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# Long non-coding RNA OIP5-AS1 promotes proliferation of gastric cancer cells by targeting miR-641

L.-W. WANG[1], X.-B. LI[2], Z. LIU[1], L.-H. ZHAO[1], Y. WANG[1], L. YUE[1]

[1]Department of Gastrointestinal Surgery, Zhoukou Central Hospital, Zhoukou, China
[2]Clinical College, Xinxiang Medical University, Xinxiang, China

**Abstract. – OBJECTIVE: Long non-coding RNAs (lncRNAs) have emerged as pivotal regulators of various tumors. Currently, lncRNA OPI5-AS1 (OPI5-AS1) has been identified as a tumor suppressor gene involved in several cancers. Therefore, the aim of this study was to investigate the function of OPI5-AS1 in gastric cancer (GC) progression.**

**PATIENTS AND METHODS: Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR) was used to detect the expressions of OPI5-AS1 and microRNA-641 (miR-641) in tissues and cells. The Cell Counting Kit-8 (CCK-8), colony formation, and 5-Ethynyl-2'-deoxyuridine (EDU) assays were used to verify the effect of OPI5-AS1 on cell proliferation. Cell cycle distribution was detected by flow cytometry. Furthermore, Western blot was performed to detect the protein expressions of cyclin D1 and *p*-AKT.**

**RESULTS: OPI5-AS1 was significantly upregulated, while miR-641 was downregulated in GC tissues and cells. OPI5-AS1 expression was remarkably inversely correlated with miR-641 in GC. Moreover, OPI5-AS1 could sponge miR-641 and regulate its expression in GC cells. Functional experiments showed that OPI5-AS1 overexpression remarkably accelerated GC cell proliferation and cell cycle. However, miR-641 overexpression could reverse the functional effects induced by OPI5-AS1 overexpression.**

**CONCLUSIONS: OPI5-AS1 overexpression promotes tumorigenesis and development of GC by sponging miR-106a-5p. In addition, our findings suggest that OPI5-AS1 may serve as an innovative and prospective therapeutic target for GC.**

*Key Words:*
LncRNA-OIP5-AS1, Proliferation, Gastric cancer (GC), MiR-641.

## Introduction

In China, gastric cancer (GC) remains one of the most malignant and prevalent cancers, posing a huge threat to people's health[1]. In recent years, great advances have been achieved in the diagnostic and therapeutic applications of GC. However, its overall survival rate is still relatively low[2]. To date, more and more GC molecular biomarkers and targeting molecules have been studied[3]. In order to improve the diagnosis and prognosis of GC, the identification of gene regulation has become a research hotspot.

Long non-coding RNA (lncRNA) is a kind of non-coding RNAs with longer than 200 nucleotides in length. They have no protein-coding function[4]. A growing number of researches have indicated that lncRNA plays a major role in GC progression and development[5]. Several researchers[6,7] have presented that long non-coding RNA MNX1-AS1 may promote the metastasis of GC by repressing CDKN1A. LncRNA PVT1 mediates apoptosis *via* increasing Bcl2 expression in GC. In addition, aberrantly expressed lncRNAs (HOTAIR, H19, UCA1, and MEG3) can modulate the proliferation, cell cycle, apoptosis, migration, invasion, metastasis, and tumorigenicity in GC[8,9]. Nevertheless, the specific function and mechanism of lncRNA remain to be further elucidated. LncRNA OIP5-AS1 is transcribed in antisense from the OIP5 gene on chromosome 15q15.1[10]. In recent years, OIP5-AS1 has been found to play an important role in diverse tumors, such as myeloma, cervical, oral tumors, and lung adenocarcinoma[11-14]. However, its expression and function in GC have not yet been fully elucidated.

With the deepening of exploration, numerous significant functions of lncRNAs in physiological and pathological processes, such as chromatin modification, transcription, and posttranscriptional processing, have been discovered[15,16]. Recently, OIP5-AS1 has been found to cause cisplatin resistance by inducing the LPAATβ/PI3K/AKT/mTOR signaling pathway and by regulating miR-340-5p in osteosarcoma[17]. OIP5-AS1 can also function as an oncogene in lung adenocarcinoma *via* miR-448/Bcl-2[14]. In this investigation,



*Corresponding Author:* Lei Yue, MM; e-mail: qiuzhiwonder@163.com

we aimed to investigate the expression level, clinical implication, biological function, and potential regulatory mechanism of OPI5-AS1 in GC.

## Patients and Methods

### Patients and Tissues

30 GC patients who underwent surgery in Zhoukou Central Hospital from February 2018 to May 2019 were selected as research subjects. GC patients who received any treatment before surgery were excluded. Subsequently, GC tissues and matched epithelial tissues were extracted from these patients. This study was approved by the Ethics Committee of Zhoukou Central Hospital. Signed written informed consents were obtained from all participants before the study. All collected tissues were immediately frozen in liquid nitrogen for further investigation.

### Cell Culture

Human gastric epithelial cell line (RGM-1), gastric cancer cell lines (HCG-27 and SGC-7901), and HEK293T cells were purchased from Chinese Academy of Sciences (Shanghai, China). All cells were cultured in Roswell Park Memorial Institute-1640 (RPMI-1640) medium (HyClone, South Logan, UT, USA) supplemented with 10% inactivated fetal bovine serum (FBS; Gibco, Rockville, MD, USA) in an incubator with 5% $CO_2$ at 37°C.

### Complementary Deoxyribose Nucleic Acid (cDNA) Synthesis and Quantitative Real Time-Polymerase Chain Reaction

The total RNA was first extracted from tissues and cells. Subsequently, extracted RNA was reverse transcribed into cDNA according to the instructions of miScript II RT Kit kit (TaKaRa, Otsu, Shiga, Japan). 1 μL of cDNA was taken for RT-PCR amplification. The specific reaction conditions were as follows: 94°C for 5 min, 95°C for 5 s, and 65°C for 35 s, for a total of 45 cycles. U6 and 18SRNA were used as internal references. The relative expression of OPI5-AS1 and miR-641 was calculated by the $2^{-\Delta\Delta Ct}$ method, where $\Delta\Delta Ct = \Delta Ct$ (sample) – $\Delta Ct$ (internal reference). The primers used in this work were as follows: OIP5-AS1-forward, 5′-TGCGAAGATGGCGGAGTAAG-3′ and reverse, 5′-TAGTTCCTCTCCTCTGGCCG-3′; 18S RNA-forward, 5′-CGAACGTCTGCCCTATCAACTT-3′ and reverse, 5′-ACCCGTGGTCACCATGGTA-3′; miR-641-forward, 5′-GGGGAAAGACATAGGATAGAGT-3′ and reverse, 5′-CAGTGCGTGTCGTGGAG3-3′; and U6-forward, 5′-CTCGCTTCGGCAGCACA-3′ and reverse, 5′-AACGCTTCACGAATTTGCGT-3′.

### Cell Transfection

Lentiviral vector was designed and synthesized by GenePharma (Shanghai, China). OPI5-AS1 overexpressing lentivirus was transfected into HCG-27 and SGC-7901 in accordance with Lipofectamine 3000 (Invitrogen, Carlsbad, CA, USA). Then, they were screened with puromycin (2 μg/mL) to harvest the stable cells. MiR-641 overexpressing lentivirus was transfected into OPI5-AS1 overexpressing HCG-27 and SGC-7901 cells to obtain stable co-expressing OPI5-AS1 and miR-641 cells.

### Luciferase Reporter Gene Assay

The OPI5-AS1 fragment sequence containing miR-641 binding site was synthesized and inserted into pGL3 Luciferase reporter vector (Promega, Madison, WI, USA). A construct containing wild-type OPI5-AS1 (OPI5-AS1-WT) or mutant OPI5-AS1 (OPI5-AS1-MUT) and miR-641 mimics were co-transfected into HEK293T cells by Lipofectamine 3000 (Invitrogen, Carlsbad, CA, USA). After 36 h, the transfected cells were harvested. Luciferase activity was detected using a Dual Luciferase Assay Kit (Promega, Madison, WI, USA).

### Cell Counting Kit-8 (CCK-8) Assay

The transfected cells were first seeded into 96-well plates at a density of 1 x $10^3$ cells/well. After incubation for indicated time points, CCK-8 solution (Dojindo Molecular Technologies, Kumamoto, Japan) was added to each well, followed by incubation for 2 h in the dark. OD (optical density) value at 450 nm was finally measured by a micro-plate reader.

### Colony Formation Assay

The transfected cells were uniformly seeded into 6-well plates (Corning, Corning, NY, USA) at a density of 1000/well. After the cells were attached, the culture medium was changed on time. After incubation for 12 days, the formed colonies were washed twice with PBS and stained with 0.1% crystal violet solution. Finally, the number of colonies containing over than 50 cells was

counted.

### 5-Ethynyl-2'-Deoxyuridine (EDU) Assay

The transfected cells were plated into 24-well plates (Corning, Corning, NY, USA) at a density of 2 x $10^4$ per well. Three replicate wells were set for each sample. The next day, EDU reagent (Ribobio, Guangzhou, China) was diluted with medium and added to each well, followed by incubation for 2 h. After washing with Phosphate-Buffered Saline (PBS), the cells were fixed with formaldehyde. Subsequently, 100 μL of glycine at a concentration of 2 mg/mL was added to each well, and formaldehyde was neutralized for 5 min. After adding the Apollo staining solution, the plate was placed on a shaker and incubated in the dark for 30 min. Next, the staining solution was discarded, and the cells in each well were washed 3 times with 100 μL of 0.5% Triton-X-100 (10 min for each time). After that, 100 μL of 4',6-diamidino-2-phenylindole (DAPI; Beyotime, Shanghai, China) was added to each well and the plate was placed on a shaker, followed by incubation for 10 min in the dark. Five fields of view were randomly selected and photographed.

### Flow Cytometric Analysis

A total of 1 x $10^6$ transfected cells were collected. After washing once with PBS, 1 mL of DNA Staining solution (Vazyme, Nanjing, China) and 10 μL of Permeabilization solution (Vazyme, Nanjing, China) were added and vortexed for 5-10 s to mix. Subsequently, the flow tubes were incubated at room temperature for 30 min in the dark. DNA content was finally measured by flow cytometry (FACScan; BD Biosciences, Franklin Lakes, NJ, USA).

### Western Blot

The total proteins were extracted from the transfected cells using radioimmunoprecipitation assay (RIPA) buffer (Beyotime, Shanghai, China) and protease inhibitors (Beyotime, Shanghai, China). Subsequently, the protein samples were separated by 10% sodium dodecyl sulphate (SDS) and transferred onto polyvinylidene difluoride membranes. After blocking with 5% non-fat milk in Tris-Buffered Saline-Tween (TBST), the membranes were incubated with the primary antibodies overnight. The primary antibodies used in this work were as follow: cyclinD1 (ab16663, Abcam, Cambridge, MA, USA) (1:1000), p-AKT (ab81283, Abcam, Cambridge, MA, USA) (1:1000) and GAPDH (ab181602, Abcam, Cambridge, MA, USA) (1:1000). On the next day, the membranes were incubated with horseradish peroxidase (HRP)-conjugated secondary antibody for 1.5 h at room temperature. Immuno-reactive bands were exposed by using enhanced chemiluminescence (Thermo Fisher Scientific, Waltham, MA, USA). Finally, the expression levels of the proteins were imaged by Quant LAS 4010 imaging system (Tokyo, Japan).

### Statistical Analysis

GraphPad Prism software (GraphPad Software, San Diego, CA, USA) was used for all statistical analysis. The experimental data were expressed as means ± standard deviation (SD). The effects of different treatments were compared by the unpaired Student's *t*-test. $p < 0.05$ was considered statistically significant.

## Results

### OPI5-AS1 Was Negatively Correlated With MiR-641 in GC Tissues and Cell Lines

QRT-PCR was first selected to detect OPI5-AS1 and miR-641 expression in GC tissues and adjacent normal tissues. OPI5-AS1 expression was significantly elevated in GC tissues, while miR-641 expression was significantly downregulated in GC tissues (Figures 1A and 1B). To further examine the role of OPI5-AS1 in GC carcinogenesis, GC patients were divided into high-level group (n = 15) and low-level group (n = 15), according to the median expression. The associations between the clinicopathological characteristics of GC patients and OPI5-AS1 expression were evaluated (Table I). OPI5-AS1 expression was significantly associated with large tumor size and advanced TNM stage. Compared with human gastric epithelial cells (RGM-1), increased OPI5-AS1 expression and decreased miR-641 expression were observed in GC cell lines (HCG-27 and SGC-7901) (Figures 1C and 1D). The expression patterns of OPI5-AS1 and miR-641 were compared by Pearson correlation coefficient. The results revealed a negative correlation between miR-641 and OPI5-AS1 expression in human GC tissues (Figure 1E). All these results suggested that aberrant expression of OPI5-AS1 and miR-641 was closely correlated with GC development.

### OPI5-AS1 Negatively Regulated MiR-641 Expression in GC Cells

Given the above results, we speculated that OPI5-AS1 could sponge to miR-641. Subsequent bioinformatics analyses showed that (Figure 2A),

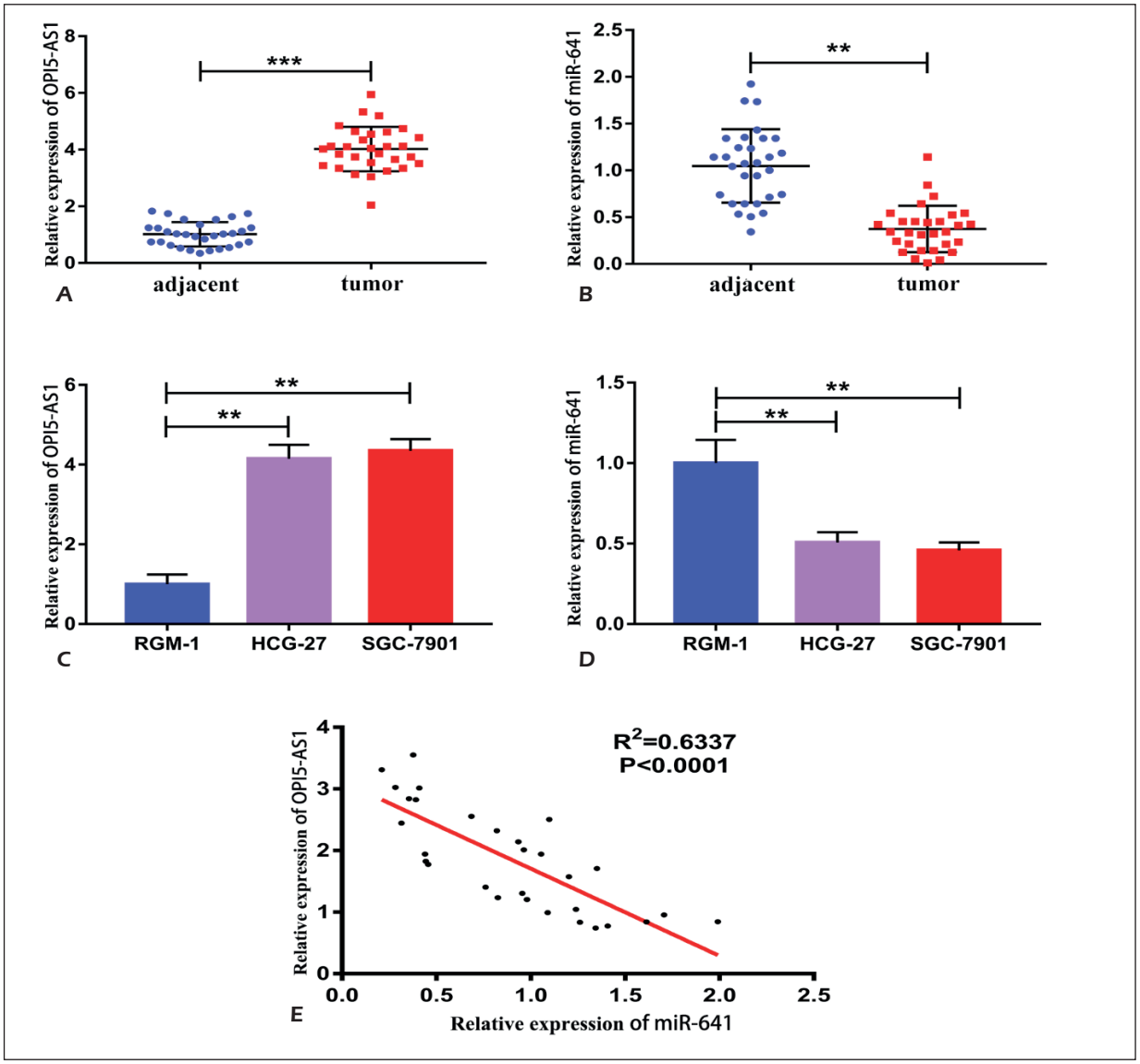


**Figure 1.** The expressions of OPI5-AS1 and miR-641 in GC tissues and cells. **A**-**B**, Expression levels of OPI5-AS1 and miR-641 in GC tissues and paired adjacent epithelial tissues were determined by qRT-PCR. **C**-**D**, The expressions of OPI5-AS1 and miR-641 in human gastric epithelial cell line RGM-1 and GC cell lines (HCG-27 and SGC-7901). **E**, Pearson correlation between OPI5-AS1 and miR-641 levels. The data were represented as mean ± SD. **indicated $p<0.01$, ***$p<0.001$.

miR-641 might be a candidate binding miRNA for OPI5-AS1. Luciferase reporter gene assay showed a substantial reduction in the Luciferase activity in OPI5-AS1-WT and miR-641 mimics co-transfected groups. However, the co-transfection of OPI5-AS1-MUT and miR-641 mimics had no significant effect on the Luciferase activity in 293T cells (Figure 2B). Next, lentiviral-OPI5-AS1 and -miR-641 were transfected into HCG-27 and SGC-7901 cells. The results revealed that the expression of OPI5-AS1 was significantly upregulated in both types of cells after transfection of lentiviral-OPI5-AS1. Meanwhile, the expression of miR-641 was significantly downregulated. After transfection of lentivirus-miR-641, the expression level of miR-641 could be restored (Figures 2C and 2D). These findings suggested that OPI5-AS1 might directly target miR-641 and negatively regulate its expression in GC cells.

### *OPI5-AS1 Promoted Proliferation of GC by Regulating MiR-641 In Vitro*

To further explore the biological role of OPI5-AS1 and miR-641, we performed a series of func-

**Table I.** Expression of OPI5-AS1and miR-541 according to patients' clinical features.

| Factors | OPI5-AS1 expression | | | miR-641 expression | | |
|---|---|---|---|---|---|---|
| | High | Low | *p*-value | High | Low | *p*-value |
| ***Gender*** | | | 0.464 | | | 0.143 |
| Male | 8 | 6 | | 5 | 9 | |
| Female | 7 | 9 | | 10 | 6 | |
| ***Age (years)*** | | | 0.438 | | | 0.269 |
| ≥50 | 6 | 11 | | 7 | 10 | |
| <50 | 9 | 4 | | 8 | 5 | |
| ***Tumor size (cm)*** | | | 0.025* | | | 0.002* |
| >5 | 9 | 3 | | 2 | 10 | |
| ≤5 | 6 | 12 | | 13 | 5 | |
| ***Lymph node metastasis*** | | | 0.028* | | | 0.003* |
| Yes | 10 | 4 | | 3 | 11 | |
| No | 5 | 11 | | 12 | 4 | |

*indicates $p<0.05$ (Chi-square test)

tional experiments. As shown in Figure 3A, the overexpression of OPI5-AS1 significantly accelerated the proliferation rate of HCG-27 and SGC-7901 cells. However, upregulation of miR-641 significantly attenuated and promoted the proliferation induced by OPI5-AS1 overexpression. Colony forming ability in HCG-27 and SGC-7901 was also remarkably enhanced by OPI5-AS1 overexpression. However, miR-641 transfection could attenuate this effect (Figure 3B). As shown in Figure 3C, after the upregulation of OPI5-AS1, EDU staining rate of HCG-27 and SGC-7901 cells remarkably increased. MiR-641 overexpression could attenuate the positive effect. Thus, these results indicated that OIP5-AS1 might regulate the proliferation of GC cells *in vitro*.

### OPI5-AS1 Promoted Cell Cycle by Targeting MiR-641

To further explore the role of OPI5-AS1 in GC progression, flow cytometric analysis was chosen to verify whether OPI5-AS1 affected cell cycle. As shown in Figure 4A, OPI5-AS1 overexpression promoted cell cycle, which resulted in a decrease in G0/G1 fraction in HCG-27 and SGC-7901 cells. However, the progression of cell cycle was significantly slowed down after overexpression of miR-641. As shown in Figure 4B, the upregulation of OPI5-AS1 markedly increased the expression of cyclin D1 and p-AKT in HCG-27 and SGC-7901 cells. However, miR-641 overexpression significantly reduced the expression levels of cyclin D1 and p-AKT in both cell lines. These results implied that OPI5-AS1 overexpression accelerated cell cycle by regulating miR-641 in GC cells.

## Discussion

An increasing number of lncRNA transcripts have been demonstrated to be in state of imbalance in cancers[18]. OPI5-AS1 has been reported significantly upregulated in diverse tumors. However, its clinical significance and biological function in GC have not been fully elucidated. In this report, we found that OPI5-AS1 was significantly upregulated in GC tissues and cells. Meanwhile, OPI5-AS1 expression was intimately associated with malignant clinicopathological features and poor prognosis of GC. Further studies showed that OPI5-AS1 could absorb miR-641 in a large amount, thereby accelerating GC tumor proliferation and cell cycle progression. Therefore, our findings compensated for the functions of OPI5-AS1 in human cancers, demonstrating that OPI5-AS1 served as an oncogene in GC.

MiRNAs are a subset of conserved, single-strand, non-coding, and short RNA molecules with 18-24 nucleotides in length[19]. MiRNAs have been found dysregulated in most human cancer types, such as lung[20], colorectal[21], breast[22], and bladder cancers[23]. Aberrant expression of miRNAs plays an important role in multiple cellular biological processes, including proliferation, cell cycle, apoptosis, metastasis, motility, and angiogenesis[24,25]. Some investigations[26-28] have found that miR-641 is involved in the development and progression of lung cancer and cervical cancer. Moreover, lncRNA Colorectal Neoplasia Differentially Expressed (CRNDE) promotes proliferation and inhibits apoptosis in non-small cell lung cancer

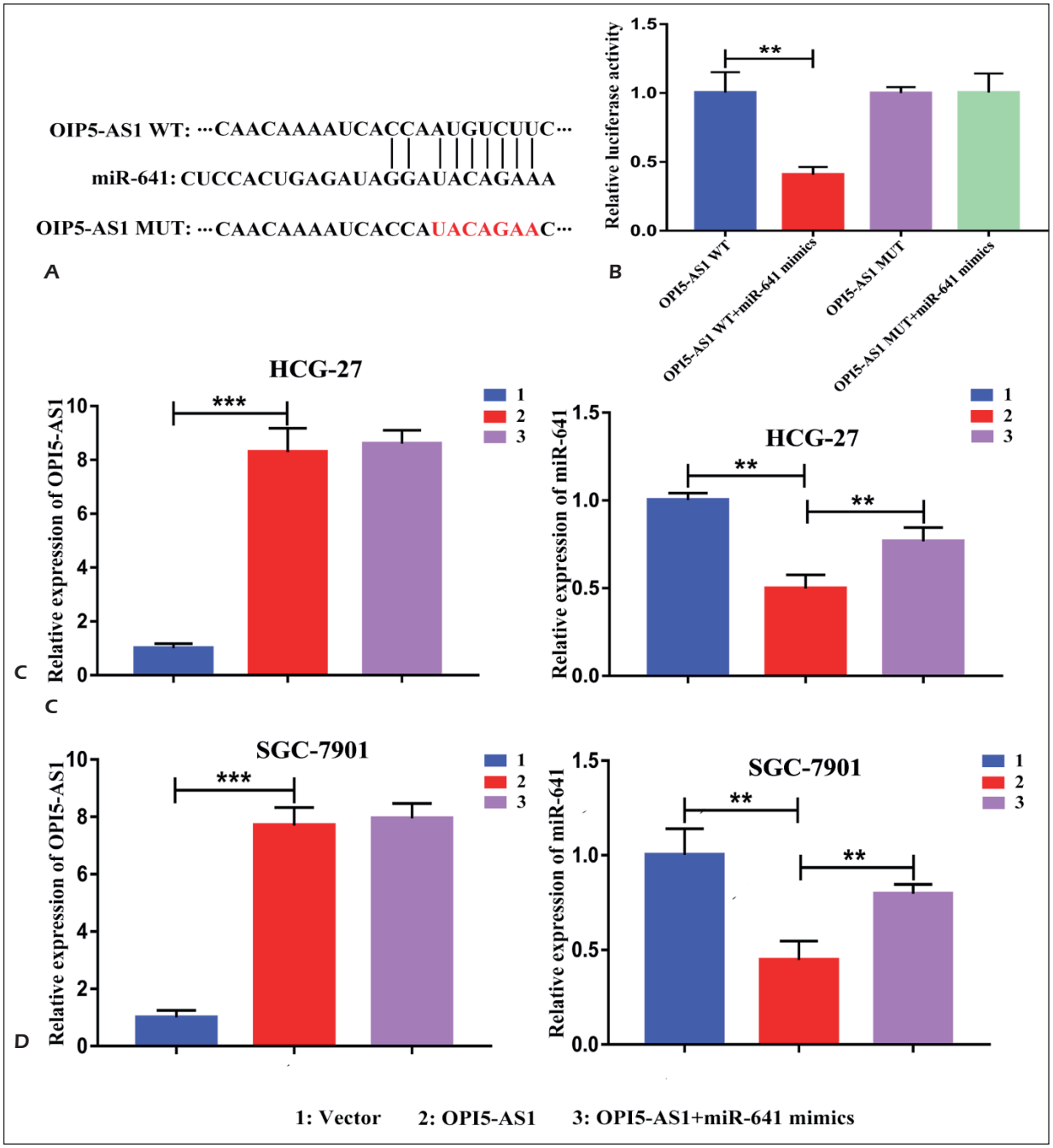


**Figure 2.** OPI5-AS1 interacted with miR-641 and negatively regulated its expression in GC cells. **A**, Bioinformatics analyses were conducted to predict the possible binding site of miR-641 in OPI5-AS1. **B**, Dual-Luciferase Reporter Assay was performed to determine the interaction of OPI5-AS1 and miR-641 in 293T cells at 48 h. **C**, QRT-PCR analyses of OPI5-AS1 and miR-641 in HCG-27 cells transfected with OPI5-AS1, OPI5-AS1 + miR-641, or vector. **D**, QRT-PCR analyses of OPI5-AS1 and miR-641 in SGC-7901 cells transfected with OPI5-AS1, OPI5-AS1 + miR-641, or vector. Data were represented as mean ± SD. **indicated $p<0.01$, ***$p<0.001$.

cells by regulating the miR-641/CDK6 axis[29]. LncRNA DLX6-AS1 promotes the proliferation and metastasis of osteosarcoma by modulating miR-641/HOXA9 signaling pathway[30]. In this analysis, we found for the first time that miR-641 could function on inhibit the development of GC.

Moreover, in this work, we first discovered the expression and clinical features of OPI5-AS1 and miR-641 in GC tissues and adjacent normal tissues. Moreover, a negative correlation was observed between OPI5-AS1 and miR-641 expressions in GC. CCK-8, colony formation, and EDU

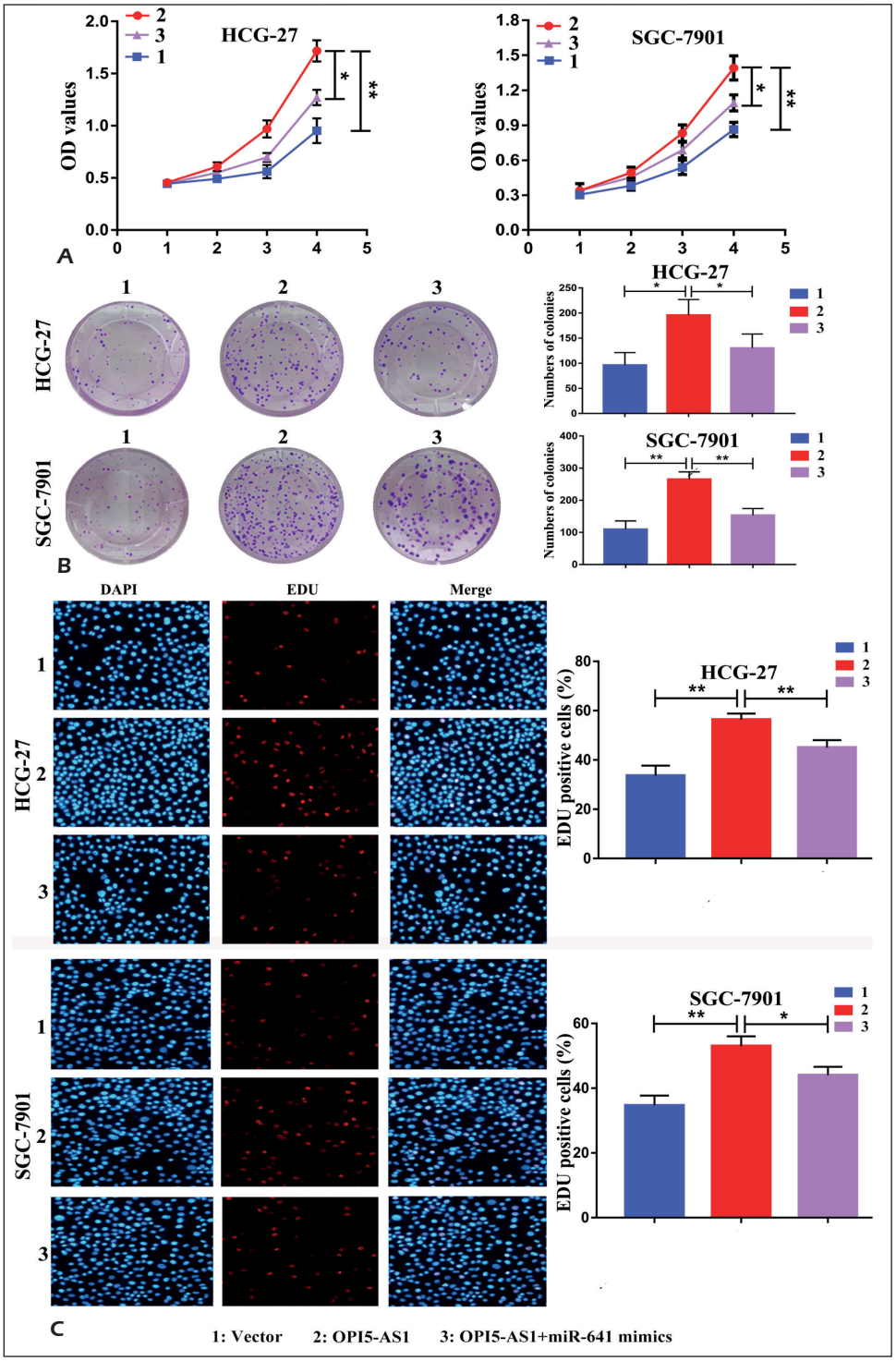


**Figure 3.** OPI5-AS1 overexpression promoted proliferation and colony formation ability of GC cells via regulating miR-641. **A**, CCK-8 assay were used to detect the proliferation of HCG-27 and SGC-7901 cells transfected with OPI5-AS1, OPI5-AS1 + miR-106a-5p, or vector at indicated time points (0, 1, 2, 3, and 4 days). **B**, The colony formation assay was conducted to measure the ability of cell survival in the transfected HCG-27 and SGC-7901 cells (magnification, x40). **C**, EDU assay was conducted to measure the ability of cell survival in transfected HCG-27 and SGC-7901 cells (magnification, x100). Data were represented as mean ± SD. *indicated $p<0.05$, **$p<0.01$.

assays demonstrated that OPI5-AS1 significantly promoted the proliferation of GC cells. Conversely, miR-641 could partially reverse the function of OPI5-AS1 *in vitro*. Further results indicated that OPI5-AS1 promoted cell proliferation by accelerating cell cycle, while miR-641 might inhibit cell cycle and arrest cells in G1 phase. Our findings revealed that OPI5-AS1 promoted the proliferation of GC cells by modulating the expression of miR-641. Whether OPI5-AS1 could play a role in promoting cancer through other molecular mechanisms remained to be elucidated.

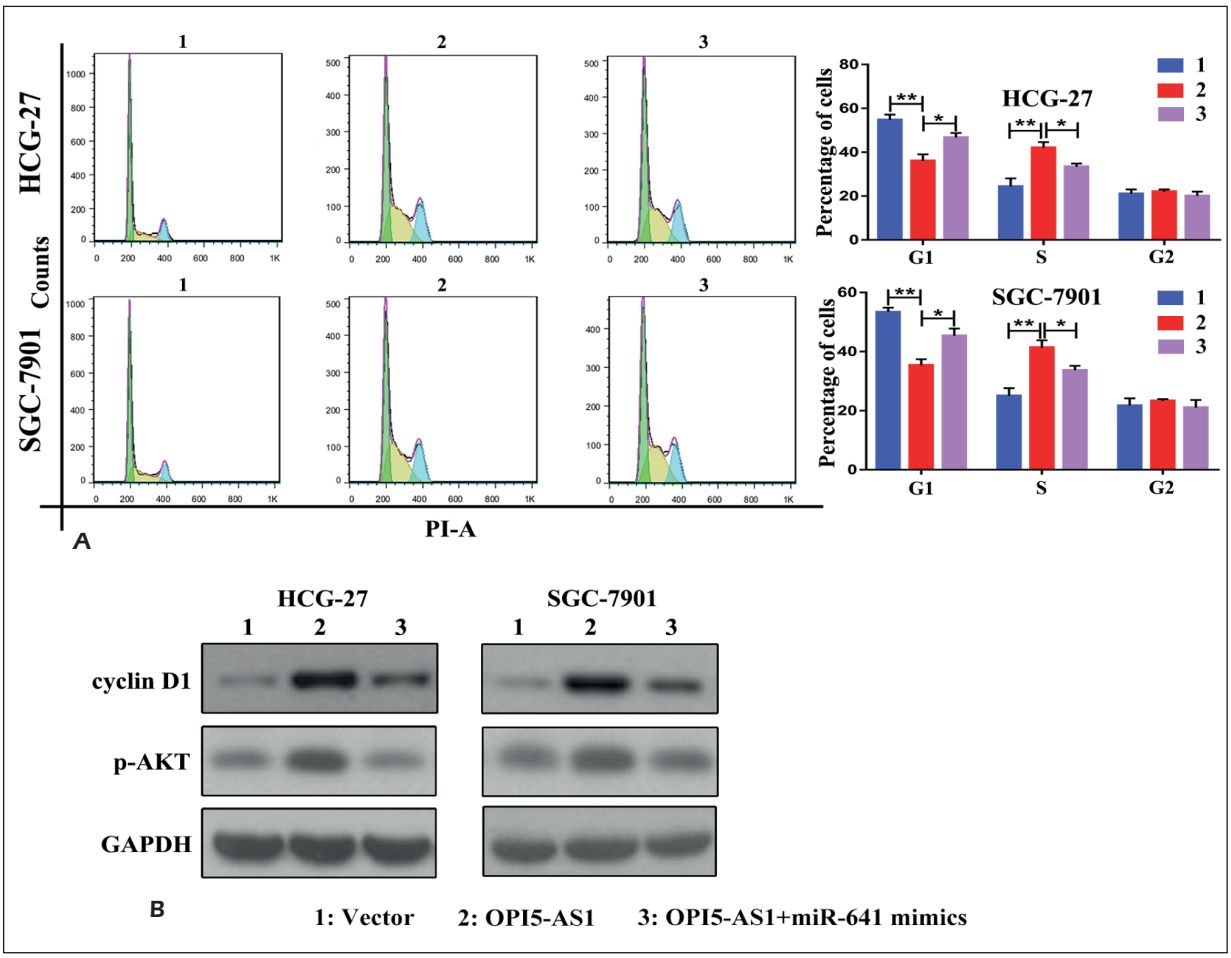


**Figure 4.** OPI5-AS1 overexpression accelerated cell cycle via regulating miR-641 in GC. **A**, Flow cytometry analyses of transfected HCG-27 and SGC-7901 cells at 48 h. **B**, Western blot was applied to determine the protein expression of cyclin D1 and p-AKT in transfected HCG-27 and SGC-7901 cells at 48 h. The data were represented as mean ± SD. *indicated $p<0.05$, **$p<0.01$.

## Conclusions

LncRNA-OPI5-AS1 exhibited a tumor-promoting effect on GC progression and proliferation *in vitro*. Besides, lncRNA-OPI5-AS1 could regulate miR-641 in part. Our findings implied that lncRNA-OPI5-AS1 might serve as an innovative and prospective therapeutic target for GC.

### Conflict of Interests

The authors declared that they have no conflict of interests.

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