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UPF1 alleviates the progression of glioma *via* targeting lncRNA CYTOR

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Abstract. – OBJECTIVE: To uncover the role of UPF1 in alleviating the progression of glioma via targeting long non-coding RNA (lncRNA) CYTOR and underlying mechanism.

PATIENTS AND METHODS: A total of 30 glioma tissues surgically resected from glioma patients and 30 brain tissues were collected from brain trauma patients undergoing craniotomy during the same period. Relative levels of UPF1 and CYTOR in collected tissues were detected by quantitative Real Time-Polymerase Chain Reaction (qRT-PCR). Correlation between levels of UPF1 and CYTOR in glioma tissues was assessed, and the regulatory effects of UPF1/CYTOR on proliferative and invasive abilities in U87 and LN229 cells were evaluated by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) and transwell assay, respectively. In addition, the interaction between UPF1 and CYTOR was explored by RIP (RNA-Binding Protein Immunoprecipitation) assay. Through Actinomycin D treatment in U87 and LN229 cells, RNA stability of CYTOR influenced by UPF1 was determined. Finally, rescue experiments were conducted to ascertain the involvement of CYTOR in UPF1-regulated progression of glioma.

RESULTS: UPF1 was downregulated in glioma tissues and cells. A lower level of UPF1 was observed in glioma tissues in the more advanced stage with a larger tumor size. Besides, the overexpression of UPF1 markedly suppressed proliferation and invasion abilities of U87 and LN229 cells, and CYTOR was upregulated in glioma tissues and cells, which was negatively correlated with UPF1 level. Moreover, the overexpression of UPF1 decreased the half-life of CYTOR in glioma cells. Furthermore, the RIP assay confirmed the interaction between UPF1 and CYTOR. Rescue experiments finally confirmed that the overexpression of CYTOR partially reversed the inhibitory effects of UPF1 on proliferation and invasion abilities in glioma.

CONCLUSIONS: UPF1 is down-regulated in glioma and alleviates the progression of glioma via targeting CYTOR.

Key Words:
UPF1, Glioma, CYTOR, Proliferation, Invasion, Progression.

Introduction

Glioma is a common intracranial malignancy, accounting for 40-65% of brain tumors. Due to tissue heterogeneity and strong invasiveness, glioma severely affects human health. More seriously, the incidence of glioma presents a younger trend[1,2]. Currently, great progress has been made in diagnostic approaches and therapeutic methods for glioma (i.e., surgery, chemotherapy, target drugs, and biochemical treatment). The prognosis of glioma, however, is still unsatisfied even after active treatment[3,4]. Great effects have been made on exploring mechanisms of the etiology and pathogenesis of glioma[5,6]. It is necessary to further uncover sensitive indicators and genetic targets for improving the survival of glioma patients. UPF1, as an RNA/DNA-dependent ATPase and ATP-dependent RNA helicase, exerts a key role in inducing mRNA decay and non-coding RNA (ncRNA) degradation. UPF1 is a core factor of the NMD (nonsense-mediated mRNA decay) pathway, which is one of the most conservative factors[7,8]. The interaction between UPF1 and other NMD factors triggers the activation of the NMD pathway. UPF1 binds to ATP and RNA, which has both RNA-dependent ATPase activity and 5'-3' RNA helicase activity[9-11]. It is reported that UPF1 mutation leads to the absence of NMD activity, thus resulting in pathological conditions. For example, UPF1/MALAT1 regulates the progression of gastric cancer[12,13]. In hepatocellular carcinoma[14], UPF1 suppresses the malignant progression by targeting UCA1, providing theoretical basis for clinical treatment. NcRNAs are extensively distributed in human bodies, which are hot topics in tumor researches. According to the length, non-coding RNAs are classified into long ncRNAs (lncRNAs) and short-chain RNAs (i.e., miRNAs, siRNAs, and piRNAs)[15,16]. LncRNAs span over 200 nucleotides and lack of protein-encoding functions, and they are widely involved

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in life activities. Besides, lncRNAs used to be considered as by-products of RNA polymerase II transcription. With in-depth researches, biological functions of lncRNAs have been identified. Synthesis of lncRNAs is similar to that of mRNAs, involving splicing, folding, capping, and polyadenylation. LncRNAs participate in epigenetic regulation, chromatin modification, transcriptional activation, and interference[17-20]. Particularly, lncRNAs are of significance in tumorigenesis[21,22]. Multiple lncRNAs have been discovered to affect malignant phenotypes of tumor diseases[23-26]. Yuan et al[27] have confirmed the critical role of CYTOR in the progression of cardiac hypertrophy, and CYTOR also affects tumor progression and serves as a therapeutic target[28-30]. It is believed that lncRNAs are promising candidates for monitoring and treatment of tumor diseases.

Patients and Methods

Patients and Samples

Thirty glioma tissues surgically resected from glioma patients from January 2015 to July 2017 in The First Affiliated Hospital, Nanchang University and 30 brain tissues of brain trauma patients undergoing craniotomy during the same period were harvested. None of the enrolled glioma patients received preoperative anti-tumor therapy. Tissue samples were immediately frozen in liquid nitrogen and preserved at –80°C. Patients and their families in this study have been fully informed. This investigation was approved by the Ethics Committee of The First Affiliated Hospital, Nanchang University.

Cell Culture and Transfection

Glioma cell lines (U251, U87, Hs683, and LN229) and a normal brain glial cell line (HEB) were purchased from American Type Culture Collection (ATCC; Manassas, VA, USA). Cells were cultured in Roswell Park Memorial Institute-1640 (RPMI-1640; HyClone, South Logan, UT, USA) containing 10% fetal bovine serum (FBS; HyClone, South Logan, UT, USA), 100 U/mL penicillin and 100 μg/mL streptomycin in an incubator with 5% CO_2 at 37°C.

pcDNA3.0-UPF1 and pcDNA3.0-CYTOR were constructed by cloning complementary deoxyribose nucleic acids (cDNAs) of UPF1 and CYTOR into pcDNA3.0 vector, respectively. Cell transfection was performed at 70% confluence using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA).

Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR)

The total RNAs were extracted from cells using TRIzol reagent (Invitrogen, Carlsbad, CA, USA). Briefly, 5×10^6 cells were lysed in 1 mL of TRIzol and 0.2 mL of chloroform. After 5-min sample resting and 10-min centrifugation at 4°C, 12000 rpm, the supernatant was removed to a new Eppendorf (EP) tube (SARSTEDT, Numbrecht, Germany), and the cells were incubated with isodose isopropanol. Subsequently, centrifuged precipitant was washed by 75% ethanol, and the collected RNAs were air dried. The obtained RNA was dissolved in diethyl pyrocarbonate (DEPC) water (Beyotime, Shanghai, China), and quantified.

High-quality RNAs were subjected to reverse transcription, and the extracted cDNAs were applied for PCR using SYBR Green method (TaKaRa, Otsu, Shiga, Japan), with glyceraldehyde 3-phosphate dehydrogenase (GAPDH) as the internal reference. Primer sequences are as follows: GAPDH, F: 5'-AGAAGGCTGGGGCTCATTTG-3', R: 5'-AGGGGCCATCCACAGTCTTC-3'; UPF1, F: 5'-ACCGACTTTACTCTTCCTAGCC-3', R: 5'-AGGTCCTTCGTGTAATAGGTGTC-3'; CYTOR, F: 5'-TTTCAAATTGACATTCCAGACA-3', R: 5'-AGGGATTAAGACACATAGAGAC-3'.

Transwell Assay

Cells were prepared to suspension at 1×10^5 cells/mL. Then, 100 μL of suspension was applied in the upper side of transwell chamber (Corning, Corning, NY, USA), whereas 500 μL of medium containing 20% FBS was applied in the bottom side. After 48 h of incubation, cells penetrated to the bottom side were fixed in methanol for 15 min, stained with crystal violet for 20 min, and counted using a microscope.

MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyl Tetrazolium Bromide) Assay

Cells were inoculated in a 96-well plate at 1×10^4 cells/well. At the appointed time points, the cells reacted with 20 μL of MTT solution (5 mg/mL) per well for 4 h (Sigma-Aldrich, St. Louis, MO, USA). Afterwards, medium was replaced and 150 μL of dimethyl sulfoxide (DMSO; Sigma-Aldrich, St. Louis, MO, USA) was added. The mixture was shaken at a low speed for 10 min to dissolve the crystals sufficiently. Ultimately, absorbance was determined at 450 nm.

RIP (RNA-Binding Protein Immunoprecipitation) Assay

RIP assay was performed following the procedures of Millipore Magna RIP Kit (Millipore, Billerica, MA, USA). Cells were incubated with anti-IgG or anti-UPF1 at 4°C overnight. Then, a protein-RNA complex was obtained after capturing intracellular specific proteins by the antibody. Subsequently, proteins were digested by proteinase K and the RNAs were extracted. During the experiment, the magnetic beads were repeatedly washed with RIP washing buffer to remove non-specific adsorption as much as possible. The immunoprecipitant RNAs were finally quantified by qRT-PCR.

Determination of RNA Stability

Cells were incubated with 5 μg/mL Actinomycin D for the appointed time. Total RNAs were extracted before and after Actinomycin D treatment, its levels were then measured, and the half-life of mRNAs was calculated.

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 13.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for data analysis. All data were expressed as mean ± SD (standard deviation). The paired two-tailed *t*-test or Chi-square test was used for the comparison between two groups. Correlation between the expression levels of two genes was conducted by Spearman correlation test. $p<0.05$ was considered to be statistically significant.

Results

UPF1 Was Downregulated With The Enlargement of Tumor Size and Elevation of Clinical Stage

A total of 30 glioma tissues and 30 normal brain tissues were collected. QRT-PCR data showed a lower level of UPF1 in glioma tissues than that of normal ones (Figure 1A). Particularly, UPF1 was

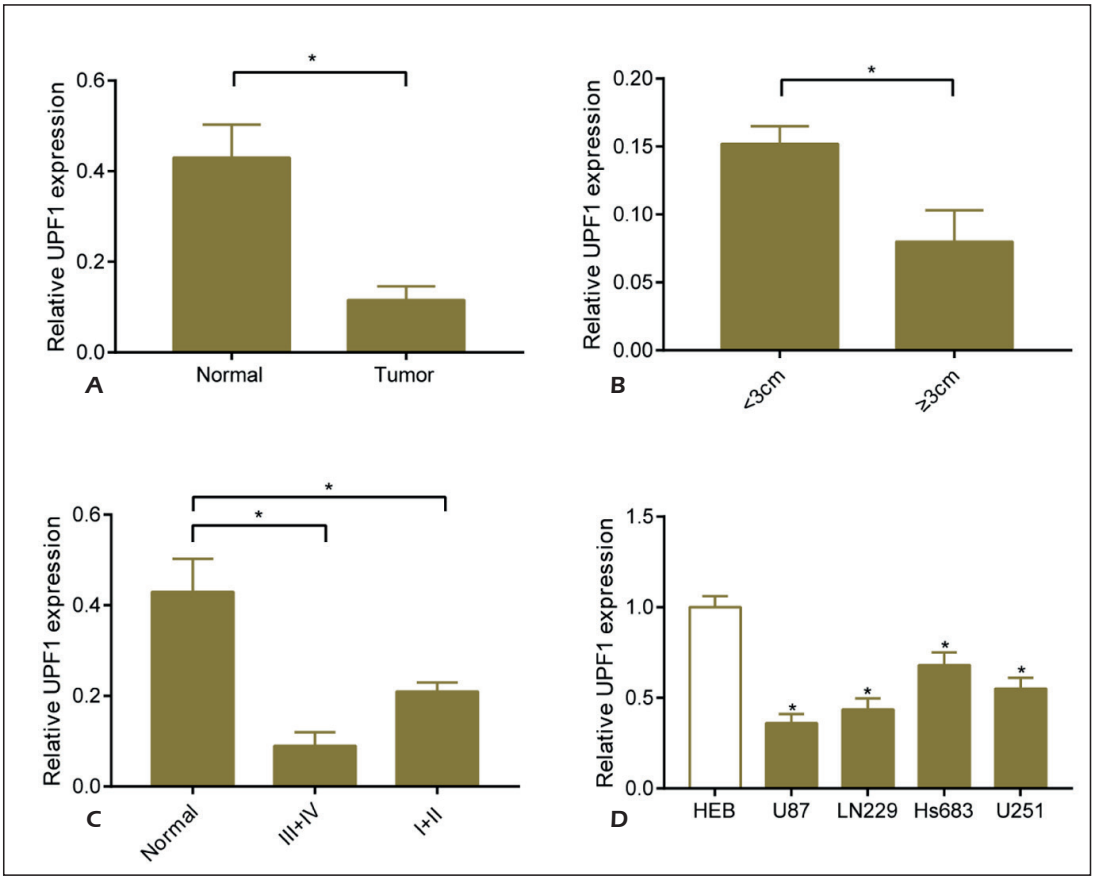

Figure 1. UPF1 is down-regulated with the enlargement of tumor size and elevation of clinical stage. **A**, UPF1 level is higher in normal brain tissues than that of glioma tissues. **B**, UPF1 level is negatively related to the size of glioma. **C**, UPF1 level is lower in advanced glioma. **D**, UPF1 level is lower in glioma cell lines (U251, U87, Hs683, and LN229) than that of normal brain glial cell line (HEB). *$p<0.05$.

down-regulated in glioma tissues with a larger tumor size (≥3 cm) and later stage (III+IV; Figure 1B, 1C). Similarly, UPF1 was down-regulated in glioma cells (Figure 1D). Therefore, it was speculated that UPF1 was involved in the malignant progression of glioma.

Overexpression of UPF1 Suppressed the Proliferation and Invasion Abilities in Glioma

Transfection of pcDNA3.0-UPF1 markedly up-regulated the protein and mRNA levels of UPF1 in U87 and LN229 cells (Figure 2A, 2B). Subsequently, MTT assay revealed the decreased viability in glioma cells overexpressing UPF1 (Figure 2C). In addition, transwell assay uncovered the attenuated invasiveness in U87 and LN229 cells with UPF1 overexpression (Figure 2D). The above results indicate that UPF1 can be a potential tumor-suppressor gene in glioma.

UPF1 Regulated the Progression of Glioma Via Targeting CYTOR

LncRNAs are able to regulate gene transcription by interacting with proteins[31]. Here, the presence of binding sites in the promoter regions of

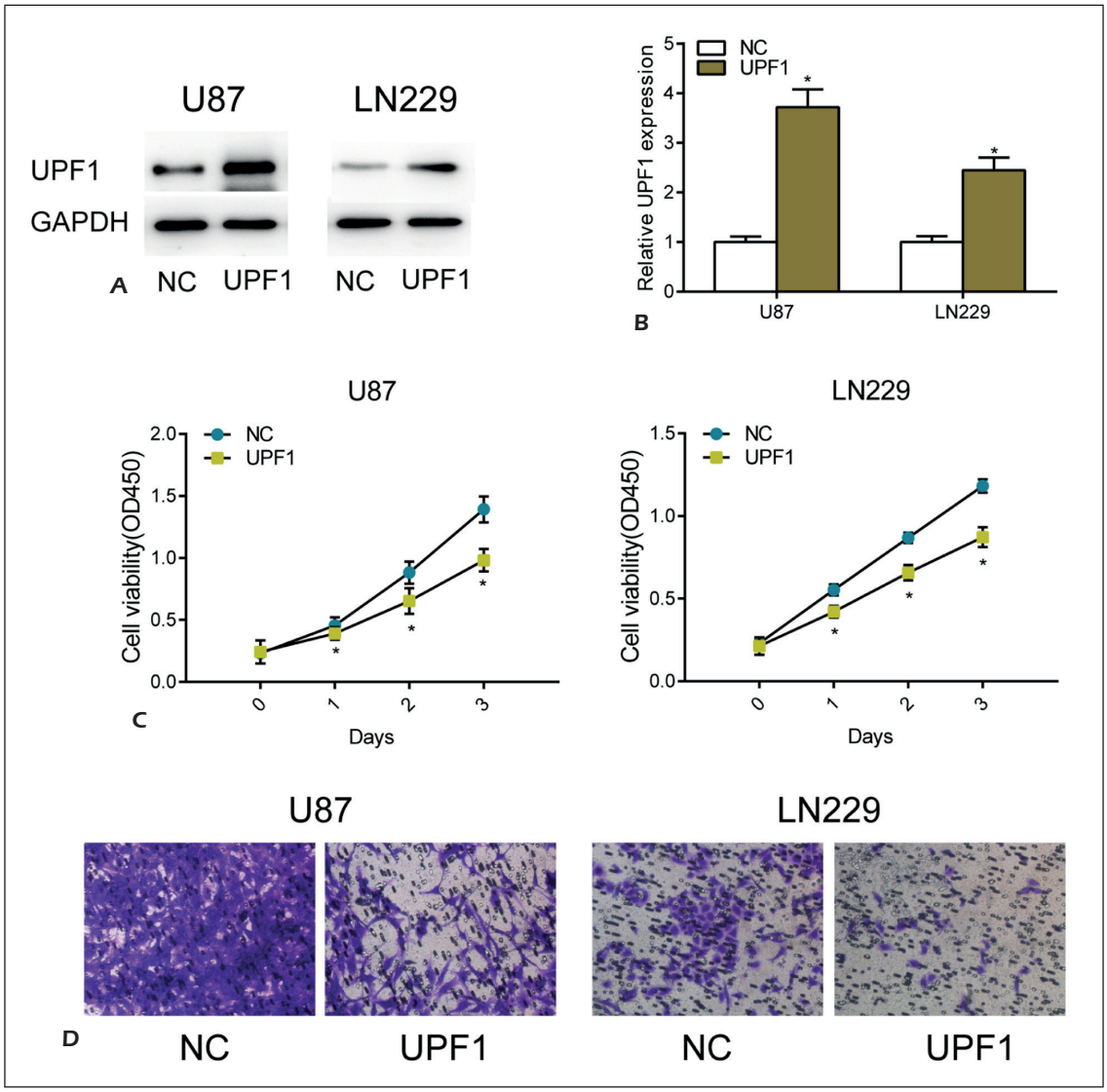

Figure 2. Overexpression of UPF1 suppresses proliferation and invasion abilities in glioma. **A**, Transfection efficacy of pcDNA3.0-UPF1 in U87 and LN229 cells detected by Western blotting. **B**, Transfection efficacy of pcDNA3.0-UPF1 in U87 and LN229 cells detected by qRT-PCR. **C**, MTT assay verifies that the viability of U87 and LN229 cells transfected with pcDNA3.0-UPF1 is decreased compared with those transfected with NC. **D**, Transwell assay reveals that the invasiveness of U87 and LN229 cells transfected with pcDNA3.0-UPF1 is attenuated compared with those transfected with NC (40X). *$p<0.05$.

UPF1 and CYTOR was predicted through starBase v2.0 and Targetscan. CYTOR was found to be up-regulated in glioma tissues (Figure 3A), which was negatively associated with the UPF1 level (Figure 3B). U87 and LN229 cells transfected with NC or pcDNA3.0-UPF1 were incubated with 5 μg/mL Actinomycin D for different time points. The results demonstrated that the overexpression of UPF1 greatly shortened the half-life of CYTOR mRNA (Figure 3C). Furthermore, RIP assay verified the interaction between UPF1 and CYTOR in glioma cells (Figure 3D), and the overexpression of UPF1 remarkably down-regulated CYTOR in U87 and LN229 cells (Figure 3E).

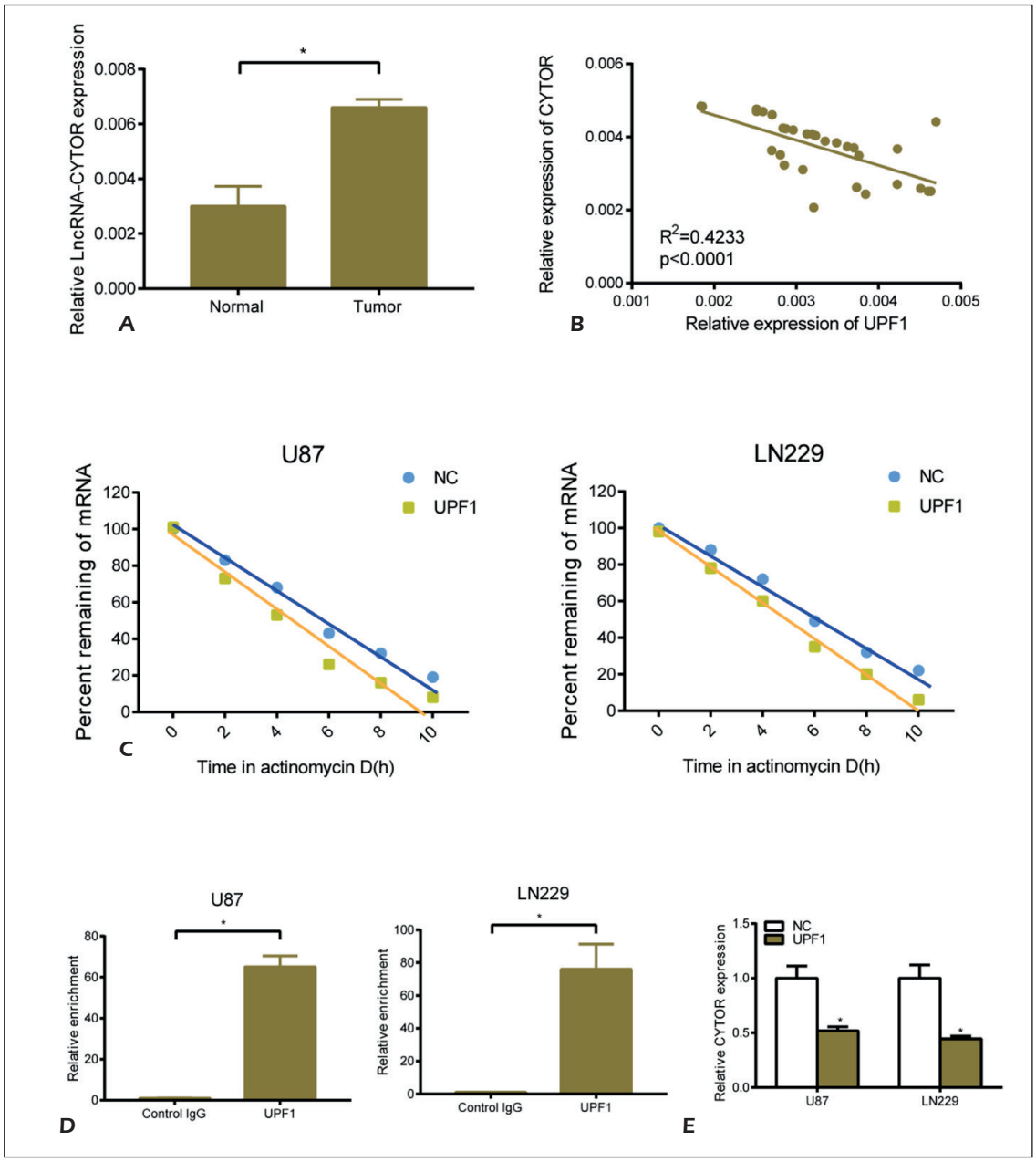

Figure 3. UPF1 regulates the progression of glioma via targeting CYTOR. **A**, CYTOR level is lower in normal brain tissues than that of glioma tissues. **B**, UPF1 level is negatively related to CYTOR level in glioma tissues. **C**, Percentage of remaining mRNA level of CYTOR in U87 and LN229 cells transfected with NC or pcDNA3.0-UPF1 and incubated with 5 μg/ml Actinomycin D for appointed time. **D**, RIP assay shows the enrichment of CYTOR in IgG and UPF1 in U87 and LN229 cells. **E**, Relative level of CYTOR in U87 and LN229 cells transfected with NC or pcDNA3.0-UPF1. *p<0.05.

Overexpression of CYTOR Partially Abolished the Inhibitory Effects of UPF1 on Growth and Invasiveness in Glioma

Based on the above findings, it was speculated that CYTOR was involved in UPF1-regulated progression of glioma. Transfection efficacy of pcDNA3.0-CYTOR was first tested in glioma cells (Figure 4A). Of note, the decreased viability in glioma cells overexpressing UPF1 was partially reversed by CYTOR overexpression (Figure 4B). The overexpression of CYTOR abolished the inhibitory effect of UPF1 on glioma invasiveness (Figure 4C), indicating that UPF1 suppresses the growth and invasiveness in glioma *via* targeting CYTOR.

Discussion

Glioma is derived from neuroepithelium, which is a common intracranial malignancy with the incidence rate of 3-8/100,000[31]. Symptoms and signs of glioma mainly depend on its occupancy effect and the affected brain function[32]. Both innate genetic factors and environmental carcinogenic factors trigger the tumorigenesis of glioma[33]. Some genetic diseases, such as neurofibromatosis and tuberculous sclerosis, are genetic predisposing factors for glioma. In addition, some environmental carcinogenic factors may also be associated with the occurrence of glioma. Electromagnetic radiation, for example, is linked to the etiology of glioma[34]. The pathogenesis of glioma is complicated and requires to be further explored.

LncRNAs are widely involved in life activities[35], and capable of regulating various aspects of tumor diseases[36,37]. With the progression made on sequencing technology and genomic analyses, differentially expressed lncRNAs in tumor tissues have been well concerned[38]. As a vital tumor-related lncRNA, CYTOR affects many types of tumors[17]. Its biological function in glioma, however, remains to be further researched. The novelty of this present study was that we first explored the biological function of CYTOR in glioma and investigated the potential mechanism.

UPF1 is a highly conserved phosphoprotein, whose complex stimulates the degradation of abnormally expressed mRNAs, and it is necessary in embryonic development and survival[39]. In NMD and non-NMD pathways, UPF1 exerts a crucial function[9]. During NMD, UPF1 is associated with a translation termination codon for post-termination complex. Besides, UPF1 enhances the possibility of NMD *via* promoting the G1/S phase[10]. As a potential mediator of MALAT1, UPF1/MALAT1 axis is a potential target for gastric cancer[40]. UPF1

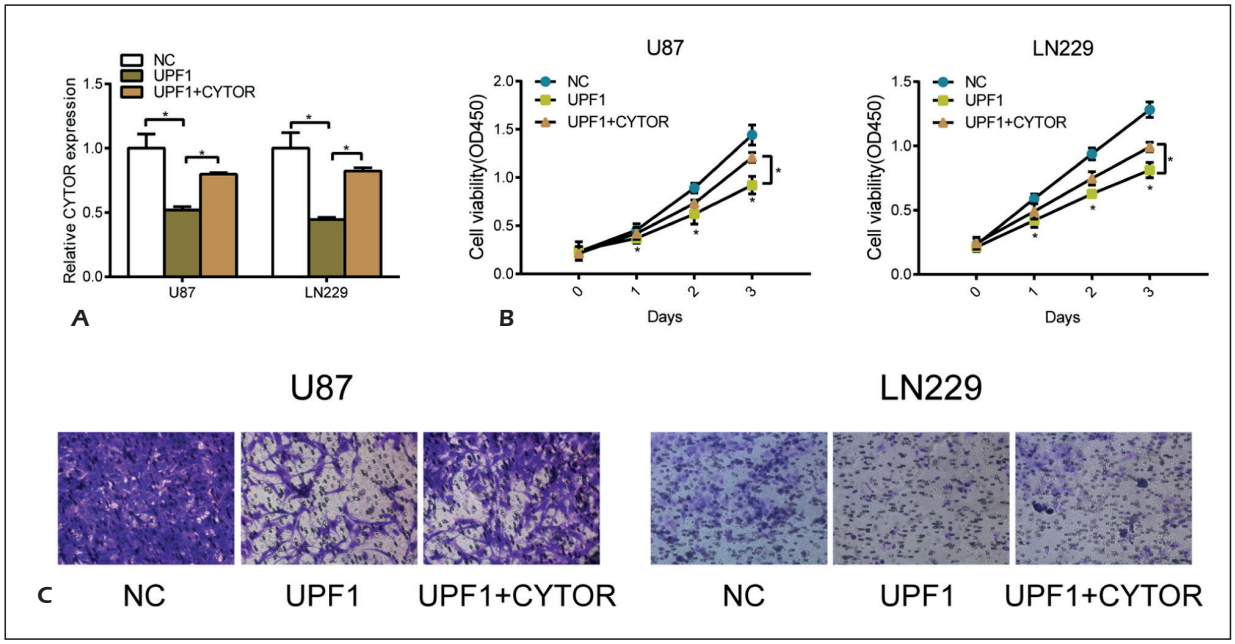

Figure 4. Overexpression of CYTOR partially abolishes the inhibitory effects of UPF1 on growth and invasiveness in glioma. U87 and LN229 cells are transfected with NC, pcDNA3.0-UPF1 or pcDNA3.0-UPF1 + pcDNA3.0-CYTOR. **A**, Relative level of CYTOR. **B**, Cell viability. **C**, Cell invasiveness (40X). *$p<0.05$.

is down-regulated in human lung adenocarcinoma, which is believed as a tumor-suppressor gene[41]. Consistently, findings in the present study uncovered that UPF1 was down-regulated in glioma tissues and cells as a tumor-suppressor gene.

Furthermore, it was discovered that overexpression of UPF1 markedly suppressed the growth and invasiveness of glioma cells. Notably, UPF1 was negatively correlated with CYTOR, and the latter was responsible for glioma progression regulated by UPF1. Collectively, the inhibitory effect of UPF1/CYTOR axis on the malignant progression of glioma was demonstrated.

Conclusions

UPF1 is down-regulated in glioma and alleviates the progression of glioma *via* targeting CYTOR. UPF1/CYTOR axis may be a promising therapeutic target for glioma.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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