the membrane was fixed in 4% methanol for 30 min and stained with a 0.1% crystal violet solution for 30 min. The cells that migrated to the lower side of the membrane were captured using an Olympus IX71 inverted fluorescence microscope and the cell number was counted using Image J software. Experiments were performed in 4 biological replicates.

2.7. Western blot analysis

The cells were cleaved and the protein lysates were subjected to 10% SDS–PAGE, transferred to a PVDF membrane (Millipore), and probed with primary antibodies (anti-β-catenin, anti-Bex2, anti-β-actin) and secondary antibodies. Bound antibodies were detected by the Pierce ECL Plus Western Blotting Substrate (Thermo Fisher Scientific Inc.) and exposed to X-ray films. Band densities were quantified by Image-Pro Plus Software (Media Cybernetics, Inc.). The relative amount of proteins was determined by normalizing the densitometry value of interest to that of the internal loading control.

2.8. Statistical analysis

Quantitative data were presented as means ± SEM. Statistical significant level was set at 0.05. One-way ANOVA and Student's *t*-test were adopted. Biostatistical analysis was achieved using Office Excel 2004 (Microsoft Corporation) and SPSS software (SPSS version 17.0).

3. Results

3.1. Expression of Bex2 and β-catenin in glioma tissues

To study the possible roles of Bex2 and β-catenin in the development of human glioma, we first examined their protein levels in clinical glioma samples. In our previous study [12], we reported that Bex2 was highly expressed in human glioma tissues. In this study, as is shown in Fig. 1A and B, we found that Bex2 and β-catenin levels are significantly up-regulated in glioma tissues. The protein level of Bex2 in glioma samples was approximately 2.2-fold higher and β-catenin level was about 2.3-fold higher than in non-tumor tissues, in line with the previous studies [12,19].

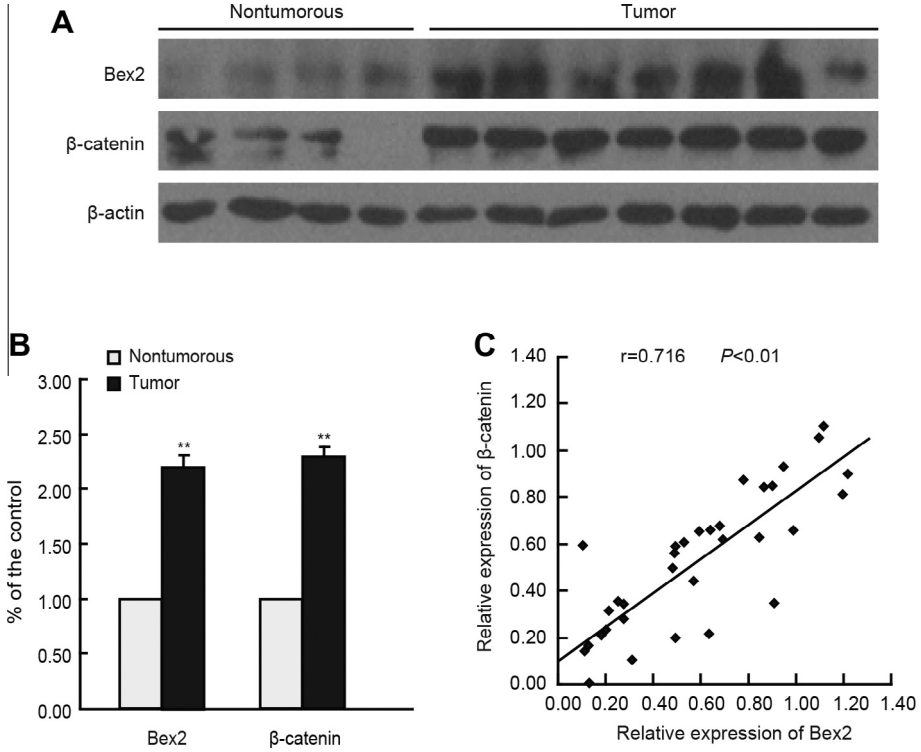

Fig. 1. Expression of Bex2 and β-catenin in glioma tissues. (A) The protein levels of Bex2 and β-catenin in nontumor tissue (four samples showed) and glioma tissue (seven samples showed) examined by Western blotting. (B) Quantification of Bex2 and β-catenin protein levels in glioma tissues ($n = 33$) and nontumor brain tissues ($n = 17$) ($^{**}P < 0.01$). (C) Direct correlation between Bex2 and β-catenin protein levels ($r = 0.716$, $P < 0.01$).

Additionally, the protein levels of Bex2 and β-catenin showed direct correlation with each other (Fig. 1C, $r = 0.716$, $P < 0.01$). These results provided us the initial evidence that Bex2 and β-catenin may play some roles in the development of human gliomas. Furthermore, these results also indicated a potential regulation relationship between Bex2 and β-catenin.

3.2. Bex2 down-regulation decreased β-catenin protein level

To explore the possibility that Bex2 regulates β-catenin, we examined β-catenin expression levels after Bex2 down-regulation in the U251 and U87 cell lines. We found that β-catenin levels significantly decreased after Bex2 down-regulation in both cells (Fig. 2A and B). However, β-catenin at the nucleotide level showed no difference between control and Bex2 down-regulation group in U251 cells (Fig. 2C and 2D). To test whether β-catenin regulates Bex2, we examined Bex2 levels after β-catenin down-regulation in the U251 and U87 cell lines. Interestingly, we did not found any Bex2 protein level change after β-catenin down-regulation (Fig. 2E and F), suggesting that Bex2 regulated β-catenin at the post-transcription level and this regulation is unidirectional.

It is reported that β-catenin shows a broad intracellular distribution and presents in the cell membrane, cytoplasm, and nucleus. As a key molecule in the downstream of the Wnt signal pathway, free β-catenin is imported into the nucleus and binds to TCF/Lef transcription factors to initiate the transcription of downstream invasion/migration-related genes, such as MMP2/7 and fibronectin, and eventually impacts the invasion/migration ability of glioma cells [24,26,27,31]. On the one hand, β-catenin is an important component of the cadherin/catenin complex, which connects extracellular adhesion molecules to the intracytoplasmic cytoskeleton and plays a critical role in maintaining the normal morphological structure of epithelial cells and intercellular connections [21,32]. We wonder which part of β-catenin level was affected by Bex2 down-regulation. We extracted and separated the total, membrane, cytoplasm and nucleus fraction of β-catenin and found that the total β-catenin level decreased after Bex2 down-regulation, in line with our findings in Fig 2A and B. Furthermore, the decreased β-catenin levels were mainly located in the cytoplasm and the nucleus, but not in the cell membrane (Fig. 2G and H). The above results suggested that Bex2 might affect β-catenin transcription function.

3.3. β-Catenin over-expression abolished the inhibition effects of Bex2 down-regulation on the invasion/migration of glioma

Previously, we found that Bex2 down-regulation decreased glioma cell migration/invasion [13]. Our results of Fig. 2A, B, G, and H showed that Bex2 regulated β-catenin protein levels. Therefore, is β-catenin involved in the effects of Bex2 on the invasion/migration ability of glioma? To address this question, we co-transfected Bex2-si472 and β-catenin to examine whether β-catenin over-expression could rescue the effect of Bex2 down-regulation on glioma cell migration/invasion. As is showed in Fig. 3A–C, the co-transfection effect of Bex2-si472 and β-catenin was very good. On the basis of this good co-transfection system, we found that Bex2 down-regulation decreased glioma cell invasion, which is examined by transwell assay and consistent with our previous study [13]. In addition, β-catenin over-expression promoted glioma cell invasion, in line with the previous reports [33]. Interestingly, the effect of Bex2 down-regulation on the invasion of U251 and U87 cells was reversed by β-catenin over-expression (Fig. 3D and E). Furthermore, we got the similar phenomenon using wound healing assay in both cells (Fig. 4 A–D). These results indicated that Bex2 regulated the invasion/migration ability of glioma cells through β-catenin.

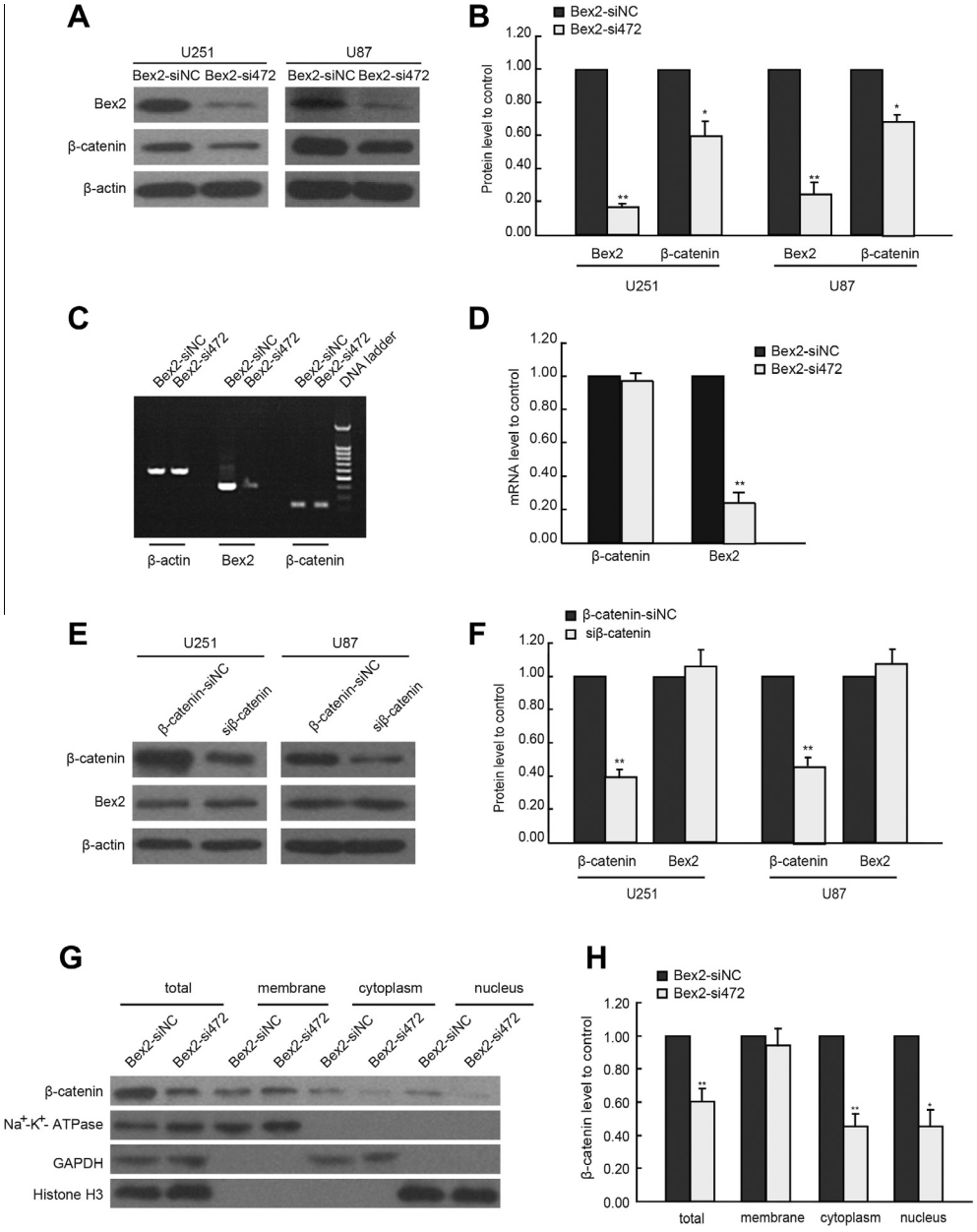

Fig. 2. Bex2 down-regulation decreased β-catenin protein level. (A) Bex2 down-regulation decreased β-catenin total protein level in the U251 and U87 cells examined by Western blotting. (B) Quantitative results of A. (C) The nucleotide level of β-catenin in the U251 cell lines examined by RT-PCR after Bex2 down-regulation. (D) Quantitative evaluation of β-catenin nucleotide levels. ($^{*}P < 0.05$; $^{**}P < 0.01$). (E) Measuring the protein level of Bex2 after β-catenin down-regulation in the U251 and U87 cell lines examined by Western blotting. (F) Quantitative evaluation of Bex2 and β-catenin levels showed in E. (G) The protein level of β-catenin in the cytoplasm, nucleus and membrane after Bex2 down-regulation in U251 cells for 24 h. Na^{+}–K^{+}-ATPase and GAPDH were used as loading control for membrane and cytosolic protein respectively. (H) Quantitative results of (G). The results were shown as the mean ± SEM of three independent experiments in triplicate ($^{*}P < 0.05$; $^{**}P < 0.01$).

4. Discussion

Bex2 was recently found to be involved in some cancer progression. For example, Naderi et al. found that Bex2 is highly expressed in breast cancer and is involved in the regulation of the proliferation and apoptosis of breast cancer cells [6]. Our previous studies demonstrated that Bex2 is up-regulated in glioma tissues and is involved in glioma cell proliferation and apoptosis regulation by impacting c-Jun NH2-terminal kinase (JNK) activation [12], as well as NF-kB expression [34]. Bex2 over-expression promotes migration and invasion of glioma cells, while Bex2 down-regulation inhibits the migration and invasion of glioma cells [13]. Further study identified that Bex2 down-regulation impacted the expression of MMP-2 and N-Cadherin [13]. However, the above report did not clarify the mechanism of Bex2 in the regulation of the invasion/migration of glioma cells. In the current study, we found that Bex2 and β-catenin were highly expressed in glioma tissues, consistent with our and other's reports [12,35], and showed direct correlation to each other. Bex2 down-regulation decreased the β-catenin protein levels, but not its mRNA level. Further study explored that β-catenin over-expression abolished the inhibition effect of Bex2 down-regulation on the invasion/migration ability of glioma cells.

It is well known that β-catenin exhibits impact on cell migration/invasion through cadherin/catenin complex or its transcription activity [32]. In the former pathway, β-catenin connects

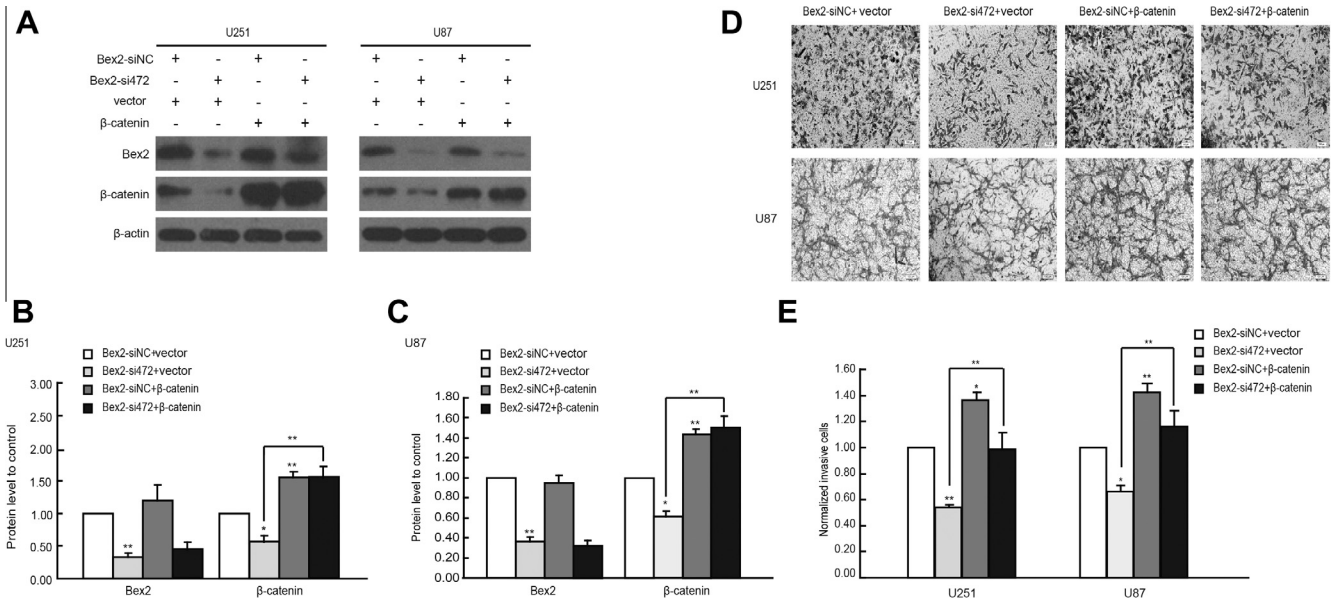

Fig. 3. β-Catenin over-expression abolished the inhibition effects of Bex2 down-regulation on the invasion ability of glioma cells. (A–C) The Bex2 siRNA472 and β-catenin were co-transfected into U251 and U87 glioma cells. Bex2 and β-catenin levels were examined by Western blotting (A) and quantified (B and C). (D) The suppression of invasion induced by Bex2 down regulation was abolished by β-catenin over-expression in U251 and U87 cells. Scale bar, 100 μm. (E) Quantitative analysis of the invasive cell numbers through the filter. Data were presented as mean ± SEM in three biological replicates ($^{*}P < 0.05$, $^{**}P < 0.01$).

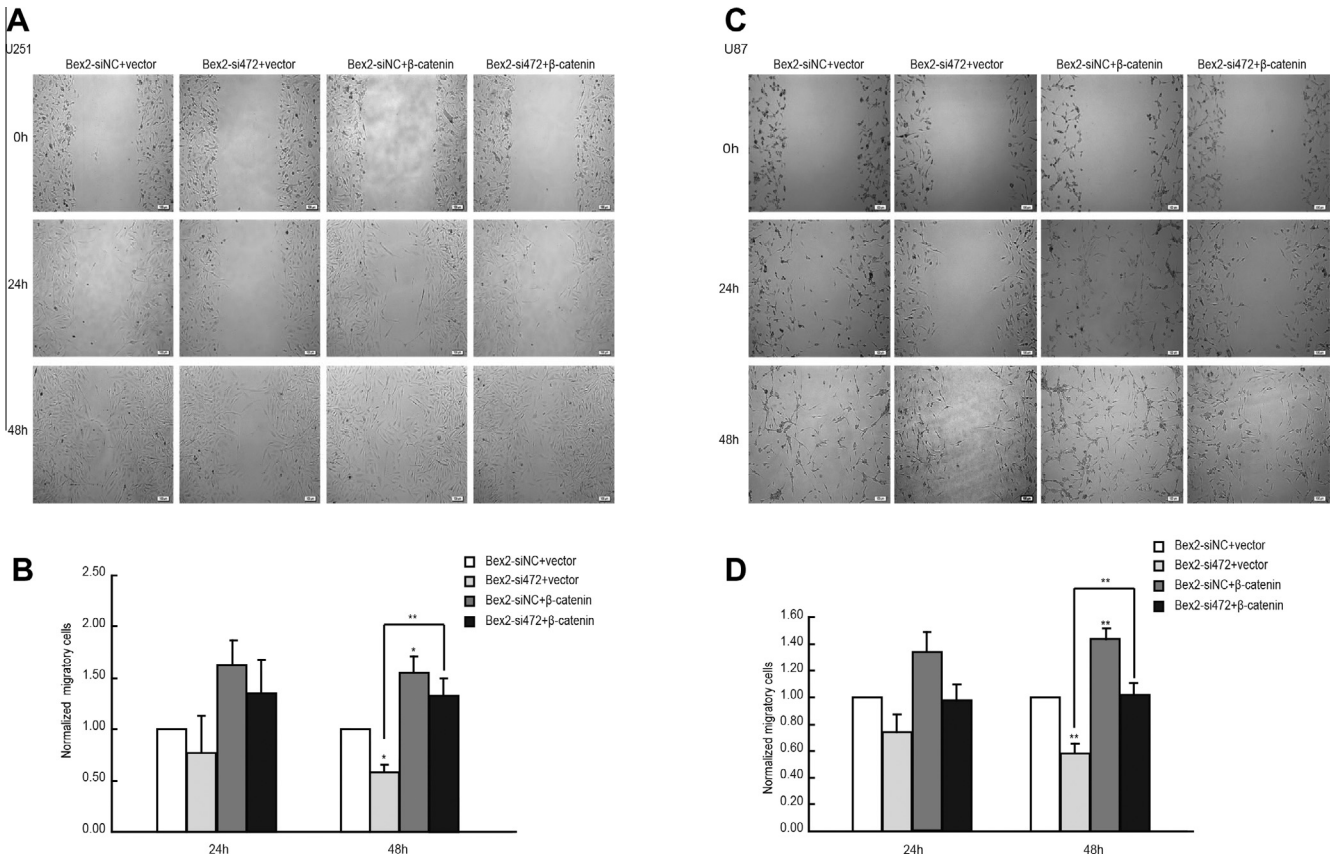

Fig. 4. β-Catenin over-expression abolished the effects of Bex2 down-regulation on the migration ability of glioma cells. (A and C) The suppression of migration induced by Bex2 down regulation was abolished by over-expression of β-catenin in U251 and U87 cells. Scale bar, 100 μm. (B and D) Quantitative analysis of the migratory cell numbers crossing the wound edge. Data were presented as mean ± SEM in three biological replicates ($^{*}P < 0.05$, $^{**}P < 0.01$).

extracellular adhesion molecules and intracytoplasmic cytoskeleton, such as actin, and plays a critical role in maintaining the normal morphological structure of epithelial cells, as well as intercellular connections [21,22]. In the second pathway, β-catenin in the nucleus binds to Tcf/Lef transcription factors and initiates the transcription of invasion/migration-related genes, including

MMP-2 [28] and eventually affects the invasion/migration ability of glioma cells [29]. Our subsequent studies found that the excretion of MMP2 decreased significantly after Bex2 down-regulation [13]. Interestingly, we found that Bex2 down-regulation decreased the β-catenin cytoplasm and nucleus protein levels, but not its membrane level, suggesting that the effect of Bex2 down-regulation on glioma cell invasion/migration did not through regulating cadherin/catenin complex.

What is the mechanism of Bex2 down-regulation on β-catenin cytoplasm protein levels? Naderi et al. reported that increased Protein Phosphatase 2A (PP2A) and its phosphorylation level were observed in Bex2 down-regulation primary breast cancer cells [7]. PP2A is a serine/threonine phosphatase, encoded by the PPP2CA gene in human beings [36]. It was reported that PP2A can affect the dephosphorylation of glycogen synthase kinase 3 beta (GSK3β) at the ser9 site [37]. However, it was found that the level of β-catenin significantly reduced after PP2A downstream is inhibited in the Wnt pathway [38]. Therefore, does Bex2 regulate β-catenin levels through regulating PP2A in glioma? It will be interesting to explore this possibility in the future. Our previous study found that the excretion of MMP2 decreased significantly after Bex2 down-regulation [13]. On the other hand, the result that Bex2 down-regulation decreased the β-catenin nucleus protein level indicates that Bex2 might exhibit its effect on glioma cell invasion/migration by regulating the transcription activity of β-catenin. Thus, to address this question, it is also interesting to examine the effect of Bex2 down-regulation on the mRNA level of transcription target genes of β-catenin. Responses to the above questions will provide an opportunity for a better understanding of how Bex2 impacts the progression of gliomas.

Conflict of interest

None.

Acknowledgments

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