doi: 10.4149/gpb_2022019

ZNF300 enhances temozolomide resistance in gliomas by regulating lncRNA SNHG12

Junqi Fu, Jun Peng and Guolong Tu

Department of Neurosurgery, Haikou People's Hospital, Haikou, Hainan Province, China

Abstract. Gliomas are the most common type of primary brain tumors, with high recurrence rate and mortality. In contrast to the high incidence, the prognosis of gliomas is dismal, and the therapeutic effect of temozolomide (TMZ), first-line chemotherapy drug for gliomas, is extremely limited by TMZ-resistance. ZNF300 is a member of zinc finger proteins, and promotes cell proliferation in several types of cancer. This study is designed to appraise the effects of ZNF300 on TMZ-resistance in gliomas. The TMZ-resistant glioma cell lines were established in U251 and A-172 cells. ZNF300 was significantly upregulated in TMZ-resistant glioma cells. ZNF300 depletion remodel TMZ sensitivity of glioma cells through inhibiting cell proliferation and promoting cell apoptosis. Meanwhile, ZNF300 depletion brought down-regulation of c-myc and SNHG12 which could be counteracted by overexpression of c-myc. Moreover, SNHG12 performed as the downstream of ZNF300 and c-myc, and overexpression of SNHG12 also could neutralize the effects of ZNF300 depletion on cell proliferation and cell apoptosis. Our data manifested that ZNF300 serves as a novel therapeutic target and biomarker of TMZ-resistant gliomas *via* mediating c-myc/SNHG12 pathway.

Key words: ZNF300 — c-myc — SNHG12 — Temozolomide — Drug resistance — Gliomas

Introduction

Gliomas are the most common type of primary brain tumors, with an annual incidence of 5.26 *per* 100,000 population, accounting for 82% of all malignant primary brain tumors, and more than half of gliomas are glioblastoma (GBM) tumors which are the most malignant brain tumors (Omuro and DeAngelis 2013; Weller et al. 2015). Gliomas occur in a way of general increases with age, and with a higher morbidity is higher in men than in women (Ostrom et al. 2014; Camilloni et al. 2021). In contrast to the high incidence, the prognosis of gliomas is dismal. At present, surgery plus temozolomide chemotherapy is the standard treatment for gliomas (Weller et al. 2017). Temozolomide (TMZ) is an oral alkylating agent which can readily cross the blood-brain barrier, and serves as the first-line chemotherapy drug for glioma, and increases the median survival to 15 months through adding a methyl group to purine and pyrimidine in DNA to cause cell death (Zhang et al. 2012; Omuro and DeAngelis 2013). Even so, ameliorations in the prognosis for gliomas are still very poor, on account of tumor resistance and postoperative tumor recurrence (Chen et al. 2012). Therefore, it is urgent to illustrate the underlying mechanisms of TMZ resistance in gliomas and detect the potential biomarkers to forecast TMZ response in gliomas.

Long non-coding RNAs (lncRNAs) are a type of non-coding RNAs with more than 200 nucleotides, and have been reported to mediate various cell physiology and pathology (Nallasamy et al. 2018). lncRNA small nucleolar RNA host gene 12 (SNHG12) locates at chromosome 1p35.3 and is defined as a tumor promoter in multiple types of tumors including endometrial cancer, lung cancer and GBM (Liu et al. 2018). It has been reported that in models of TMZ resistant gliomas *in vivo* and *in vitro*, SNHG12 was upregulated and knockdown of SNHG12 reconstructed TMZ sensitivity in

Correspondence to: Junqi Fu, Department of Neurosurgery, Haikou People's Hospital, No. 43 Renmin Avenue, Haikou, Hainan Province, China
E-mail: fujunqi0211@163.com

glioma cells (Lu et al. 2020). Moreover, several studies demonstrated that c-myc which is a transcription factor could interact with the promoter region of SNHG12 and promote the expression of SNHG12 in NKTCL (nasal-type natural kiler/T-cell lymphoma) cells and TNBC (triple-negative breast cancer) cells, while inhibiting c-myc resulted in sensitivity to cisplatin in NKTCL cells (Wang et al. 2017; Zhu et al. 2019). Additionally, c-myc is significantly upregulated in TMZ-resistant glioma cells as well, and acts as a potential biomarker for TMZ resistance in gliomas (Higuchi et al. 2018; Lan et al. 2020; Luan et al. 2021a). Nevertheless, it is still unknown whether c-myc/SNHG12 pathway is implicated in TMZ-resistant gliomas.

ZNF300 is a member of zinc finger proteins, and promotes cell proliferation in several types of cancer, such as non-small-cell lung cancer, ovarian cancer and gastric cancer (Gloss et al. 2014; Yu et al. 2020; Zhou et al. 2021). In HeLa cells, overexpression of ZNF300 leaded to upregulation of c-myc (Wang et al. 2012). However, the effects of ZNF300 on gliomas and TMZ-resistant gliomas have not been identified and whether ZNF300 contributes to TMZ-resistant gliomas through c-myc/SNHG12 pathway remains unknown.

Thus, the purpose of this study was three-fold: (1) to explore the effect of ZNF300 on glioma cells; (2) to assess the effect of ZNF300 on TMZ-resistant glioma cells; (3) to evaluate whether ZNF300 contributes to TMZ-resistant gliomas through c-myc/SNHG12 pathway.

Materials and Methods

Cell culture and treatment

HEB cells, U251 cells and A-172 cells were bought from American Type Culture Collection (ATCC, Manassas, USA) and cultured in 10% FBS DMEM medium (FBS; Gibco, Rockville, MD, USA) with 1% penicillin/streptomycin in incubator at 37°C and 5% CO_2. TMZ-resistant glioma cells were established following the description in the study Li et al. (2021). Namely, U251 cells and A-172 cells were incubated with TMZ (1 μM) for 2 weeks, and then incubated with TMZ (2 μM) for another 2 weeks, and finally incubated with TMZ (400 μM). The TMZ-resistant glioma cells obtained finally were named as U251/TR cells and A-172/TR cells.

Cell viability assays

HEB cells, U251 cells, U251/TR cells, A-172 cells and A-172/TR cells were seeded into 96-well plates. With different treatment, cell viability of the different groups was evaluated by CellTiter 96 AQueous One Solution Cell Proliferation Assay (Promega).

Cell transfection

The SNHG12 cDNA and the plasmid vectors carrying human *ZNF300* gene were obtained from GenePharma (Shanghai, China). U251/TR cells and A-172/TR cells were seeded into 6-well plates at 1×10^6 cells *per* well and transduced at approximately 70% confluence with the *ZNF300* plasmid vectors/SNHG12 cDNA for 24 h according for the protocol.

Colony formation assay

U251/TR cells and A-172/TR cells were seeded into 6-well plates for 10 days. With different treatment, U251/TR cells and A-172/TR cells were washed with PBS and then fixed with 4% paraformaldehyde and then photoed by microscope (Olympus, Ishikawa, Japan).

Flow cytometry

U251/TR cells and A-172/TR cells were seeded into 6-well plates for different treatment (knockdown of ZNF300 through transfecting with sh-ZNF300). 1×10^5 of U251/TR cells and A-172/TR cells were firstly collected into 1.5 ml EP tubes and then incubated with propidium iodide (PI) and FITC-conjugated Annexin V for 15 min and finally assessed by flow cytometry analysis (BD FACSLyric^{TM}, California, USA).

Western blot

Cell lysates were extracted with RIPA buffer (Beyotime, Hangzhou, China), protease and phosphatase inhibitors, and the protein concentration measurement of cell lysates were analyzed by BCA Protein Assay kit (Beyotime, Hangzhou, China). SDS-PAGE, 7.5% and 10%, were used to separate proteins with 7 different molecular weight (ZNF300, MRP-1, p-gp, Bcl-2, Bax, c-myc and GAPDH). Then the proteins were transferred from SDS-PAGE to polyvinylidene fluoride membranes which then were incubated with primary antibodies against ZNF300, MRP-1, p-gp, Bcl-2, Bax, c-myc (all from Abcam, Cambridge, UK) and GAPDH (Santa Cruz, California, USA) for 16 h at 4°C. Finally, the blots were incubated with horseradish peroxidase (HRP)-conjugated secondary antibodies (Beyotime, Jiangsu, China), and evaluated by Molecular Imager ChemiDoc XRS+System (Bio-Rad, Philadelphia, PA).

Statistical analysis

SPSS software was used for statistical analysis. Unpaired two-tailed Student's *t* test was used to perform statistical analyses. Data were presented as mean ± standard error of

the mean (SEM). Differences were considered significant when $p < 0.05$.

Results

ZNF300 was high expressed in glioma cells and TMZ-resistant glioma cells

Firstly, we detected the cell viability of glioma cell lines and calculated the value of half maximal inhibitory concentration (IC_{50}) to verify the establishment of TMZ-resistant glioma cells. As shown in Figure 1A, cell viability was reduced by the treatment of TMZ in a dose-dependent way, and the IC_{50} values of TMZ were significantly increased in U251/TR cells and A-172/TR cells. Then we assessed the expression of ZNF300 in glioma cells. As displayed in Figure1B, ZNF300 was high expressed in glioma cells. Moreover, compared with U251 cells and A-172 cells, the protein level of ZNF300 was remarkably upregulated in U251/TR cells and A-172/TR cells, indicating that ZNF300 should contribute to TMZ-resistant gliomas.

Knockdown of ZNF300 enhanced TMZ sensitivity and suppressed cell proliferation in TMZ-resistant glioma cells

We further explored the effects of ZNF300 on TMZ-resistant glioma cells through transfection of sh-ZNF300#1 and sh-

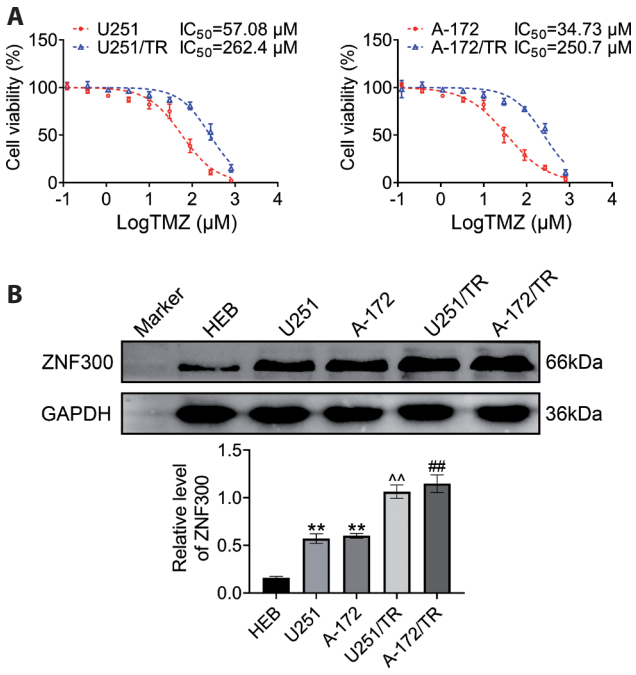

Figure 1. ZNF300 was up-regulated in TMZ-resistant glioma cells. **A.** Dose-dependent effects of TMZ on cell viability. **B.** Representative images of Western blot results and optical density for the protein blot of ZNF300. Data were expressed as means ± SEM; $n = 5$ *per* group. ** $p < 0.01$ *vs.* HEB cells, ^^ $p < 0.01$ *vs.* U251 cells, ## $p < 0.01$ *vs.* A-172 cells. TMZ, temozolomide.

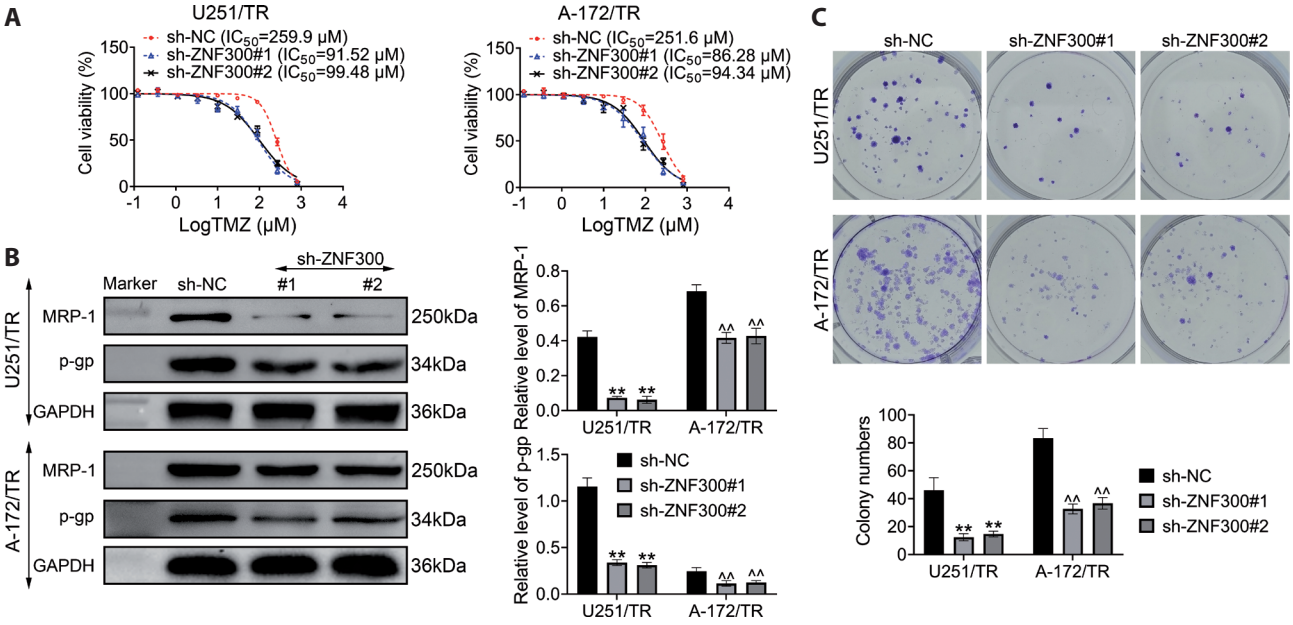

Figure 2. Knockdown of ZNF300 suppressed cell proliferation in TMZ-resistant glioma cells. **A.** Dose-dependent effects of TMZ on cell viability. **B.** Representative images of Western blot results and optical density for the protein blot of MRP-1and p-gp against GAPDH in TMZ-resistant glioma cells upon the indicated treatment. **C.** Representative images of colony formation assays in TMZ-resistant glioma cells upon the indicated treatment. Data were expressed as means ± SEM; $n = 5$ *per* group. ** $p < 0.01$ *vs.* sh-NC of U251/TR cells, ^^ $p < 0.01$ *vs.* sh-NC of A-172/TR cells. TMZ, temozolomide; sh-NC, negative control.

ZNF300#2 to knock down ZNF300 in U251/TR cells and A-172/TR cells. The results showed that knockdown of ZNF300 significantly decreased the IC_{50} values of TMZ, and the protein levels of TMZ-resistant marker proteins MRP-1 and p-gp in U251/TR cells and A-172/TR cells (Fig. 2A and B). The results of colony formation assay indicated that knockdown of ZNF300 reduced the rate of colony formation in U251/TR cells and A-172/TR cells (Fig. 2C).

Knockdown of ZNF300 induced cell apoptosis in TMZ-resistant glioma cells

As shown in Figure 3A, knockdown of ZNF300 resulted in the increase of the rate of apoptotic cells in U251/TR cells and A-172/TR cells. Bax, a member of proapoptotic proteins, plays an important role in apoptotic pathway, while Bcl-2 is an antiapoptotic protein which is inhibited in cell apoptosis. Western blot results (Fig. 3B) revealed that knockdown of ZNF300 dramatically increased the protein level of BAX, and decreased the protein level of Bcl-2 in U251/TR cells and A-172/TR cells.

Overexpression of c-myc inverted the effects of ZNF300 depletion on TMZ-resistant glioma cells

To explore the underlying mechanisms of ZNF300 in TMZ-resistant gliomas, we evaluated the expression of c-myc and SNHG12. Knockdown of ZNF300 leaded to remarkable decrease in the expression of c-myc and SNHG12 (Fig. 4A and B). While overexpression of c-myc reversed the inhibitory effects on the expression of c-myc and SNHG12, suggesting that ZFN300 induced TMZ-resistant glioma cells through c-myc/SNHG12 pathway (Fig. 4C and D).

Overexpression of SNHG12 counteracted the effects of ZNF300 depletion on TMZ-resistant glioma cells

To determine the role of SNHG12, which is the direct transcription target of c-myc, in the ZNF300-mediated TMZ-resistant gliomas, we detected the rate of colony formation and apoptotic cells in ZNF300 deficient glioma cells through SNHG12 overexpression. The results

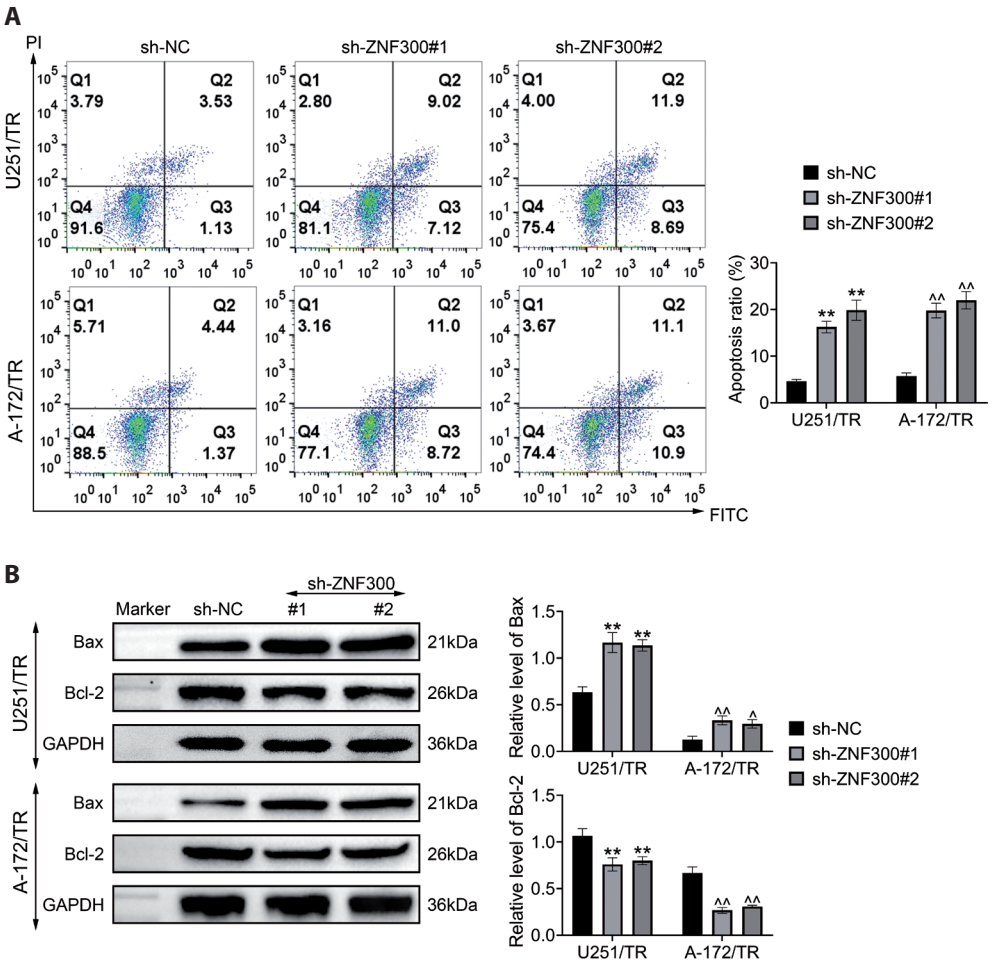

Figure 3. Knockdown of ZNF300 suppressed cell apoptosis in TMZ-resistant glioma cells. **A.** Representative images of flow cytometry for apoptosis assay in TMZ-resistant glioma cells upon the indicated treatment. **B.** Representative images of Western blot results (left panel), Optical density for the protein blot of Bax and Bcl-2 against GAPDH (right panel) in TMZ-resistant glioma cells upon the indicated treatment. Data were expressed as means ± SEM; $n = 5$ *per* group. ** $p < 0.01$ *vs.* sh-NC of U251/TR cells, ^ $p < 0.05$, ^^ $p < 0.01$ *vs.* sh-NC of A-172/TR cells. TMZ, temozolomide; sh-NC, negative control.

demonstrated that overexpression of SNHG12 reversed the inhibition of cell proliferation and promotion of cell apoptosis which were induced by ZNF300 knockdown (Fig. 5A and B). These results indicated that SNHG12 performed as the executor in ZNF300-mediated TMZ-resistant gliomas.

Discussion

Glioma is characterized by rapid proliferation ability and is hard to completely remove through surgery (Lapointe et al. 2018). Chemotherapy or postoperative adjuvant chemotherapy can improve the quality of life of patients to a certain extent, but the efficacy of chemotherapy is limited due to the difficulty of drugs to penetrate the blood-brain barrier and drug resistance. In order to better guide the selection of chemotherapy drugs and reduce drug resistance, more and more key targets need to be found. Even with standard chemotherapy and surgical resection, the median survival time of gliomas patients is still less than 15 months. TMZ is the first-line chemotherapy for glioma. However, the resistance to TMZ greatly restricts its therapeutic effects (Minniti et al. 2009). Therefore, we explored the underlying mechanism of TMZ-resistant gliomas. Our results revealed that ZNF300 contributed to TMZ-resistant gliomas through regulating c-myc/SNHG12 signaling pathway. As far as we know, this is the first time to reveal that ZNF300 mediates TMZ-resistant gliomas.

In this study, we successfully constructed a TMZ-resistant gliomas cell line following the description in the study Li et al. (2021). Our data further confirmed the effects of ZNF300 on this type of cell line. In fact, the role of ZNF300 on the progression of cancers has been widely revealed. ZNF300 was widely expressed in multiple organs, such as heart, brain, and testis (Cao et al. 2007). What's more, the expression of ZNF300 was much higher in various tumors than in normal tissues. In non-small-cell lung cancer, ZNF300 was found to contribute to chemoresistance through suppressing MAPK/ERK pathway and regulating MYC/AURKA/BORA/PLK1 axis (Yan et al. 2017; Yu et al. 2020). Meanwhile, TMZ-resistance in glioma was occurred by increased

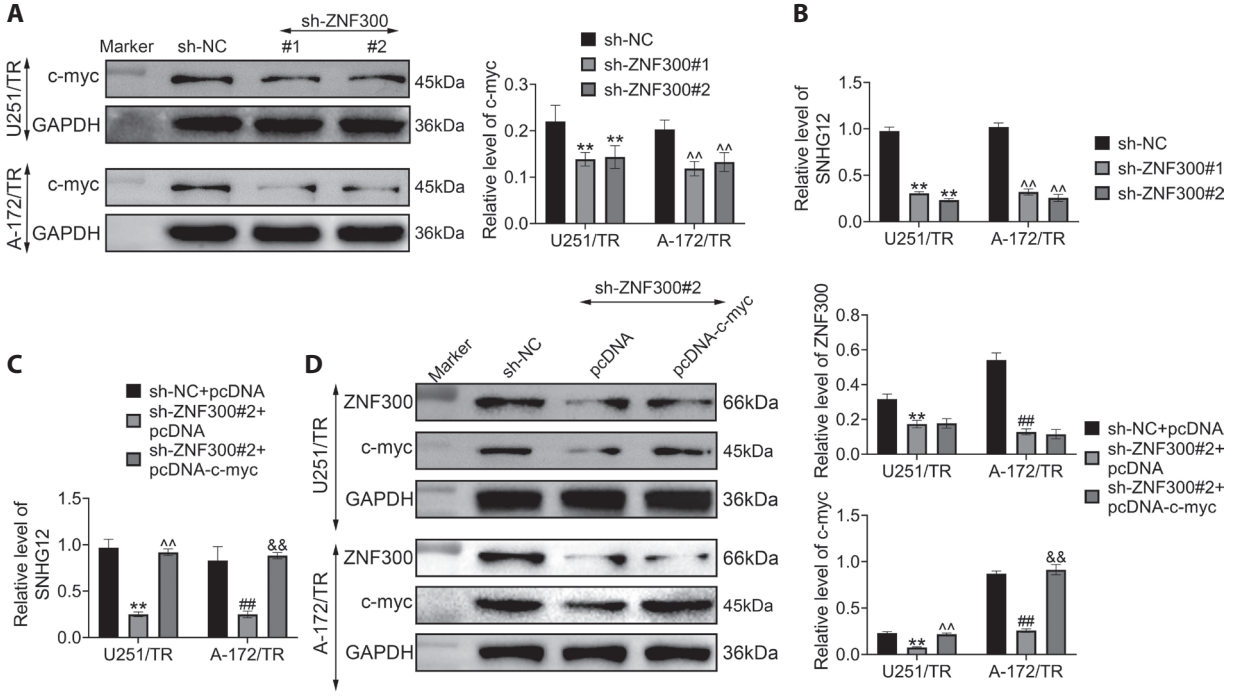

Figure 4. Overexpression of c-myc inverted the effects of ZNF300 depletion on TMZ-resistant glioma cells. **A.** Representative images of Western blot results and optical density for the protein blot of c-myc against GAPDH in TMZ-resistant glioma cells upon the indicated treatment. **B.** Relative level of SNHG12. **C.** Relative level of SNHG12 in TMZ-resistant glioma cells upon the indicated treatment. **D.** Representative images of Western blot results and optical density for the protein blot of ZNF300 and c-myc against GAPDH in TMZ-resistant glioma cells upon the indicated treatment. Data were expressed as means ± SEM; $n = 5$ *per* group. ** $p < 0.01$ *vs*. sh-NC of U251/TR (in A, B) and *vs*. sh-NC+pcDNA of U251/TR (in C, D), ^^ $p < 0.01$ *vs*. sh-NC of A-172/TR (in A, B) and *vs*. shZNF300#2+pcDNA of A-172/TR (in C, D), ## $p < 0.01$ *vs*. sh-NC of A-172/TR, && $p < 0.01$ *vs*. sh-ZNF300#2+pcDNA of A-172/TR. TMZ, temozolomide; sh-NC, negative control.

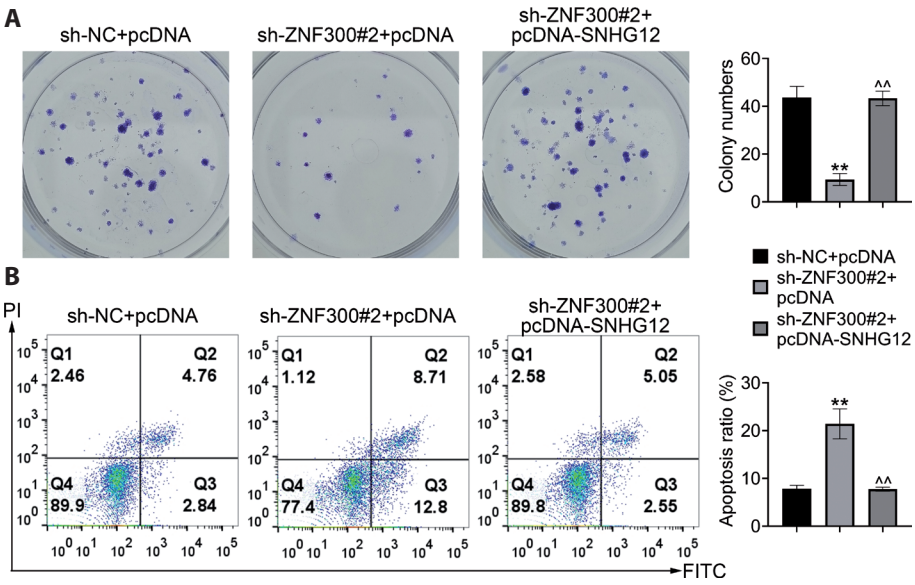

Figure 5. Overexpression of SNHG12 counteracted the effects of ZNF300 depletion on TMZ-resistant glioma cells. **A.** Representative images of colony formation assays in TMZ-resistant glioma cells upon the indicated treatment. **B.** Representative images of flow cytometry for apoptosis assay in TMZ-resistant glioma cells upon the indicated treatment. Data were expressed as means ± SEM; $n = 5$ *per* group. ** $p < 0.01$ *vs.* sh-NC+pcDNA, ^^ $p < 0.01$ *vs.* sh-ZNF300#2+pcDNA. TMZ, temozolomide; sh-NC, negative control.

MDR1 and p-gp (Munoz et al. 2015; Luan et al. 2021b). Our results showed that the upregulated ZNF300 was related with TMZ-resistance in glioma cells, and knockdown of ZNF300 reversed the high expression of MRP-1 and p-gp. Thus, we focused on the role of ZNF300 in cell proliferation and cell apoptosis in TMZ-resistant glioma cells through knockdown of ZNF300. The assays displayed that ZNF300 depletion leaded to an increase in rate of apoptotic cells and a decrease in the rate of cell proliferation in TMZ-resistant glioma cells through regulation the expression of c-myc. All these studies confirmed the effects of ZNF300 on the progression and chemoresistance of tumors, and the precise mechanism needs further study.

c-myc is a basic helix-loop-helix transcriptional factor which plays a key role in cell proliferation and apoptosis in gliomas (Lan et al. 2020). In triple-negative breast cancer, c-myc regulated cell proliferation and apoptosis through bounding to SNHG12 promoter regions and enhancing the expression of SNHG12 (Wang et al. 2017). Consistently, in NKTCL, c-myc/SNHG12 pathway suppressed drug sensitivity in NKTCL, while inhibition of c-myc/SNHG12 pathway enhanced sensitivity to cisplatin (Zhu et al. 2019). Therefore, we evaluated the role of c-myc/SNHG12 signaling pathway in ZNF300-mediated TMZ-resistant gliomas. The data demonstrated that the effects of ZNF300 depletion on TMZ-resistant glioma cells could be reversed by overexpression of c-myc and SNHG12, and SNHG12 performed as the downstream of c-myc.

To sum up, this study has indicated that ZNF300 is greatly upregulated in TMZ-resistant glioma cells and the high expression of ZFN300 is upstream of c-myc/SNHG12 pathway. Knockdown of ZNF300 reversed the resistance to TMZ in glioma cells, showing significant inhibition of cell proliferation and enhancement of cell apoptosis. Moreover, our results displayed that ZFN300 may promote TMZ-resistant gliomas through activating c-myc/SNHG12 pathway. Therefore, ZNF300 should be a novel therapeutic target and biomarker of TMZ-resistant gliomas *via* mediating c-myc/SNHG12 pathway.

Funding. This work was supported by Hainan Medical Research Fund. (Grant No. 20A200009).

Conflict of interests. The authors state that there are no conflicts of interest to disclose.

Authors' contributions. JF designed the study and carried them out; JP supervised the data collection, analyzed the data, interpreted the data; GT prepare the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

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Received: February 15, 2022
Final version accepted: April 1, 2022