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Original Article

MicroRNA-181 inhibits the proliferation, drug sensitivity and invasion of human glioma cells by targeting Selenoprotein K (SELK)

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Abstract: Gliomas are aggressive type of brain tumors and cause significant human mortality world over. The frequent relapses, development of drug resistance, the adverse effects of the chemotherapy and dearth of the therapeutic targets form the major hurdles in glioma treatment. Several studies suggest that microRNAs (miRs) are involved in the development and progression of different cancers. Herein, the therapeutic potential of miR-181 was explored in human glioma cells. The results showed that miR-181 is significantly downregulated in human glioma cells. Overexpression of miR-181 caused significant inhibition in the proliferation of U87 and U118 glioma cells. The miR-181 triggered growth inhibition was found to be mainly due to the induction of apoptosis which was concomitant with increase in the Bax/Bcl-2 ratio. Additionally, miR-181 enhanced the chemosensitivity of the glioma cells to temozolomide and suppressed their invasion. Bioinformatic analysis showed that miR-181 exerts its effects by inhibiting the expression of Selenoprotein K (SELK). The expression of SELK was found to be significantly upregulated in glioma cells and silencing of SELK suppressed the proliferation of glioma cells. Nonetheless, overexpression of SELK could nullify the effects of miR-181 on the proliferation of the glioma cells. Taken together, miR-181 may exhibit therapeutic implications in the treatment of glioma.

Keywords: Glioma, MicroRNA, cell cycle arrest, SELK, migration, invasion

Introduction

Considered to be among the most destructive human cancers, gliomas cause tremendous human mortality and morbidity throughout the globe [1]. Gliomas account for 80% of all the primary tumors of brain, and includes all tumors of glial origin [2]. Surgery followed by chemo- and/or radiotherapy is generally employment for the treatment of gliomas [3]. Despite improvements in treatment, the average survival still remains 16 months for grade four gliomas [4]. Therefore, there is need for the identification of biomarkers for early detection and exploration of novel therapeutic targets for efficient treatment of gliomas [5]. Over the last few decades, research endeavours have been directed to explore the roles of microRNAs (miRs) in human cells. The miRs control majority of the human genes and are thus involved in vital cellular functions [6]. They have been found to regulate the expression of target genes via post transcriptional regulation [7]. The dysregulation of miR expression has been shown to be responsible for the development of deadly diseases such as cancer. Thus, miRs exhibit therapeutic implications in treating human diseases such as cancer [8]. The miR-181 has been shown to be dysregulated in number of cancer types and considered to be of therapeutic importance [9]. It has been found to exhibit Prognostic significance in acute myeloid leukemia [10]. In non-small cell lung cancer, miR-181 acts as a tumor suppressor by inhibiting the expression of Bcl-2 [11]. In prostate cancer cells, miR-181 targets DAX-1 to regulate their proliferation [12]. The miR-181 targets WIF-1 in colorectal cancer to regulate their growth [13]. In yet another study, miR-181 has been reported to control the growth and metastasis of adenoid cystic carcinoma metastasis [14]. Moreover, a preliminary study has also indicated the role of miR-181 in proliferation of glioma [15]. However, the role and thera-

peutic implications of miR-181 in glioma are yet to be fully investigated. This study therefore designed to investigated expression of miR-181 in glioma and its effects on drug sensitivity and invasion. Additionally, this study for the first time explores Selenoprotein K as the target of miR-181 in glioma. Herein it was found that miR-181 is significantly downregulated in glioma cells and regulates the growth, drug sensitivity and invasion of the human glioma cells via modulation of SELK expression. Taken together, miR-181 may exhibit therapeutic implications in glioma and may prove useful in glioma treatment.

Materials and methods

Cell culture

The normal astrocytes and the glioma cell lines (U-87, U-118, M059K and Hs 683) were obtained from Type Culture Collection of Chinese Academy of Sciences, Shanghai, China. The cell lines were subjected to culturing in Roswell Park Memorial Institute 1640 (RPMI 1640; Gibco, Carlsbad, CA, USA) medium supplemented with 10% foetal bovine serum and 0.2% penicillin and streptomycin (Invitrogen, Carlsbad California, United States). All cells were cultured in a 5% CO_2 incubation chamber at 37°C.

cDNA synthesis and qRT-PCR

The TRIzol reagent (Invitrogen/Life Technologies, Carlsbad, CA, USA) was used for the extraction of RNA form the tissues and cell lines. Subsequently, the total RNA was reverse-transcribed by RevertAid cDNA synthesis kit (Fermentas). Thereafter the quantitative RT-PCR was performed by using SYBR Green master mix (Applied Biosystems; Foster City, Calif, USA) on an ABI 7900HT system. The cycling conditions were as follows: 95°C for 20 sec, followed by 40 cycles of 95°C for 15 sec, and 58°C for 1 min. All reactions were carried out in triplicates and the gene expression was determined by the $2^{-\Delta\Delta Ct}$ method. The primers for SELK were sense, 5'-AGCACAAACTCACGAGCAGG-3' and antisense, 5'-GAAGCCGAGCCTCATCAAC-3'.

Analysis of cell proliferation

The proliferation rate of U87 and U118 cells was monitored by WST-1 assay. In brief, U87 cells were cultured in 96 well plates at the density of 2×10^5 cells/well. The cells were then transfected with miR-NC or miR-181 mimics and again incubated for 24 h at 37°C. This was followed by the incubation of the cells with WST-1 at 37°C for 4 h. The absorbance was then measured at 450 nm using a victor 3 microplate reader to determine the proliferation rate at 0, 12, 24, 48 and 96 h time intervals.

Cell transfection

The miR-181 mimics and NC were synthesized by RiboBio (Guangzhou, China). The transfection was then carried out by the Lipofectamine 2000 reagent (Invitrogen, Carlsbad, CA, USA) as per the manufacturer's instructions. As the U87 cells reached 80%, the appropriate concentrations of miR-181 mimics or NC was transfected into these cells.

Analysis of cell death

After transfection with miR-NC or miR-181 mimics, the U87 and U118 cells were cultured in twenty four well plates for 24 h at 37°C. The cells were then collected by centrifugation and washed with PBS. After this the cells were stained with DAPI. The U87 and U118 cells were then washed with PBS and observed both by fluorescence microscopy. For annexin V/PI assay, the miR-NC or miR-181 mimics transfected U87 and U118 cells (5×10^5 cells per well) were incubated for 24 h. This was followed by the staining of these cells with annexin V-FITC or PI. The percentage of apoptotic U87 cells was determined by flow cytometery.

Cell invasion assay

Transwell chambers with Matrigel employed to monitor invasion of the U87 and U118. In brief, the cells were transfected with appropriate constructs and 48 h post-transfection, the cells were harvested and suspended in fresh media. While as 200 µL of the cell suspension containing approximately 5×10^4 cells was placed onto the upper compartment, a fresh 500 µmedia was placed in the lower compartment. After 24 hours cells present at the upper compartment were removed by swabbing while cells that invaded to the lower surface were fixed and then subsequently stained with 0.05% crystal violet. Finally, ten random fields were selected

to determine the invasion under the light microscope.

Dual-luciferase reporter assay

The miR-181 target was identified by TargetScan online software (http://www.targetscan.org). The miR-181 mimics or NC were co-transfected with Plasmid pGL3-SELK'-UTR-WT or pGL3-SELK'-UTR-MUT into U87 cells. Dual-luciferase reporter assay (Promega) was carried out at 48 h after transfection. *Renilla* luciferase used for normalization.

Western blotting

The normal and the glioma cell lines were cultured at 37°C for 24 and then centrifuged at high speed. The cell pellet was washed with PBS and then suspended again in RIPA lysis buffer. Thereafter the concentrations of the proteins were determined and equal concentrations of the proteins were loaded on SDS-PAGE gel (15%). The samples were transferred to polyvinylidene fluoride membranes and blocking was done using 5% skimmed milk powder. This was followed by membrane incubation with primary antibodies at 4°C for 24 h. Next the membranes incubated with horseradish peroxidase-linked secondary biotinylated secondary antibodies for 2 h. The membranes were washed and immunoreactive bands observed by ECL-PLUS/Kit as per manufacturer's guidelines.

Statistical analysis

The experiments were done in three biological replicates and the values represent the mean of three replicates ± standard deviation (SD). $P < 0.05$ was considered as significant difference. Student's t test using Graph Pad prism 7 software was used for the statistical analysis.

Results

miR-181 suppresses the proliferation of glioma cells

To unveil, the role of miR-181 in glioma, the expression prolife of miR-181 was examined in four different glioma cell lines as well as the normal astrocytes by qRT-PCR. Results showed that miR-181 was significantly suppressed in the glioma cells relative to its expression in normal astrocytes (**Figure 1A**). The expression of miR-181 was observed to be 6.7 folds lower in the glioma cells. Additionally, the expression of miR-181 was found to be highly downregulated in the U87 and U118 cells. To ascertain the role of miR-181 in the proliferation of the glioma U87 and U118 cells, the cells were transfected with miR-NC or miR-181 mimics. The overexpression of miR-181 in U87 and U118 cells was validated by qRT-PCR which showed 7.2 and 6.9 fold increase in the miR-181 expression (**Figure 1B**). Next, the proliferation rate of miR-181 overexpressing U87 and U118 cells was monitored at different time periods. The results showed that miR-181 overexpression resulted in significant decrease in the proliferation rate of the U87 and U118 glioma cells (**Figure 1C**).

The effects of miR-181 overexpression were also assessed on the colony formation potential of the glioma U87 and U118 cells. The results revealed that miR-181 overexpression caused significant decrease in the proliferation of the glioma U87 and U118 (**Figure 2**).

miR-181 induces apoptosis in glioma cells

The underlying mechanism for inhibition of U87 and U118 cell proliferation upon miR-181 overexpression was ascertained by DAPI staining. It was found that miR-118 triggered remarkable changes in the morphology of the U87 and U118 cells such as nuclear fragmentation indicative of apoptosis (**Figure 3A**). Annexin V/PI staining also showed increase in the percentage of the U87 and U118 apoptotic cells upon miR-181 overexpression (**Figure 3B**). Western blot analysis showed that miR-181 caused upregulation of Bax and downregulation of Bcl-2 expression in U87 and U118 cells further confirming the apoptotic cell death (**Figure 3C**).

miR-181 enhances the drug sensitivity of glioma cells

The effects of miR-181 were examined on the sensitivity of the glioma U87 and U118 cells to temozolomide. The glioma U87 and U118 cells were transfected with miR-181 mimics or treated with 50 μM temozolomide or transfected miR-181 mimics plus treated with 50 μM temozolomide and then subjected to WST-1 assay.

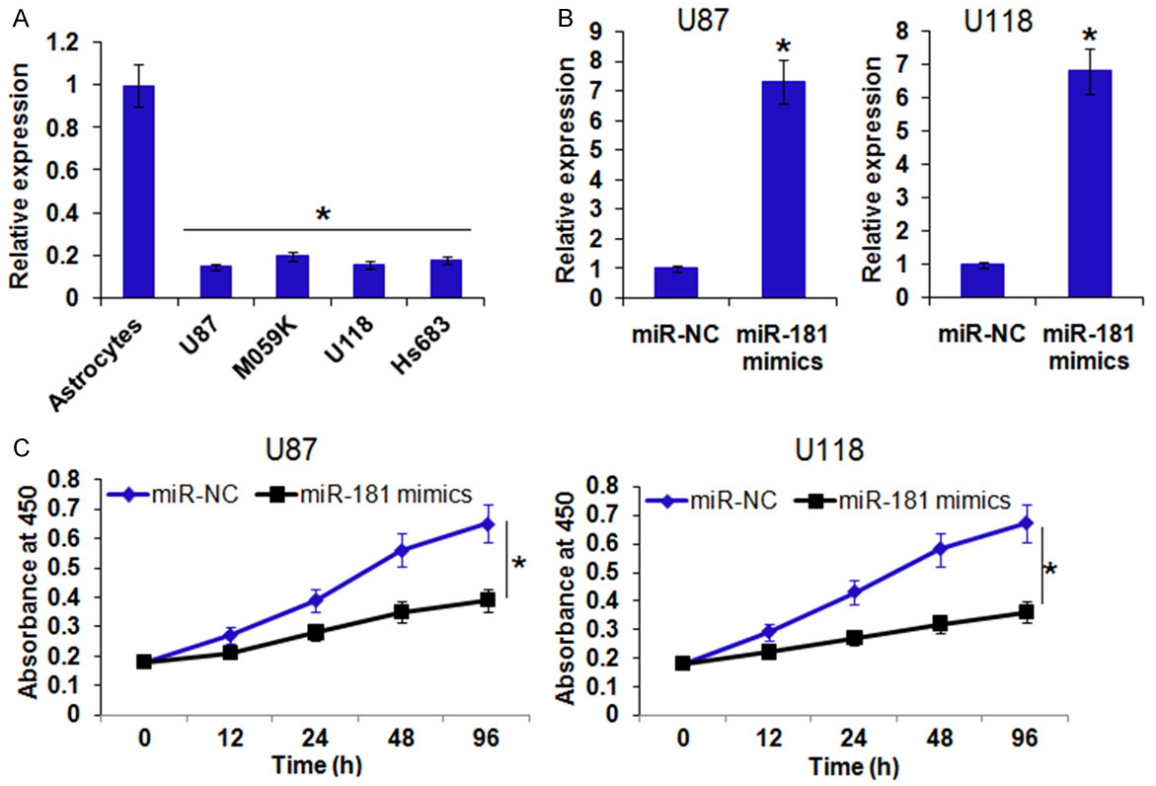

Figure 1. miR-181 inhibits the proliferation of Glioma cells. A. Expression of miR-181 in normal astrocytes and human glioma cell lines as determined by qRT-PCR. B. Expression of miR-181 in miR-NC or miR-181 mimics transfected U87 and U118 cells. C. Cell viability of the miR-NC or miR-181 mimics transfected U87 and U118 cells. The experiments were performed in triplicate and expressed as mean ± SD (*P < 0.05).

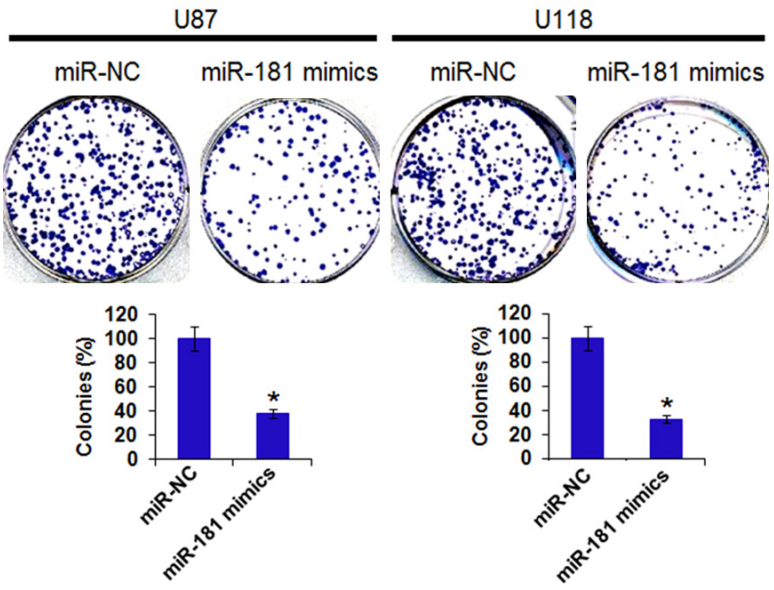

Figure 2. Colony formation assay showing the colon formation in miR-NC and miR-181 mimics transfected U87 and U118 cells. The experiments were performed in triplicate and expressed as mean ± SD (*P < 0.05).

The results showed that effects of miR-181 mimics and temozolomide treatment were more profound on the U87 and U118 cell proliferation then miR-181 mimics or temozolomide individually (**Figure 4**) suggesting miR-181 overexpression enhances the drug sensitivity of glioma cells.

miR-181 suppresses the invasion of glioma cells

The effects of miR-181 on the migration of the U87 cells were determined by transwell assay. The results showed that miR-181 caused significant decrease in the invasion of the U87 and U118 cells. The invasion of the U87

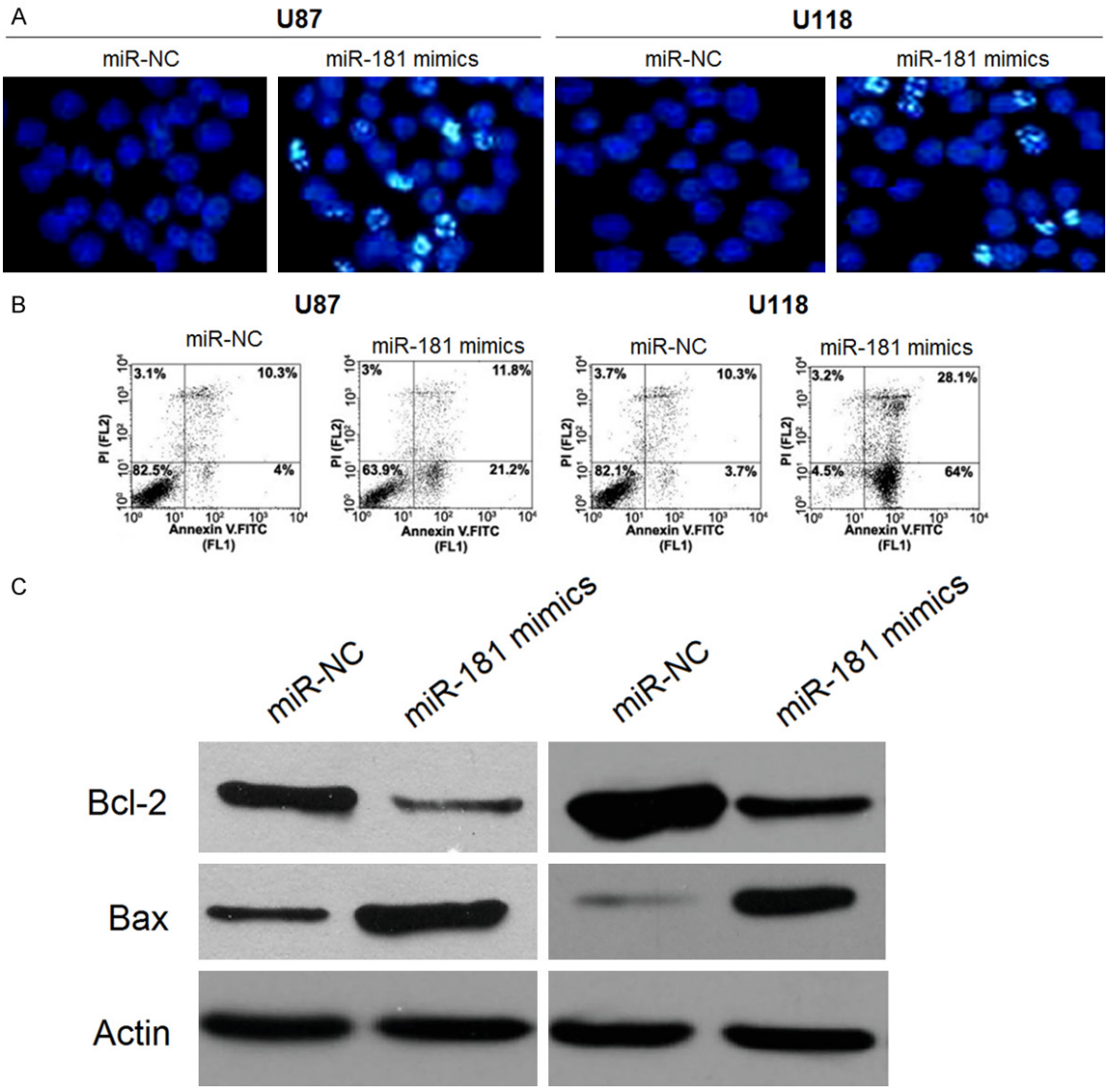

Figure 3. miR-181 induces apoptosis in glioma cells. (A) DAPI staining and (B) annexin V/PI staining of miR-NC and miR-181 mimics transfected U87 and U118 cells showing induction of apoptosis. (C) Western blot analysis showing the expression of Bcl-2 and Bax in miR-NC and miR-181 mimics transfected U87 and U118 cells. The experiments were performed in triplicate and expressed as mean ± SD (*P < 0.05).

and U118 cells was decreased by cells suppressed by 67 and 65% respectively upon miR-181 overexpression (**Figure 5**).

miR-181 targets SELK in glioma cells

The TargetScan revealed that SELK acts as the target of miR-181 in glioma cells (**Figure 6A**). SELK was further confirmed as the target of miR-181 by dual luciferase assay (**Figure 6B**). The western blotting results further revealed that the SELK was significantly overexpressed in the all the glioma cells as compared to the normal astrocytes (**Figure 6C**). Nonetheless, overexpression of miR-181 resulted in suppression of SELK expression in U87 cells (**Figure 6D**), confirming SELK as the target of miR-181.

SELK overexpression promotes the proliferation of glioma cells

Next to assess the effects of SELK on the proliferation of the U87 glioma cells, its expression was silenced in U87 and U118 glioma cells (**Figure 7A**). The results showed that silencing of SELK resulted in decrease of the U87 and

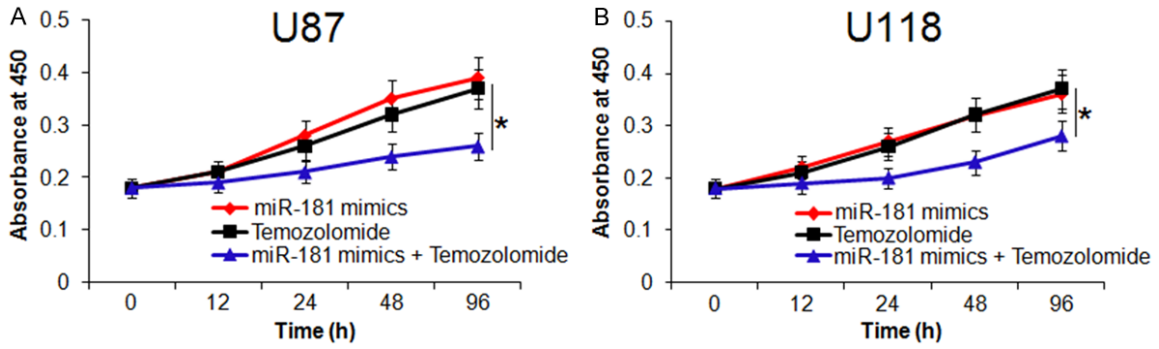

Figure 4. WST-1 assay shows that overexpression of miR-118 in U87 and U118 enhances their sensitivity to temozolomide. The experiments were performed in triplicate and expressed as mean ± SD (*P < 0.05).

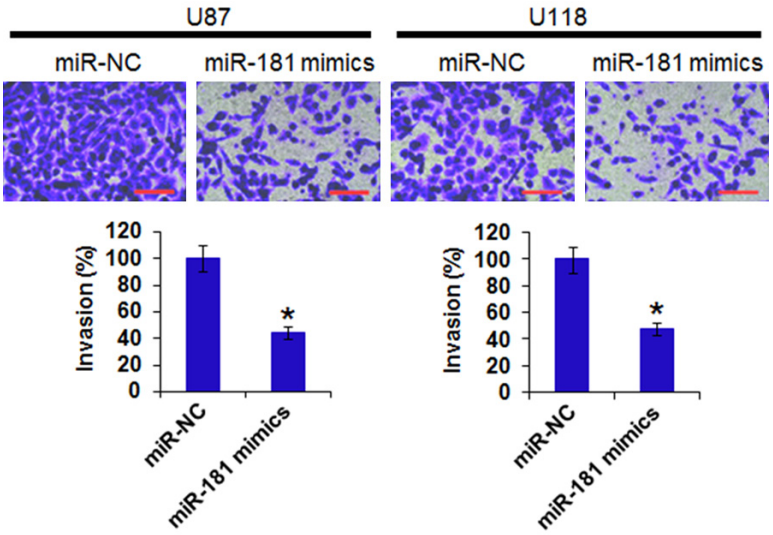

Figure 5. Transwell assay showing the effect of miR-181 overexpression on the invasion of U87 and U118 cells. The experiments were performed in triplicate and expressed as mean ± SD (*P < 0.05).

U118 cell proliferation (**Figure 7B**). However, it was found that overexpression of SELK in U87 cells could promote the growth of the U87 cells and nullified the growth inhibitory effects of miR-181 overexpression on U87 cell proliferation (**Figure 7C**).

Discussion

Gliomas prevalent brain tumors in adults occurring in any part of the central nervous system [16]. Although gliomas are generally malignant, some of them may not always behave as malignant. The gliomas may have astrocytic or oligodendrocytic in origin and in some cases may be mix of these two cell types [17]. Being aggressive types of brain tumors, approximately 18000 new glioma cases and 13000 deaths are reported in USA annually [18]. The limited availability of the reliable and efficient therapeutic targets/agents hurdles the treatment of glioma [19]. The wide array of roles that miRs carry out in human by regulating the expression of human genes suggests that miRs may prove useful therapeutic targets for treating human diseases including cancer [20]. In this study, we deciphered the role of miR-181 in glioma. It was found the expression of miR-181 is significantly downregulated in glioma cells. Previously carried out studies have also shown that the expression of miR-181 is dysregulated in cancer cells. For example the expression of miR-181 has been shown to be downregulated in oral squamous cell carcinoma and in actue leukemia cells [21, 22]. To unveil the role of miR-181, it was overexpressed in U87 and U118 glioma cells. It was observed that miR-181 overexpression resulted in significant decline in the proliferation rate and colony formation of the U87 and U118 cells. Hoechst staining as well as the phase contrast microscopy revealed that that miR-181 overexpression resulted in the nuclear fragmentation of the U87 and U118 cells. This was also accompanied with increase in Bax and decrease in the Bcl-2 expression. These results are in agreement with a previous study wherein miR-181 has been shown to promote the apoptosis of the

Figure 6. miR-181 targets SELK in glioma cells. A. TargetScan analysis showing SELK as the target of miR-181. B. Dual luciferase assay. C. Western blot showing the expression of SELK in normal astrocytes and glioma cell lines. D. Western blot showing the expression of SELK in miR-NC and miR-181 mimics transfected U87 cells. The experiments were performed in triplicate and expressed as mean ± SD (*P < 0.05).

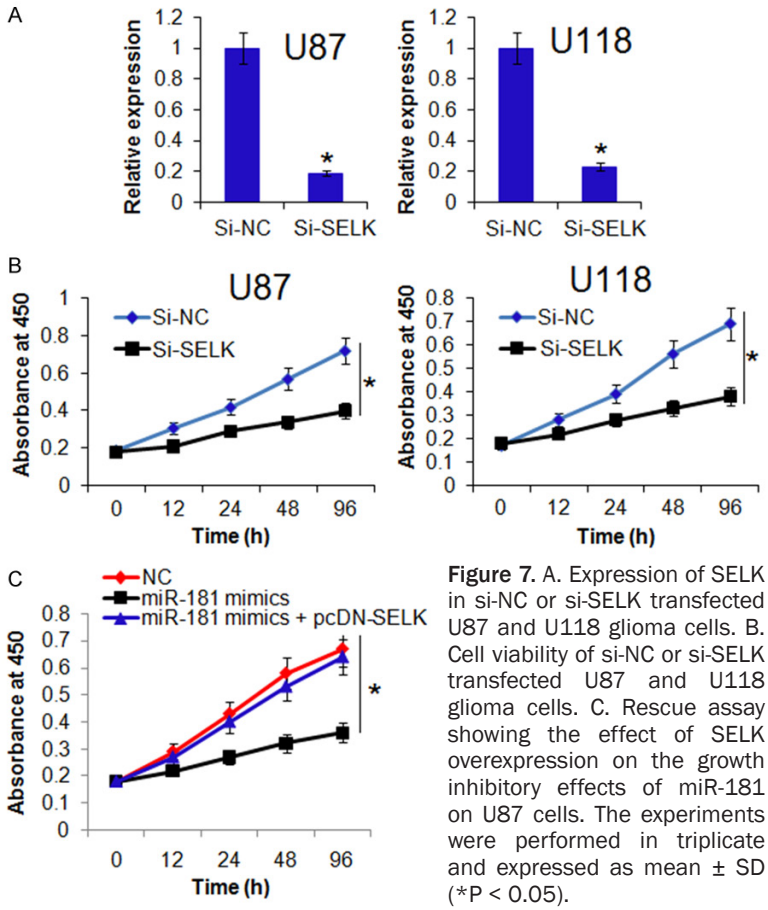

Figure 7. A. Expression of SELK in si-NC or si-SELK transfected U87 and U118 glioma cells. B. Cell viability of si-NC or si-SELK transfected U87 and U118 glioma cells. C. Rescue assay showing the effect of SELK overexpression on the growth inhibitory effects of miR-181 on U87 cells. The experiments were performed in triplicate and expressed as mean ± SD (*P < 0.05).

chondrocytes as well as the chronic myelogenous leukemia [23, 24]. The frequent relapses and the development of the drug resistance among the glioma cells to anticancer drugs such as temozolomide often makes it difficult to manage [25]. Herein we also investigated the effects of miR-181 overexpression on the sensitivity of the glioma U87 and U118 cells to the anticancer drug temozolomide and the results showed that miR-181 enhanced chemosensitivity of the U87 and U118 cells to temozolomide. These results are in agreement with the previous investigations wherein miR-181 has been shown enhance the drug sensitivity of the mitoxantone-resistant breast cancer cells [26]. Similarly, miR-181b enhances the chemosensitivity of the myeloid leukemia cells by modulating the expression of HMGB1 [27]. Additionally, the results of the present study are also supported by the observation that Aplysin enhances the temozolomide sensitivity of the glioma cells by upregulating the miR-181 expression [28]. A previously carried out study had also indicated that Activin and TGFβ enhance the microRNA-181 family to regulate the invasion of breast cancer cells [29]. Therefore we performed the transwell assay to assess the effects of miR-181 on the invasion of the glioma U87 and U118 cells.

Interestingly, it was found that miR-181 suppressed the invasion other U87 and U118 glioma cells indicating the implications of the miR-181 in the management of metastatic cancers. The miRs exert their effects by suppressing the expression of the target genes and each miR has several targets [30]. Herein bioinformatic analysis together with dual luciferase assay showed that miR-181 exerts its effects by targeting SELK. Additionally, the expression of SELK was considerably increased in all the glioma cells and overexpression of miR-181 could inhibit the expression of SELK. These observations are consistent with previous studies wherein SELK has been reported to be aberrantly overexpressed in colorectal cancer [30]. Moreover SELK1 has been shown to promote the metastasis of melanoma [31]. Taken together, the findings of the present study revealed that miR-181 is downregulated in the glioma cells. Overexpression of miR-181 in U87 and U118 glioma cells inhibited their proliferation by targeting SELK. Overexpression of miR-181 also suppressed the invasion enhanced the chemosensitivity of U87 glioma cells indicative of the therapeutic implications of miR-181 in glioma treatment.

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Disclosure of conflict of interest

None.

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