SEPT7 overexpression inhibits glioma cell migration by targeting the actin cytoskeleton pathway

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Received September 15, 2015; Accepted October 23, 2015

DOI: 10.3892/or.2016.4609

Abstract. Glioma cell metastasis is a serious obstacle for surgical treatment and prognosis, of which locomotion of the cytoskeleton is a key contributor of cancer cell spreading. SEPT7 is documented as a cytoskeletal protein with GTPase activity and involved in glioma progression. However, the underlying mechanism of SEPT7 in glioma invasion remains unresolved. Our study investigated whether SEPT7 influences glioma cell migration involved in cytoskeleton modulation. The SEPT7 expression in various glioma cell lines was markedly decreased compared to in normal human brain cells. It was demonstrated that SEPT7 overexpression significantly inhibits LN18 cell migration and chemotaxis induced by IGF-1 ($P<0.01$ and $P<0.01$). Moreover, MMP-2 and MMP-9 were dramatically depressed after SEPT7 upregulation. To understand the mechanisms by which SEPT7 modulates homeostasis of the actin cytoskeleton, the F-actin/G-actin ratio and cofilin expression were determined. The data revealed that the F-actin/G-actin ratio and cofilin were reduced, and p-cofilin increased conversely in cells with SEPT7 overexpression, indicating that SEPT7 reduced glioma cell migration by promoting cofilin phosphorylation and depolymerizing actin. Then, to understand the role of cofilin in SEPT7-mediated actin dynamic equilibrium and cell migration, cofilin siRNA was transfected into cells. Surprisingly, cell migration and actin polymerization which had been improved by SEPT7 siRNA were significantly reversed, and the accompanying cofilin phosphorylation increased, indicating that cofilin phospho-regulation played an important role in SEPT7-mediated cytoskeleton locomotion and glioma cell migration. In conclusion, SEPT7 is involved in glioma cell migration with the assistance of cofilin phospho-mediated cytoskeleton locomotion.

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Key words: SEPT7, glioma, cell migration, cytoskeleton, cofilins

Introduction

Glioma is the most common primary intracranial tumor, accounting for 35.26-60% of human intracranial tumors and including up to 60% of malignant neuroastrocytomas, leading to poor prognosis and high mortality (1). One characteristic of glioma is that glioma cells often invade important functional areas of the normal brain tissue; these 'satellite lesions' surrounding the primary lesion are formed around the primary lesion (2-6). Therefore, simple excision always presents obvious limitations between ensuring cerebral function and removing the tumor fractions (7,8). Since glioma pathogenesis has not been fully defined, the discussion regarding its etiology, pathogenesis, biological characteristics and new effective treatments has become a hot topic in neurosurgery.

SEPT7 is a member of the septins family with GTPase activity, and is also a kind of cytoskeletal protein that is highly expressed in the central nervous system (9,10). Since the physiological functions and biochemical characteristics of SEPT7 protein were discovered, the results have shown that SEPT7 is involved not only in the cytoskeleton and participates in the regulation of cytokinesis, but is also involved in various diseases. As a consequence, the relationship between SEPT7 expression and human glioma has gradually become a concern. The study by Jia *et al* (9) showed that the overexpression of SEPT7 can inhibit cell proliferation and cell cycle arrest in the G0/G1 phase, further suppressing glioma cell growth both *in vitro* and *in vivo*. Suppressing the tumor-suppressor gene SEPT7 can promote glioblastoma cell migration and invasion, and it was verified that SEPT7 affected remodeling of the actin cytoskeleton in glioblastoma cells (11). Upregulation of SEPT7 gene can inhibit cell invasion, and downregulate the expression of MMP2/9, MT1-MMP, and integrin $\alpha(v)\beta(3)$ (12).

Previous studies have demonstrated that cofilin is involved in the homeostasis of actin polymerization and severing (13,14). Cofilin is inactivated by phosphorylation at Ser-3 by LIMK1/2 and TESK1/2 and reactivated by dephosphorylation by SSHs, CIN and the other protein phosphatases, such as PP1 and PP2A (14). Cofilin activation can prompt actin polymerization, while cofilin inactivation, on the contrary, can lead to actin severing. Similarly, SEPT7 has also been shown to be

involved in the migration of actin cytoskeleton *in vitro* and it is conceivable that there is a link between SEPT7 and cofilin in stabilizing actin filaments (15).

Until now, the molecular mechanisms by which SEPT7 impact glioma cell invasion are still unclear. In the present study, we examined the role of SEPT7 as a cytoskeletal proteins with GTPase activity, in the rearrangement of the actin cytoskeleton and tumor cell migration and invasion, to further examine interactions between SEPT7 and cofilin phospho-regulation in LN18 glioma cells.

Materials and methods

Cell culture. The human brain glioma cell lines LN229 and LN18 were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA), U87 and U251 were obtained from Sigma-Aldrich (St. Louis, MO, USA) and the normal human brain gliocyte cell line (HEB) was obtained from Shanghai, China. Cells were cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 100 U/ml penicillin, and 100 mg/ml streptomycin (all from Invitrogen, Carlsbad, CA, USA) and maintained at 37˚C in a humidified incubator of 5% CO_2.

Western blot analysis. Total proteins were extracted using the Tissue or Cell Total Protein Extraction kit (Amresco, Solon, OH, USA) from LN229, LN18, U87 and U251 cell lines. All of the primary antibodies were purchased from Abcam (Cambridge, UK). The proteins were separated by SDS-PAGE followed by electrotransfer to an NC membrane; the membranes were probed using antibodies against SEPT7 (1:2,000), MMP-2 (1:1,000), MMP-9 (1:1,000), cofilin (1:1,000), phospho(ser3)-cofilin (1:1,000), and actin (1:5,000), followed by a horseradish peroxidase (HRP)-conjugated second antibody (GAPDH, 1:10,000) (Abcam). Bands were revealed with ECL reagent (Millipore, Billerica, MA, USA) and recorded on X-ray film (Kodak, Xiamen, China). The densitometry of each band was quantified by a Gel imaging system and Quantity One 4.62 software (Bio-Rad, Hercules, CA, USA).

RT-PCR. Total RNA was extracted using TRIzol reagents (Invitrogen) from LN229, LN18, U87 and U251 cell lines. Isolated RNA was electrophoresed on 1% agarose gel to detect the purity of total RNA. The first-strand cDNA was synthesized using 1 μg total RNA and SuperScript® III Reverse Transcriptase (Invitrogen). PCR amplification was performed using the PCR amplification kit (Takara Bio, Inc., Otsu, Japan). The specific primers were designed using Primer Premier 6.0 software and synthesized by Sangon Biotech (Shanghai, China). The primers for SEPT7 were 5'-CTCTTGCTGTGG TAGGTAG-3' (forward) and 5'-GCTTCTGTAGTTCTCATA GTG-3' (reverse). The primers for GAPDH as an internal control were 5'-GAGTGAGTGGAAGACAGAAT-3' (forward) and 5'-GCAGAGAAGCAGACAGTTA-3' (reverse).

The SEPT7 overexpression vector and siRNA transfection. The pcDNA3.1(+)/SEPT7 expression vector was constructed by cloning SEPT7 fragment from normal human cDNA into pcDNA3.1(+) (Invitrogen) between *Bam*HI and *Eco*RI sites to express SEPT7 in abundance in *E. coli* DH5α cells. The primers for SEPT7 were as follows: forward primer, 5'-gga GGATCCCTCTTGCTGTGGTAGGTAG-3' (including *Bam*HI site GGATCC and three protection bases) and reverse primer, 5'-ctcGAATTCGCTTCTGTAGTTCTCATAGTG-3' (including *Eco*RI site GGATCC and three protection bases). The recombinant plasmid was identified by endonuclease digestion and DNA sequencing. The pcDNA3.1(+)/SEPT7 and pcDNA3.1(+) plasmids were separately transfected into the glioma cells mediated by Lipofectamine 2000 (Invitrogen) as per the manual. The stably transfected clones were screened by G418, and identified by western blot analysis and RT-PCR. Finally, the siRNA or control siRNA was also transfected into the glioma cells mediated by Lipofectamine 2000 (Invitrogen) as manual. Within 24 h after transfection, the protein level was detected by western blot analysis and RT-PCR. The siRNA primers sequences were designed by Invitrogen Block-iT RNAi designer.

Transwell migration and cell chemotaxis assay. The cells were added into Transwell chambers (Millipore) and FBS was added into lower chamber. Cells were cultured at 37˚C for 24 h in a humidified incubator of 5% CO_2, and then the hematoxylin and eosin (H&E) stained cells in the lower chamber were counted under the microscope. The cells in 10 high power fields were randomly chosen and the average transmembrane cell number per high-power field was shown as cell migration ability. For the cell chemotaxis assay, the different concentrations of IGF-1 (0, 1, 10 and 100 ng/ml) were added into the lower chamber of chemotaxis chambers (Millpore) with 30 μl per well. There were membranes with 8 μm gaps between the upper and lower chambers. Then, 50 μl of cell suspension with was added into the upper chamber of each well. After cells were cultured at 37˚C for 24 h, the H&E stained cells in the lower chamber were counted under the microscope. The chemotactic index was presented as cell migration number under IGF-1 and without IGF-1.

F-actin/G-actin ratio determination. The cells were broken, homogenized in cold lysis buffer (10 mM K_2HPO_4, 100 mM NaF, 50 mM KCl, 2 mM $MgCl_2$, 1 mM EGTA, 0.2 mM DTT, 0.5% Triton X-100, 1 mM sucrose, pH 7.0) and centrifuged at 15,000 x g for 30 min. Soluble actin (G-actin) was measured in the supernatant. The insoluble F-actin in the pellet was resuspended in lysis buffer plus an equal volume of buffer 2 (1.5 mM guanidine hydrochloride, 1 mM sodium acetate, 1 mM $CaCl_2$, 1 mM ATP and 20 mM Tris-HCl, pH 7.5) and incubated on ice for 1 h to convert F-actin into soluble G-actin, with gentle mixing every 15 min. The samples were centrifuged at 15,000 x g for 30 min, and F-actin was measured in this supernatant. Samples from the supernatant (G-actin) and pellet (F-actin) fractions were proportionally loaded and analyzed by western blot analysis using a specific actin antibody (Millipore, Temecula, CA, USA).

Statistical analysis. Data are presented as means ± SD. Statistical analysis was performed with SPSS13.0 software (IBM, Armonk, NY, USA). Statistical evaluation of the data was performed using one-way ANOVA and LSD for multiple comparisons. $P<0.05$ was considered to indicate a statistically significant difference.

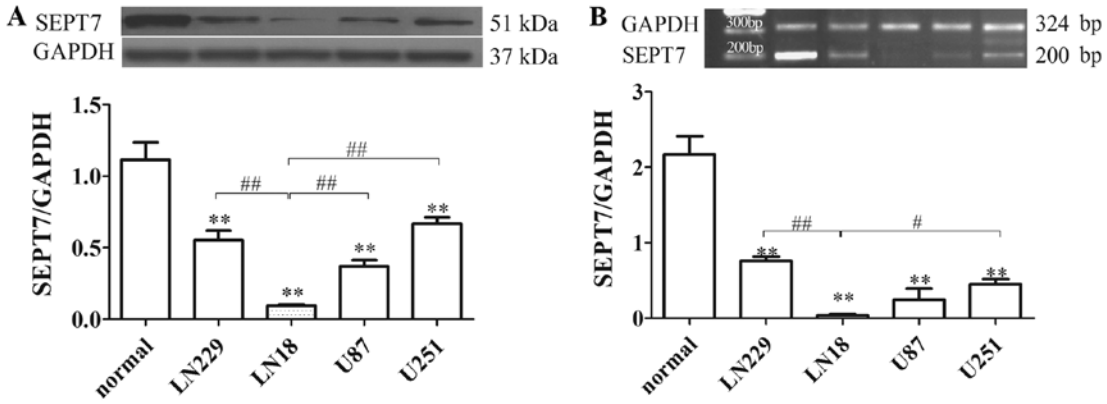

Figure 1. SEPT7 levels in different glioma cells. (A) SEPT7 expression in protein level in different glioma cells; (B) SEPT7 expression in mRNA level in different glioma cells. The values are means ± SD of 4 independent experiments. **P<0.01 vs. normal; $^{\#}$P<0.05 vs. LN18; $^{\#\#}$P<0.01 vs. LN18.

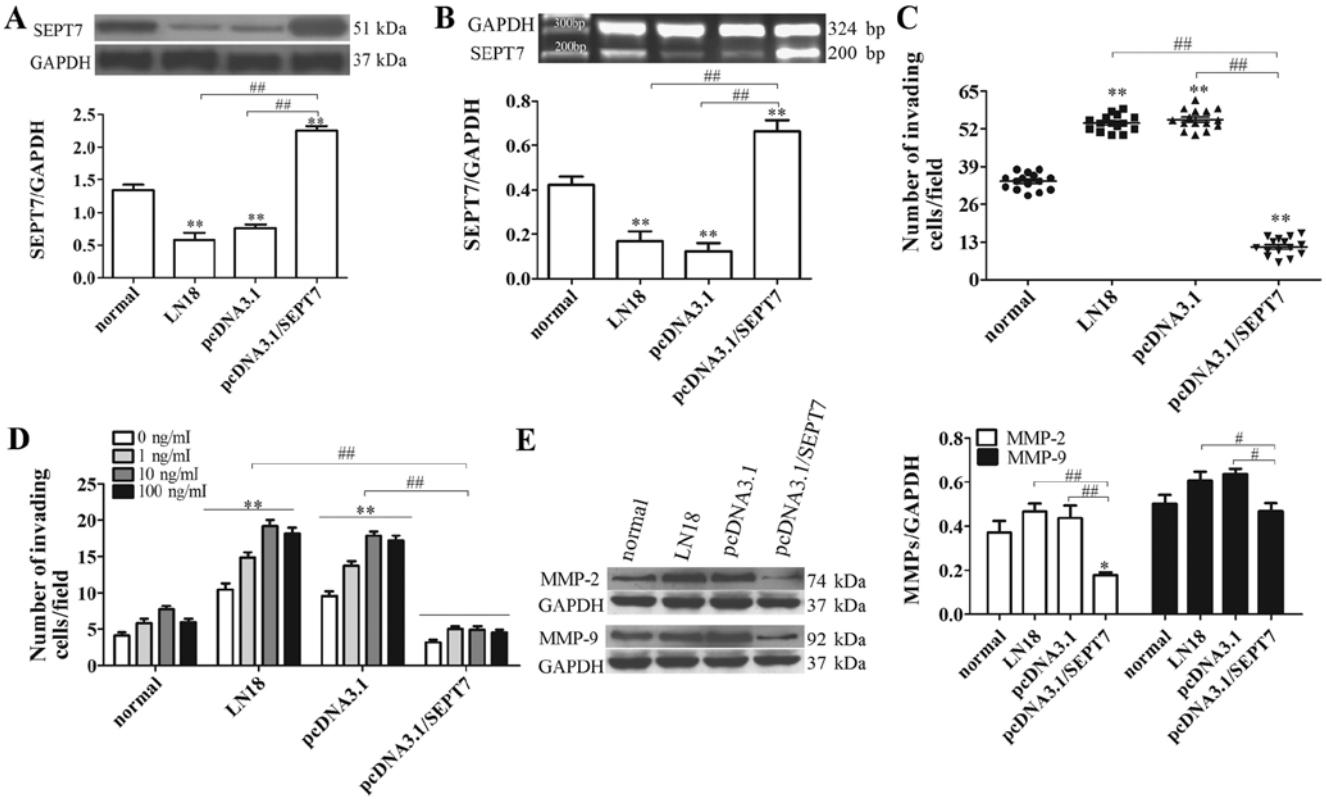

Figure 2. SEPT7 overexpression depresses glioma cell migration, chemotaxis and extracellular matrix. Cells were transfected with pcDNA3.1 or pcDNA3.1/SEPT7 overexpression plasmid. (A) Analysis of SEPT7 expression in protein level in LN18 cells after transfection with SEPT7 overexpression plasmid; (B) total RNA was extracted and probed by reverse transcription-PCR using SEPT7 specific primers; (C) effect of SEPT7 overexpression on the migration of LN18 cells as detected by Transwell assay; (D) cell chemotaxis experiment with 0, 1, 10 and 100 ng/ml IGF-1 induction was performed using Transwell chambers; (E) cell extracts were subjected to immunoblotting with MMP-2 and MMP-9 antibodies. GAPDH as an internal control. The values are means ± SD of 4 independent experiments except for Fig. 2C. *P<0.05 vs. normal; **P<0.01 vs. normal; $^{\#}$P<0.05 vs. pcDNA3.1/SEPT7; $^{\#\#}$P<0.01 vs. pcDNA3.1/SEPT7.

Results

SEPT7 is downregulated in human brain glioma cells. SEPT7 expression was identified by western blot analysis and RT-PCR in various glioma cells. The results showed that SEPT7 levels in glioma cells were reduced by 50% or less compared to normal human brain cells. SEPT7 levels in LN18 cell lines were lower than in other glioma cells (Fig. 1). LN18 was derived from a patient with a grade IV glioma in the right temporal lobe (ATCC). The subsequent tests therefore used the LN18 cell line as the research object.

SEPT7 overexpression suppresses human brain glioma cell migration. To verify whether SEPT7 influences glioma invasion, a SEPT7 overexpression vector was constructed and transfected into the LN18 cell line (Fig. 2A and B). Analysis of SEPT7 expression in LN18 cells after transfection with SEPT7 overexpression plasmid indicated that the level of SEPT7

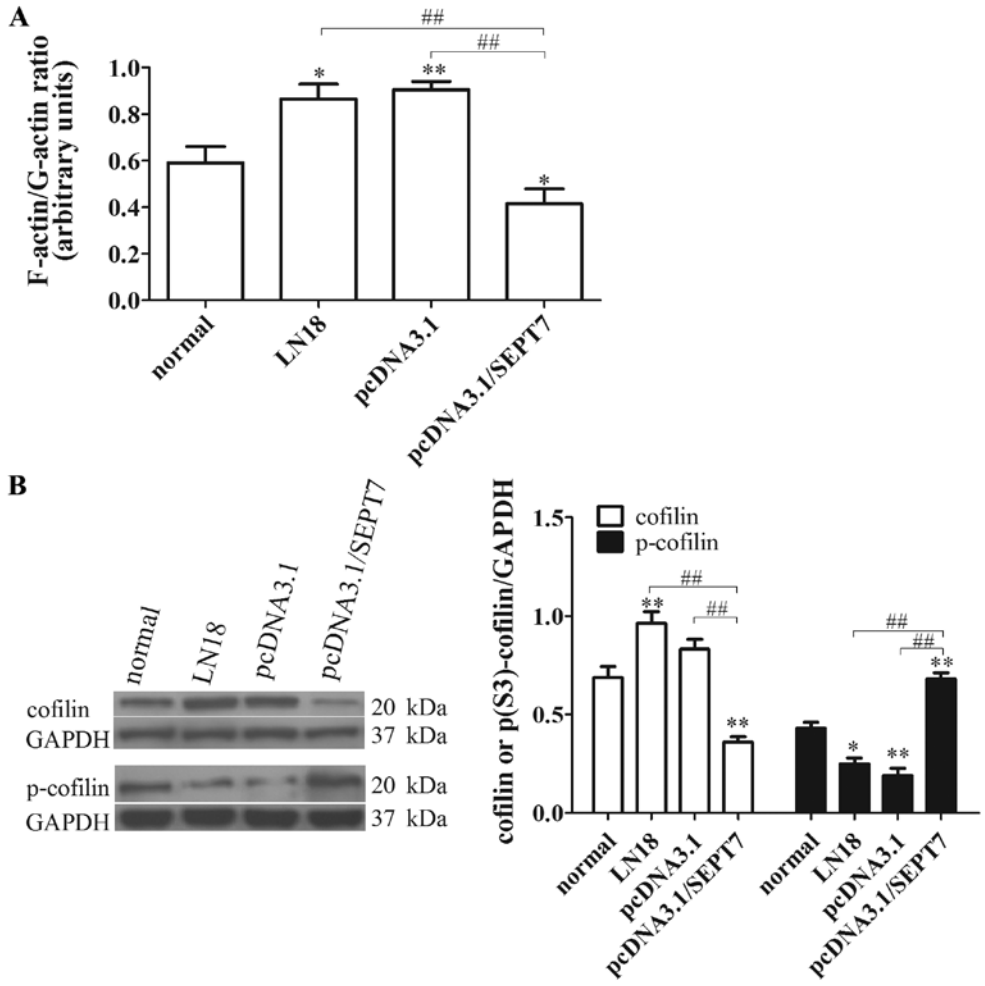

Figure 3. SEPT7 overexpression inhibits cytoskeleton locomotion in glioma cells. (A) The F-actin/G-actin ratio was expressed as the ratio with G-actin in pellet and supernatant at the same volume. (B) Cofilin and p(Ser3)-cofilin were detected by western blot analysis; GAPDH as an internal control. The values are means ± SD of 4 independent experiments. *P<0.05 vs. normal; **P<0.01 vs. normal; $^{\#}$P<0.05 vs. pcDNA3.1/SEPT7; $^{\#\#}$P<0.01 vs. pcDNA3.1/SEPT7.

in pcDNA3.1/SEPT7 had a marked elevation compared to LN18 (P<0.01) (Fig. 2A and B). Malignant tumor invasion and metastasis mainly depend on cell migration, as well as extracellular matrix degradation and the induction of chemokines. Given the increased SEPT7 levels in pcDNA3.1/SEPT7, we examined whether a redundancy in SEPT7 alone accounts for the failure of glioma cells to invade and transfer. The results showed that the number of invading cells in the pcDNA3.1/SEPT7 group were significantly reduced in contrast to the LN18 group (P<0.01) (Fig. 2C), indicating that SEPT7 made no contribution to tumor cell migration. The effect of SEPT7 on tumor cell invasion and metastasis was further studied using an IGF-1-induced cell chemotaxis assay. Under the treatment of IGF-1 at different concentrations, glioma cell chemotaxis had a significant difference; overall, 10 ng/ml IGF-1 was the most powerful for glioma cell chemotaxis, either in LN18 or pcDNA3.1/SEPT7 (Fig. 2D). Consistent with cell migration results, the chemotaxis assay revealed that SEPT7 overexpression markedly diminished IGF-1 induced tumor cell chemotaxis compared to LN18 (P<0.01) (Fig. 2D). These results indicated that increased SEPT7 inhibits glioma cell migration and chemotaxis.

Activation of MMP-2 and MMP-9 regulates both matrix degradation and motility, thereby facilitating cellular invasion (16,17). The levels of MMP-2 and MMP-9 were probed with western blot analysis, indicating that the levels of MMP-2 and MMP-9 in pcDNA3.1/SEPT7 were markedly depressed, respectively, compared to LN18 (P<0.01 and P<0.05) (Fig. 2E). These results suggest that increased SEPT7 suppresses extracellular matrix degradation, consequently opposing cellular invasion.

SEPT7 overexpression inhibits cytoskeleton locomotion in human glioma cells. SEPT7 is a cytoskeletal protein and is involved in the entry of axonal microtubules into nascent filopodia, enabling the formation of collateral branches (18). Increased SEPT7 binds to the actin filaments and promotes F-actin ring formation, against cell migration (19). Consistent with this conclusion, our study indicated that the F-actin/G-actin ratio in pcDNA3.1/SEPT7 was significantly reduced compared with the LN18 group (P<0.01) (Fig. 3A), revealing that SEPT7 upregulation can promote actin depolymerization.

Cofilin also acts as an actin-binding protein that plays an essential role in regulating actin filament dynamics and reorganization by stimulating the severance and depolymerization of actin filaments (14). Therefore, we speculated that a possible relationship exists between SEPT7 and cofilin phospho-regulation to modulate actin filament dynamics.

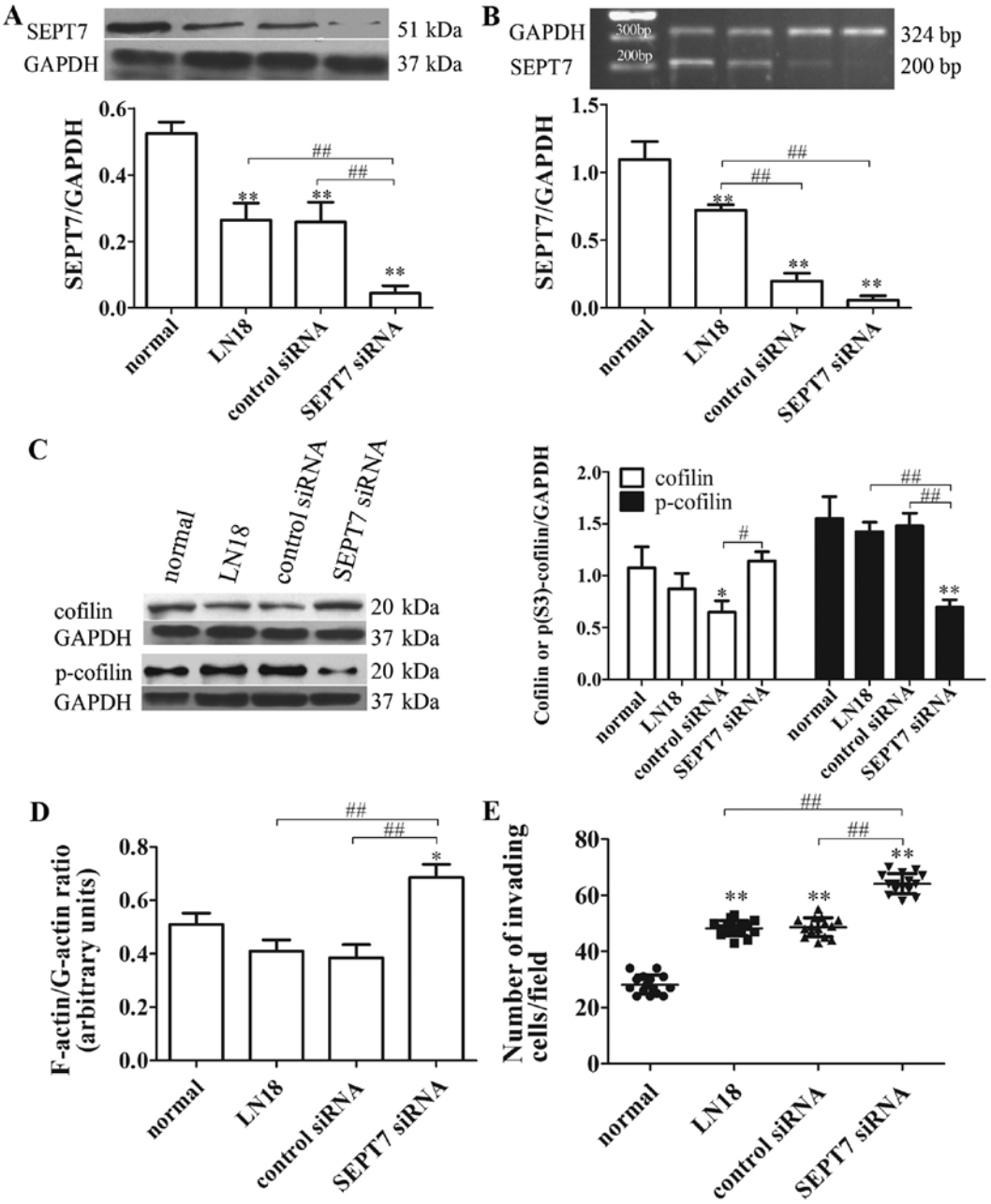

Figure 4. SEPT7 siRNA increased cell migration and cytoskeleton locomotion in human glioma cells. (A) Analysis of SEPT7 expression in protein in LN18 cells after transfection with SEPT7 siRNA. (B) Total RNA was extracted and probed by reverse transcription-PCR using SEPT7 specific primers; **P<0.01 vs. normal; $^{\#\#}$P<0.01 vs. LN18. (C) Cofilin and p(Ser3)-cofilin were detected by western blot analysis, respectively. GAPDH was used as an internal control. (D) F-actin/G-actin ratio was expressed as the ratio with G-actin in pellet and supernatant at same volume. (E) Effect of reduced SEPT7 on migration of LN18 cells as detected by Transwell assay; The values are means ± SD of 4 independent experiments. *P<0.05 vs. normal; **P<0.01 vs. normal; $^{\#}$P<0.05 vs. SEPT7 siRNA; $^{\#\#}$P<0.01 vs. SEPT7 siRNA.

To verify this conjecture, the levels of cofilin and p-cofilin were tested; the results showed that cofilin level in the pcDNA3.1/SEPT7 group decreased visibly compared with the LN18 group (P<0.01), while the p-cofilin level showed the opposite results (P<0.01) (Fig. 3B). These findings preliminary clarified that increased SEPT7 promotes the depolymerization of actin filaments, and is concerned with cofilin phospho-regulation.

SEPT7 siRNA increases cell migration and cytoskeleton locomotion in human glioma cells. To further explore the roles of cytoskeleton signaling in reduced SEPT7-mediated glioma cell migration, the control siRNA and SEPT7 siRNA were transfected into the LN18 cells. The degrees of transfection were tested at the protein and nucleic acid levels, revealing that the amount of SEPT7 was markedly reduced compared with the LN18 group (P<0.01 and P<0.01) (Fig. 4A and B). Cofilin, F-actin/G-actin ratio and cell migration in the SEPT7 siRNA group were significantly improved compared with the LN18 group (P<0.05, P<0.01 and P<0.01) (Fig. 4C-E), while p-cofilin expression reduced (P<0.01) (Fig. 4C). Thus, these experiments show that the knockdown of SEPT7 enhances the motility of glioma cells through cofilin phospho-regulation, which accelerates actin polymerization.

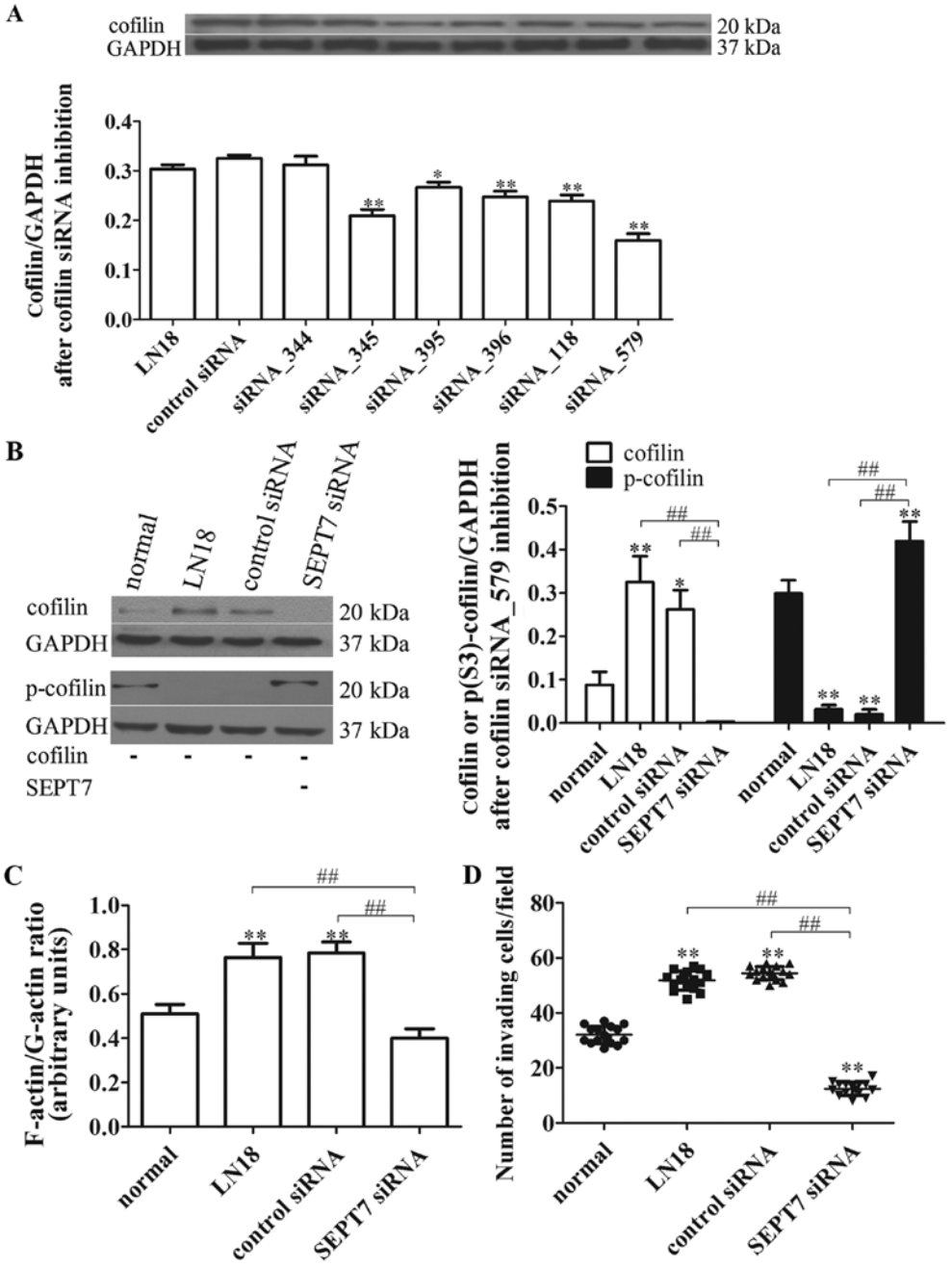

Figure 5. Cofilin inhibition suppresses SEPT7 siRNA-induced cell migration. (A) The different cofilin siRNA was transfected into LN18 cell lines and measured; GAPDH was used as an internal control. *P<0.05 vs. LN18; **P<0.01 vs. LN18. (B) Cofilin and p(Ser3)-cofilin were detected after cofilin inhibition treatment. The - indicates the protein silence. GAPDH as an internal control. (C) F-actin/G-actin ratio was expressed as the ratio with G-actin in pellet and supernatant at the same volume after cofilin inhibition treatment. GAPDH as an internal control. (D) Effect of downregulation of SEPT7 and cofilin on the migration of LN18 cells as detected by Transwell assay; The values are means ± SD of 4 independent experiments. *P<0.05 vs. normal; **P<0.01 vs. normal; $^{\#}$P<0.05 vs. SEPT7 siRNA; $^{\#\#}$P<0.01 vs. SEPT7 siRNA.

Cofilin inhibition suppresses SEPT7 siRNA-induced cell migration. In view of the critical roles of SEPT7 and cofilin in linking signaling pathways to actin cytoskeleton remodeling, we further tested whether cofilin is involved in the process of SEPT7 siRNA-induced actin aggregation. The different cofilin siRNA were designed and transfected, respectively, into the LN18 cell lines, and the degrees of transfection were tested, showing that cofilin siRNA_579 was the best for inhibiting cofilin protein expression (P<0.01) (Fig. 5A). Afterwards, the cofilin siRNA_579 was transfected, respectively, into the normal, LN18, control siRNA and SEPT7 siRNA group cells. The cell migration and cytoskeleton locomotion were measured; as shown in Fig. 5B, the levels of cofilin and p-cofilin after cofilin inhibition were reduced in general in all groups compared with unrestrained cofilin (Figs. 4C and 5B). However, the level of cofilin in the SEPT7 siRNA group was further reduced compared with the LN18 group (P<0.01), while the p-cofilin level was just the opposite (P<0.01) (Fig. 5B).

Importantly, the F-actin/G-actin ratio and cell migration under cofilin inhibition in SEPT7 siRNA group was remarkably declined compared with the LN18 group (P<0.01 and P<0.01) (Fig. 5C and D). These findings suggest that actin

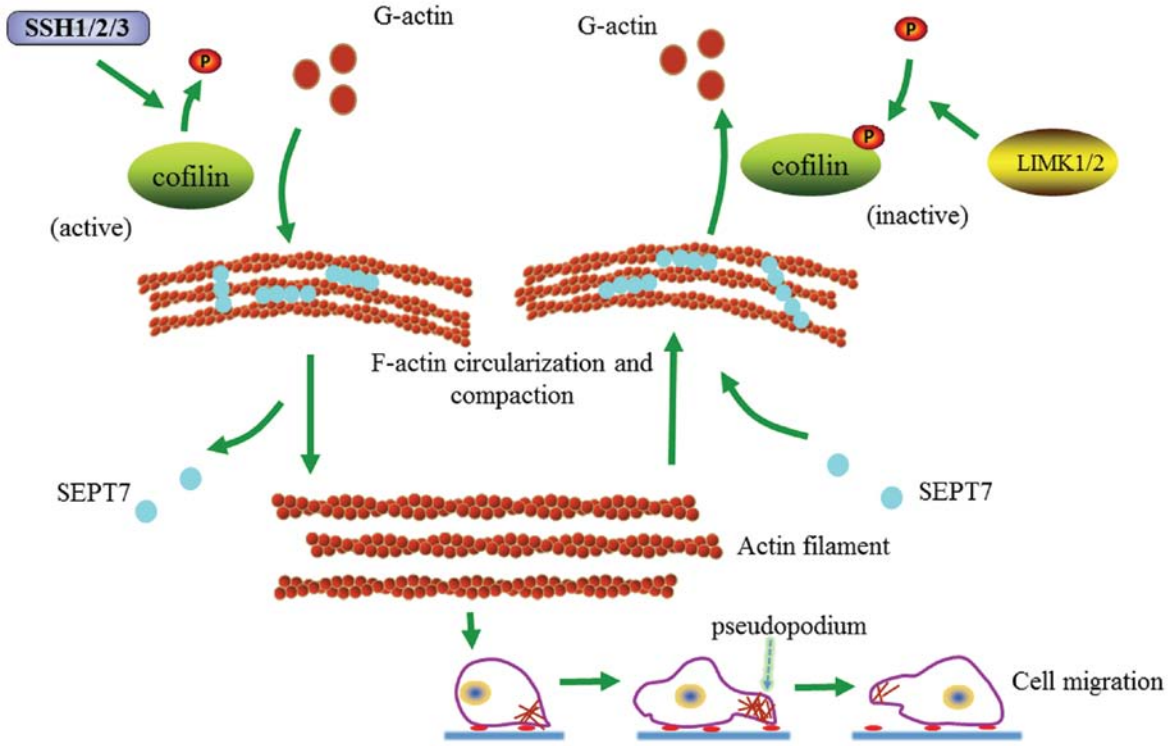

Figure 6. Proposed pathway to expound the interaction among SEPT7, cofilin phospho-regulation and actin dynamic equilibrium. The proposed pathway was drawn based on our research. On the one hand, improved SEPT7 monomers form additional SEPT7 rods and bind to actin filaments making them bent or cyclized, before subsequently recruiting phosphorylated cofilin and binding to actin filaments; cofilin is inactivated by phosphorylation using LIMK1/2 and urge actin severing. On the other hand, dissociated SEPT7 from bent or cyclized actin filaments cause SEPT7 rods to diminish and drop, and SEPT7 monomers that have detached from the actin filaments can help activated cofilin, which was dephosphorylated by SSH1/2/3 fast binding to the actin filaments, causing actin polymerization and accelerating cell migration. At this time, when cofilin is inhibited, cofilin binding to actin filaments and SEPT7 reduction decrease, causing slower cell migration.

polymerization and cell migration of SEPT7 siRNA-induced are reversed by cofilin inhibition and are cofilin-dependent.

Discussion

In the past two decades, although there has been a series of active comprehensive treatment of glioma developed in clinical practice, the effect is still not ideal as tumor cells find it easy to migrate and are difficult to control. Therefore, human gliomas are still considered a refractory disease in the neurosurgery field. As a result, it is necessary to determine the molecular mechanism of glioma cell locomotion and invasion.

The interstitial movement is encephalic motion in glioma cells; tumor cells in the subependymal zone and soft membrane area can migrate via an amoeboid movement (20,21). During cell migration, the formation of front-end protuberance lamellipodia and filopodia plays an important role, and lamellipodia are considered to be the main driver of cell motility (22,23). However, lamellipodia are formed during actin polymerization and assemble in the front-end protuberance of lamellipodia (24). Consistently, our analyses suggested that actin polymerization accelerates cell migration through cytoskeleton signaling molecules and actin-binding proteins.

SEPT7 has been identified in all eukaryocytes. The study by Jia *et al* (9) observed that SEPT7 expression was much lower in high-grade than low-grade gliomas. SEPT7 gene expression was negatively correlated with the ascending order of glioma grades. It has also been confirmed that SEPT7 expression in different glioma cells is significantly different. Currently, most research on SEPT7 is performed at the cellular level, such as the relationship between SEPT7 and cell growth and the cell cycle. Our study also found that SEPT7 overexpression can inhibit cell migration and increase extracellular matrix degradation. However, our focus was on the interplay and molecular mechanism responsible for SEPT7 modulating the cytoskeleton locomotion and cell migration (Fig. 6).

Recent studies have shown that SEPT7 promotes F-actin ring formation by crosslinking actin filaments into curved bundles (15). Therefore, SEPT7 could conceivably crosslink with F-actin into loose contractile networks and SEPT7-mediated actin curving in cells may act in synergy with myosin-induced actin filament buckling (19,25,26). Our findings show that increased SEPT7 induces actin depolymerization and cell migration is consequently hindered. At the same time, it is accompanied by an increasing cofilin/p-cofilin ratio. Research has shown that SEPT7 can stabilize actin filaments bent by cofilin (15). It is obvious that cofilin and p-cofilin play important roles in the SEPT7 regulation of actin depolymerization and cell migration. On the contrary, the downregulation of SEPT7 can increase cell migration and actin polymerization accompanied by a depressed cofilin/p-cofilin ratio. Nevertheless, increased actin polymerization and SEPT7 siRNA-induced cell migration were reversed when cofilin was inhibited, also accompanied by a change in the cofilin/p-cofilin ratio. Hence, our study preliminarily suggests that SEPT7 interacts with cofilin phospho-regulation in modulating the

dynamic equilibrium of actin and cytoskeleton locomotion, offering a promising candidate for novel therapeutic pathways against glioma.

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