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# Long noncoding RNA OIP5-AS1 exhibits oncogenic activity in bladder cancer through miR-217 and MTDH

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**Abstract. – OBJECTIVE: The aim of this study was to investigate the role of long non-coding Opa-interacting protein 5 antisense RNA 1 (OIP5-AS1) in bladder cancer (BCa), and the mechanism of OIP5-AS1/microRNA-217 (miR-217)/metadherin (MTDH) in promoting the progression of BCa.**

**PATIENTS AND METHODS: OIP5-AS1, miR-217 and MTDH expressions in BCa tissues and cells were detected by qRT-PCR or Western blot. CCK-8 and transwell assays were used to determine the proliferation and invasion of BCa cells. The correlation between OIP5-AS1 and miR-217, miR-217 and MTDH, and OIP5-AS1 and MTDH were studied by Luciferase reporter assay and Spearman correlation analysis. Statistical analysis of test data was performed using t-test.**

**RESULTS: OIP5-AS1 was upregulated in BCa tissues and cells, and OIP5-AS1 knockdown could inhibit the proliferation and invasion of BCa cells. MiR-217 was a direct-acting target of OIP5-AS1, and MTDH was a target of miR-217. OIP5-AS1 knockdown inhibits human BCa cell proliferation and invasion through miR-217/MTDH axis.**

**CONCLUSIONS: This study systematically explored the effect of OIP5-AS1 in human BCa. MiR-217/MTDH pathway mediated the promotion of OIP5-AS1 in BCa cells proliferation and invasion. OIP5-AS1, as an oncogene, could be used as a biomarker for the treatment of BCa.**

*Key Words:*
OIP5-AS1, Bladder cancer, MiR-217, MTDH.

## Introduction

BCa has the highest mortality rate among urinary tract tumors, and its incidence has increased year by year[1]. According to the histopathological features, BCa is divided into two types: muscular infiltration and non-muscular infiltration[2]. 90% of BCa are transitional cell carcinomas, which rarely develop into invasive cancer but are prone to recurrence after surgery[3]. At present, radiotherapy, chemotherapy and surgery are the main methods for clinical treatment of BCa[4]. Although surgical treatment can prolong survival of patients to some extent, long-term survivorship is still an issue. The early onset of BCa is relatively insidious, often characterized by occult metastasis, high recurrence rate and low 5-year survival rate[5]. The pathogenesis of BCa has not been fully elucidated, which is thought to be related to the disorder of multigene, multilevel cellular signal network[6,7]. Therefore, it is of great significance to study the molecular mechanism of BCas metastasis for the treatment for patients.

LncRNA is originally considered to be the "noise" or "transcription junk" of genome transcription, and has no biological function[8,9]; it is involved in the regulation of cell proliferation, differentiation, and apoptosis, which is associated with the formation of various malignant tumors[10]. LncRNA is dysregulated in many tumors and contributes to tumor formation and suppression[11]. Although the researches on lncRNAs have made rapid progress in recent years, the function of most lncRNAs is still unclear.

MiRNA is a kind of endogenous small molecule RNA, which can bind to the 3'UTR region of the target gene mRNA, thus promoting the degradation of mRNA or silencing its expression to regulate the corresponding cell biolog-

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ical behavios[12]. LncRNA acts as a sponge/bait for miRNA or competes with miRNA to bind mRNA, thereby reducing the inhibitory effect of miRNA on the target gene and increasing its stability[13]. LncRNAs play the biological role by regulating gene expression at different levels through a variety of mechanisms, and its interaction with miRNAs involves in the development of cancer[14].

OIP5-AS1 served as an oncogene in multiple cancers, such as lung cancer[15], gastric cancer[16], and cervical cancer[17]. In BCa, it could regulate cell proliferation and apoptosis, and associated with poor prognosis[18]. However, researches on OIP5-AS1 regulatory mechanisms still limited. Here, we detected OIP5-AS1, miR-217, and MTDH expressions in BCa and the effect of OIP5-AS1 on BCa cells behavior were identified. Then, we further explored the possible interrelationships between the above factors and their possible mechanism of action involved in the biological behavior of BCa cells, in order to provide new therapeutic for BCa treatment.

## Patients and Methods

### Clinical Samples

The specimens of BCa and adjacent tissues (3 to 5 cm from the tumor edge) from 30 patients were obtained at Caoxian People's Hospital. Inclusion criteria were: (1) pathological section, imaging examination and cystoscopy, confirmed diagnosis of BCa. (2) No chemotherapy or other treatment intervention. Exclusion criteria were: (1) combined with other malignant tumors, cardiovascular and cerebrovascular diseases, immune system diseases, acute and chronic infections. (2) History of mental illness. The study was approved by the Caoxian People's Hospital Ethics Committee, and all patients gave informed consent. This study was conducted in accordance with the Declaration of Helsinki.

### Cell Culture and Transfections

Normal bladder epithelial cell line (SV-HUC-1) and BCa cells (TCCSUP, UMUC3, SW780 and T24) were cultured in Roswell Park Memorial Institute-1640 (RPMI-1640) medium containing 10% fetal bovine serum (FBS, Gibco, Rockville, MD, USA). The culture conditions were saturated humidity with 5% $CO_2$ at 37°C. The si-OIP5-AS1 (small interfering RNA directed against OIP5-AS1), si-NC, miR-217 mimic (mimic), miR-NC, miR-217 inhibitor (inhibitor), pc-MTDH (MTDH-overexpressing plasmid) and pc-NC were synthesized by GenePharma (Shanghai, China) and transfected into BCa cells alone or in combination according to the instructions of Lipofectamine2000 (Invitrogen, Carlsbad, CA, USA).

### CCK-8 Assay

CCK-8 method was used to detect cell proliferation. The cells were seeded in a 96-well plate with $2 \times 10^3$ per well and cultured in an incubator. CCK-8 solution (10 μl/well, Dojindo Molecular Technologies, Japan) was added at 24, 48, 72, and 96 h respectively. Then, the plate was incubated in the incubator for 1 h. The microplate reader was used to measure the optical density (OD) at 450 nm, and each time point was repeated three times.

### Transwell Assay

Transfected cells were collected, and the cell density was adjusted to $2.5 \times 10^5$ cells/ml. Matrigel (BD Biosciences, Franklin Lakes, NJ, USA) was spread evenly in the upper chamber of the transwell chamber (Corning, Corning, NY, USA) and solidified at 37°C for 30 minutes. We added 200 μl/well cell suspension and 600 μl/well of medium containing 10% FBS to the upper chamber and lower chamber respectively, and then placed the transwell chamber in the incubator. The culture was continued for 1 d, cells were fixed and stained. Then, the cells that did not pass through the basement membrane were gently wiped with a cotton swab. After drying at room temperature, the number of cells was counted by a microscope. 4 visual fields were randomly selected for counting per well. Experiments were repeated three times.

### Dual-Luciferase Reporter Assay

The bioinformatics software Starbase 2.0 (http://starbase.sysu.edu.cn/index.php) and TargetScan (http://www.targetscan.org/) analysis showed that OIP5-AS1 and miR-217, miR-217 and MTDH had complementary binding sites respectively. Mutant and wild-type Luciferase reporter vectors (OIP5-AS1-wt, OIP5-AS1-mut, MTDH-wt and MTDH-mut) were constructed, respectively. Then, they were co-transfected into BCa cells with miR-217 mimic or miR-NC. After 48 h of culture, Luciferase activity was detected using a Luciferase activity detection kit (Promega, Madison, WI, USA).

### RIP Assay

Cells were lysed by RIP lysate according to the EZ-Magan RIP Kit (Millipore, Billerica, MA, USA) instructions. Lysates were added to the magnetic beads and incubated with Ago2 or IgG antibodies (Abcam, Cambridge, MA, USA). Samples were digested with proteinase K and the immunoprecipitated RNA was isolated. qRT-PCR was performed to detect the expression of OIP5-AS1 and miR-217.

### qRT-PCR

TRIzol reagent (Invitrogen, Carlsbad, CA, USA) was used to extract tissue and cell's total RNA. SuperScript RT Kit (TaKaRa, Otsu, Shiga, Japan) was used to reverse transcribe into complementary DNA (cDNA). QRT-PCR was performed using SYBR Green PCR master Mix kit (TaKaRa, Otsu, Shiga, Japan) with Roche LightCycler 480 (LC480) system (Roche, USA). The relative expression of RNAs is expressed as $2^{-\Delta\Delta Ct}$. U6 and GAPDH were used as internal reference. Primers are listed in Table I.

### Western Blot Assay

The protein lysate (RIPA, Beyotime, China) was used to dissolve cell samples to obtain the total protein. The extracted protein was quantified according to the bicinchoninic acid (BCA) protein concentration determination kit (Pierce, Appleton, WI, USA). 25 μg of total protein was separated by 10% sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to the polyvinylidene difluoride (PVDF) membrane. Then, the membrane was blocked with 5% skimmed milk powder at room temperature for 1 h and incubated with the corresponding primary antibody (MTDH and GAPDH, Abcam, Cambridge, MA, USA) at 4°C overnight. After washed with PBS, the membrane was incubated with the horseradish HRP-conjugated secondary antibody at room temperature for 1 hour. Enhanced chemiluminescent kit (Millipore, Billerica, MA, USA) visualized blotting images.

**Table I.** Primer sequences for real-time fluorescence quantification PCR.

| Gene name | Primer sequences (5′-3′) |
|---|---|
| GAPDH | F CGCTCTCTGCTCCTCCTGTTC |
| | R CCGTTGACTCCGACCTTCAC |
| U6 | F CTCGCTTCGGCAGCACA |
| | R AACGCTTCACGAATTTGCGT |
| OIP5-AS1 | F TGCGAAGATGGCGGAGTAAG |
| | R TAGTTCCTCTCCTCTGGCCG |
| miR-217 | F TACTCAACTCACTACTGCATCAGGA |
| | R TATGGTTGTTCTGCTCTCTGTGTC |
| MTDH | F CCCTCCTTACTCAGGAACCC |
| | R CGAAGGCTAGGGATGTGTCA |

### Statistical Analysis

Data processing was performed using GraphPad Prism 5.0 software (San Diego, CA, USA). The data were expressed by mean ± SD, and the comparison between the two groups was performed by *t*-test. $p < 0.05$ indicates that the difference between the two groups was statistically significant.

## Results

### OIP5-AS1 Expression was Increased in BCa

To find out the role of OIP5-AS1 in BCa tissues, we examined the expression level of OIP5-AS1 in 30 pairs of BCa and adjacent tissues. Results showed that OIP5-AS1 expression was significantly enhanced in the patient's tumor tissue (Figure 1A). In addition, we further detected OIP5-AS1 expression in BCa cell lines. Compared with the SV-HUC-1, OIP5-AS1 expression was also significantly increased in the four BCa cells (TCCSUP, UMUC3, SW780 and T24) (Figure 1B). It was also found that OIP5-AS1 in SW780 and T24 cells was higher expressed than others (Figure 1B). Thus, we selected the SW780 and T24 cells to perform the subsequent experiments.

### OIP5-AS1 Knockdown Suppressed BCa Cell Proliferation and Invasion

OIP5-AS1 knockdown vector (si-OIP5-AS1) was constructed and transfected into SW780 and T24 cells separately. The qRT-PCR method was used to detect the transfection efficiency of siRNAs to avoid off-target effects. After transfecting the si-OIP5-AS1 interfering fragment, OIP5-AS1 expression in the cells decreased significantly (Figure 2A and 2B). This demonstrated that OIP5-AS1 knockdown had achieved a good effect, and the next experiment continued.

In the previous experiment, we indicated that OIP5-AS1 was significantly increased both in BCa tumor specimens and cells. It was suggested that OIP5-AS1 might promote the occurrence and development of BCa. Therefore, we further explored whether down-regulating OIP5-AS1 af-

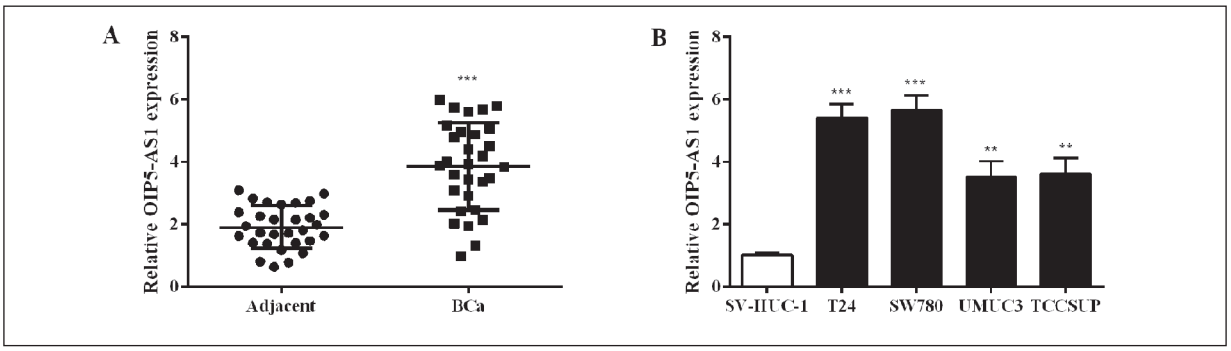


**Figure 1.** OIP5-AS1 expression in BCa tissues and cells. **A**, Expression of OIP5-AS1 was increased in BCa tissues. **B**, OIP5-AS1 expression was elevated in BCa cells. $^{**}p < 0.01$, $^{***}p < 0.001$.

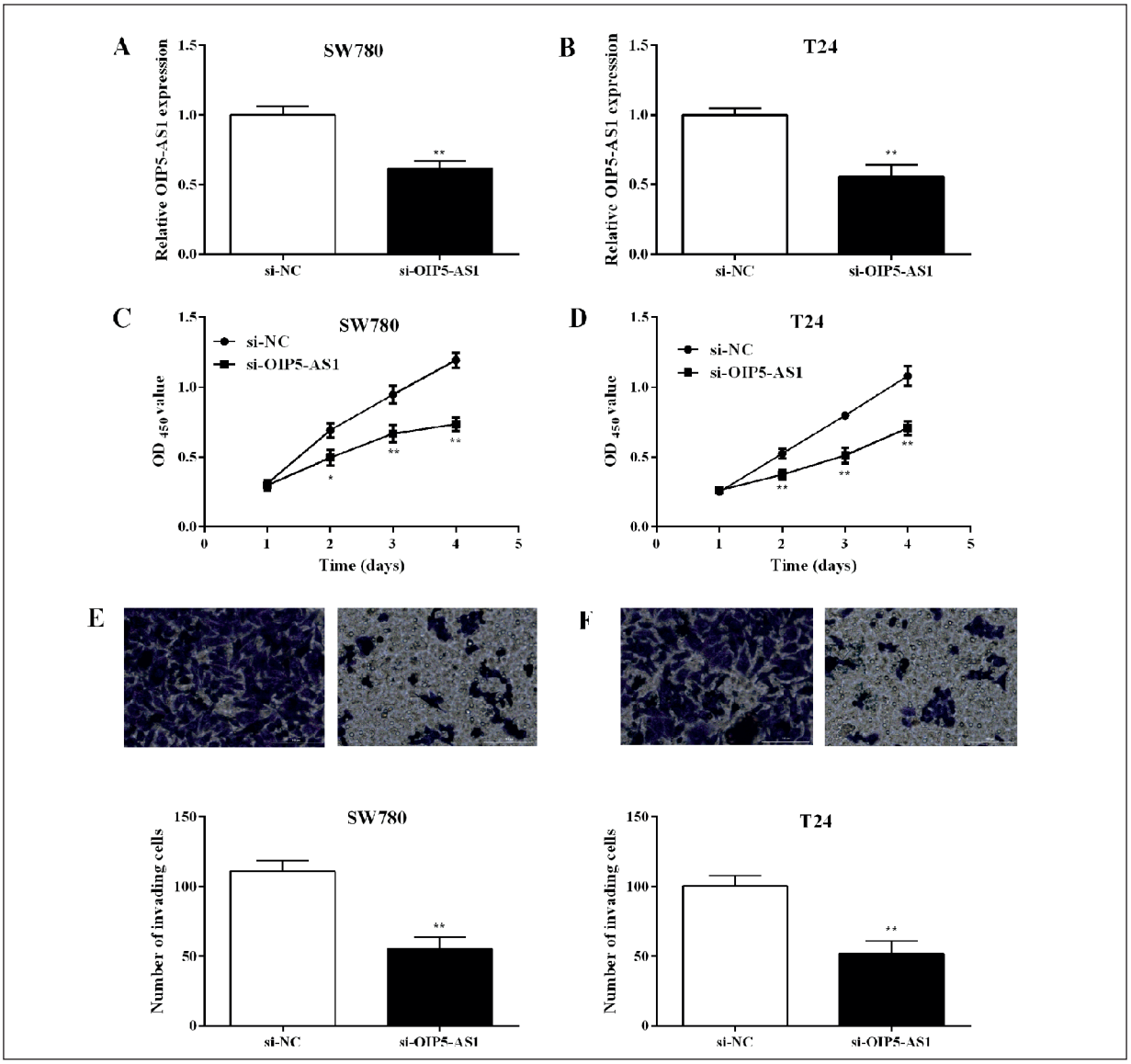


**Figure 2.** OIP5-AS1 knockdown inhibited proliferation and invasion of BCa cells. **A, B**, OIP5-AS1 expression in SW780 and T24 cells after si-OIP5-AS1 transfected. **C, D**, Cell proliferation of SW780 and T24 cells with si-OIP5-AS1 transfection. **E, F**, Number of invaded SW780 and T24 cells after OIP5-AS1 knockdown (200×). $^{*}p < 0.05$, $^{**}p < 0.01$.

fected the proliferation and invasion of BCa cells. CCK-8 results proved that the viability of cells transfected with si-OIP5-AS1 was significantly reduced compared to the si-NC group (Figure 2C and 2D). Cells transfected with si-OIP5-AS1 also had significantly fewer cells permeating the membrane versus si-NC group (Figure 2E and 2F). It could be seen that OIP5-AS1 downregulation significantly reduced the proliferation and invasion ability of BCa cells.

### *OIP5-AS1 Directly Targeted to MiR-217*

To clarify the molecular mechanism of OIP5-AS1, bioinformatics analysis was performed through the Starbase 2.0 database. Findings revealed OIP5-AS1 contained the conserved target site of miR-217 (Figure 3A). Next, a Dual-Luciferase reporter assay was used to detect the binding between OIP5-AS1 and miR-217. Experimental data revealed that transfection of miR-217 mimic significantly reduced the Luciferase activity of OIP5-AS1-wt instead of OIP5-AS1-mut (Figure 3B and 3C). qRT-PCR test results showed that OIP5-AS1 knockdown could signally elevate miR-217 expression (Figure 3D). In addition, miR-217 expression was markedly decreased in BCa tissues (Figure 3E). Spearman correlation analysis showed that OIP5-AS1 and miR-217 expression were negatively correlated in BCa tissues (Figure 3F). The above results suggested that OIP5-AS1 directly acted on miR-217 and regulated miR-217 expression.

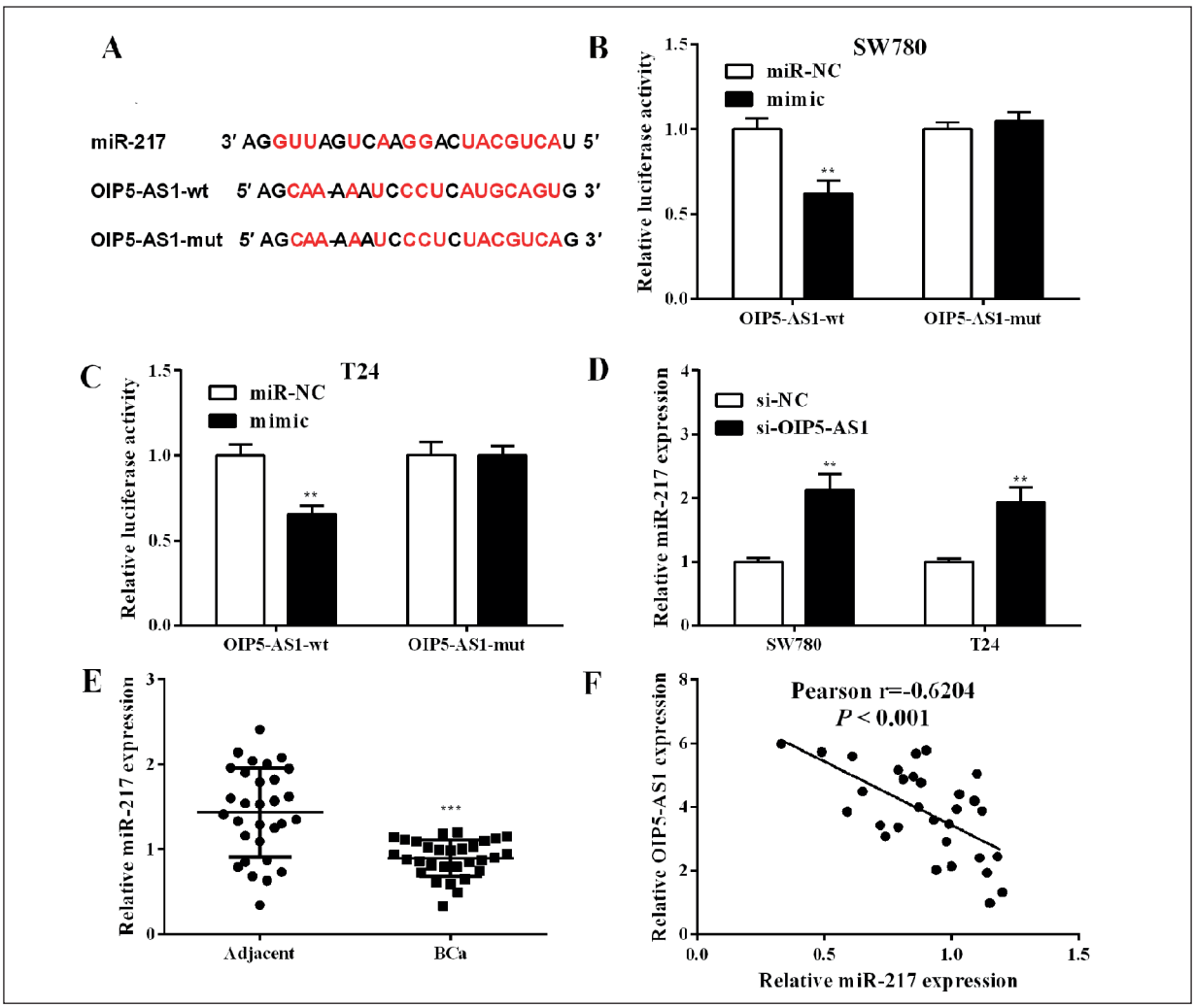


**Figure 3.** OIP5-AS1 directly targets miR-217. **A**, Predicted binding site between miR-217 and OIP5-AS1. **B, C**, The Luciferase activity in SW780 and T24 cells. **D**, MiR-217 expression in SW780 and T24 cells treated with si-OIP5-AS1. **E**, Expression of miR-217 was decreased in BCa tissue. **F**, Correlation analysis between OIP5-AS1 and miR-217 expressions in BCa tissues. $^{**}p < 0.01$.

### MTDH was a Target of MiR-217

TargetScan software was used to predict miR-217 downstream target gene, and we found the binding sequences to miR-217 existed on the 3'UTR of MTDH (Figure 4A). To further confirm the binding of miR-217 and MTDH, detection was performed by Dual-Luciferase reporting experiment. Results verified that the co-transfection of miR-217 mimic and MTDH-wt induced a decreasing for Luciferase activity (Figure 4B and 4C). To further show the regulatory relationship between OIP5-AS1 and miR-217, we next tested whether OIP5-AS1 could regulate the expression of miR-227's target gene MTDH. First, we verified that miR-217 mimic reduced MTDH expression in BCa cells by qRT-PCR and Western blot experiments (Figure 4D). Second, si-OIP5-AS1 inhibited MTDH expression versus si-NC in BCa cells, while co-transfection of si-OIP5-AS1 and miR-217 inhibitor increased si-OIP5-AS1-induced downregulation of MTDH (Figure 4E and 4F). Moreover, MTDH was negatively correlated with OIP5-AS1 and positively correlated with miR-217 in BCa tissues (Figure 4G and 4H). The results showed that OIP5-AS1 reduced the inhibitory effect of miR-217 on the target gene MTDH through competitively binding to miR-217.

### OIP5-AS1 Facilitated BCa Cell Progression and Invasion via MiR-217 and MTDH

T24 cell was co-transfected with si-OIP5-AS1 and miR-217 or pc-MTDH to detect whether OIP5-AS1 inhibited the proliferation and invasion of BCa cells through miR-217 or MTDH. Transfection of pc-MTDH significantly increased MTDH expression (Figure 5A). OIP5-AS1 knockdown inhibited the proliferation, migration and invasion of SW780 and T24 cells in above mentioned experiments. Either miR-217 inhibitor or pc-MTDH and si-OIP5-AS1 co-transfection could reverse these changes (Figure 5B-5E). Therefore, OIP5-AS1 regulated BCa proliferation and invasion through miR-217 and MTDH.

## Discussion

In recent years, with the development of molecular biology technology, targeted therapy has become an important adjuvant therapy for BCa[19]. Finding effective molecular therapeutic targets for BCa has important clinical significance in improving the prognosis of patients. Several studies have showed that lncRNA has significant abnormally expressed in tumor tissues and is widely involved in regulating the differentiation, proliferation, invasion and apoptosis of tumor cells, clinical stage, and prognosis of patients[20]. As the number of lncRNAs is much more than that of the coding RNA molecule, and they have a wide range of functions, the relationship between lncRNAs and diseases (especially tumors) naturally attracts people's attention. Compared with the application of lncRNA in the diagnosis of BCa, the current research on lncRNA in the treatment of BCa is still insufficient, mainly because the latter requires a large number of clinical cases for scientific evaluation.

LncRNAs play an important role in the occurrence and development of BCa and they can affect cell proliferation, apoptosis, invasion and migration, and tumor resistance, providing new ways for clinical diagnosis and treatment and prognosis of BCa[21]. OIP5-AS1, which is located in 15q15.1 chromosome, played carcinogenesis roles in various cancers[22]. In lung adenocarcinoma, OIP5-AS1 regulated miR-448/Bcl-2 axis to facilitate its progression[23]. OIP5-AS1 accelerated osteosarcoma tumorigenesis by inhibiting miR-223 to upregulate CDK14[24]. OIP5-AS1 affected glioma cell proliferation, invasion and migration through regulation of miR-410/Wnt-7b[25]. This study found that OIP5-AS1 expression was up-regulated in BCa, and knockdown of OIP5-AS1 significantly inhibited the proliferation and invasion of BCa cells.

LncRNA can regulate the expression of target genes by binding to miRNA and affecting the binding of miRNA to its target genes, which is the ceRNAs regulatory network[26]. Zhang et al[27] reported that lncRNA OIP5-AS1 acted as a ceRNA through binding with miR-195-5p to upregulate NOB1 in human hemangioma endothelial cells. In cervical cancer, OIP5-AS1 could act as a competing endogenous RNA of miR-143-3p to regulate the ITGA6 expression[28]. OIP5-AS1 functioned as a ceRNA to elevate ZNF217 expression through sponging miR-137 in epithelial ovarian cancer[29]. Online software analysis prediction revealed that miR-217 has complementary sequences to OIP5-AS1, and miR-217 could be complemented to MTDH mRNA. MiR-217 acts as a tumor suppressor to inhibit cell proliferation and invasion in BCa[30]. The MTDH gene localized on human chromosome 8 (8q22) was highly expressed in a variety of primary tumors and was closely related to the progression and

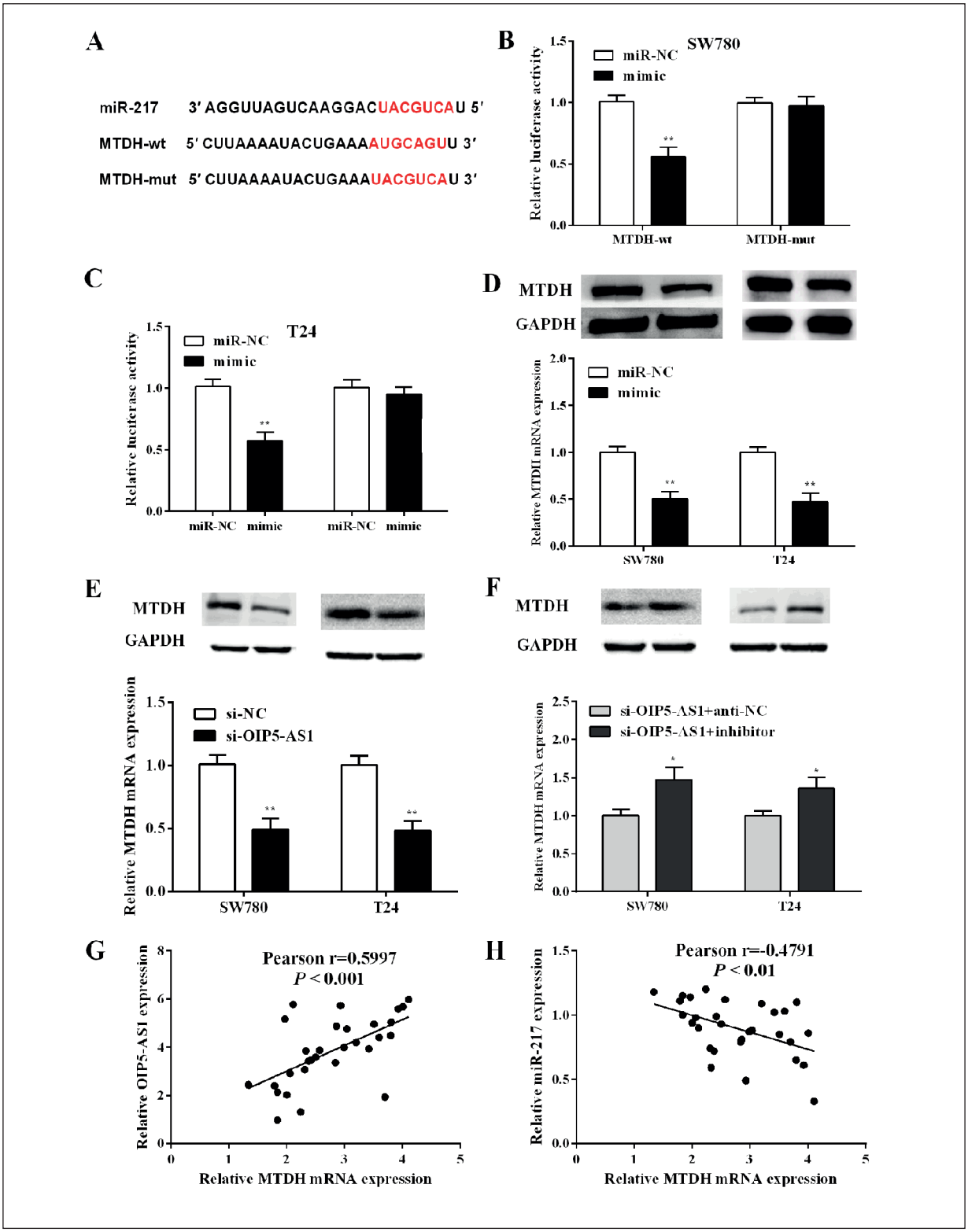


**Figure 4.** MTDH is a target of miR-217. **A**, Predicted binding site between miR-217 and OIP5-AS1. **B, C**, The Luciferase activity in SW780 and T24 cells. **D**, MTDH expression in SW780 and T24 cells treated with mimic. **E**, **F**, Expression of MTDH in SW780 and T24 cells treated with si-OIP5-AS1 and inhibitor. **G**, Correlation analysis between OIP5-AS1 and MTDH mRNA expressions in BCa tissues. **H**, Correlation analysis between MTDH mRNA and miR-217 expressions in BCa tissues. $^{**}p < 0.01$. $^{**}p < 0.01$.

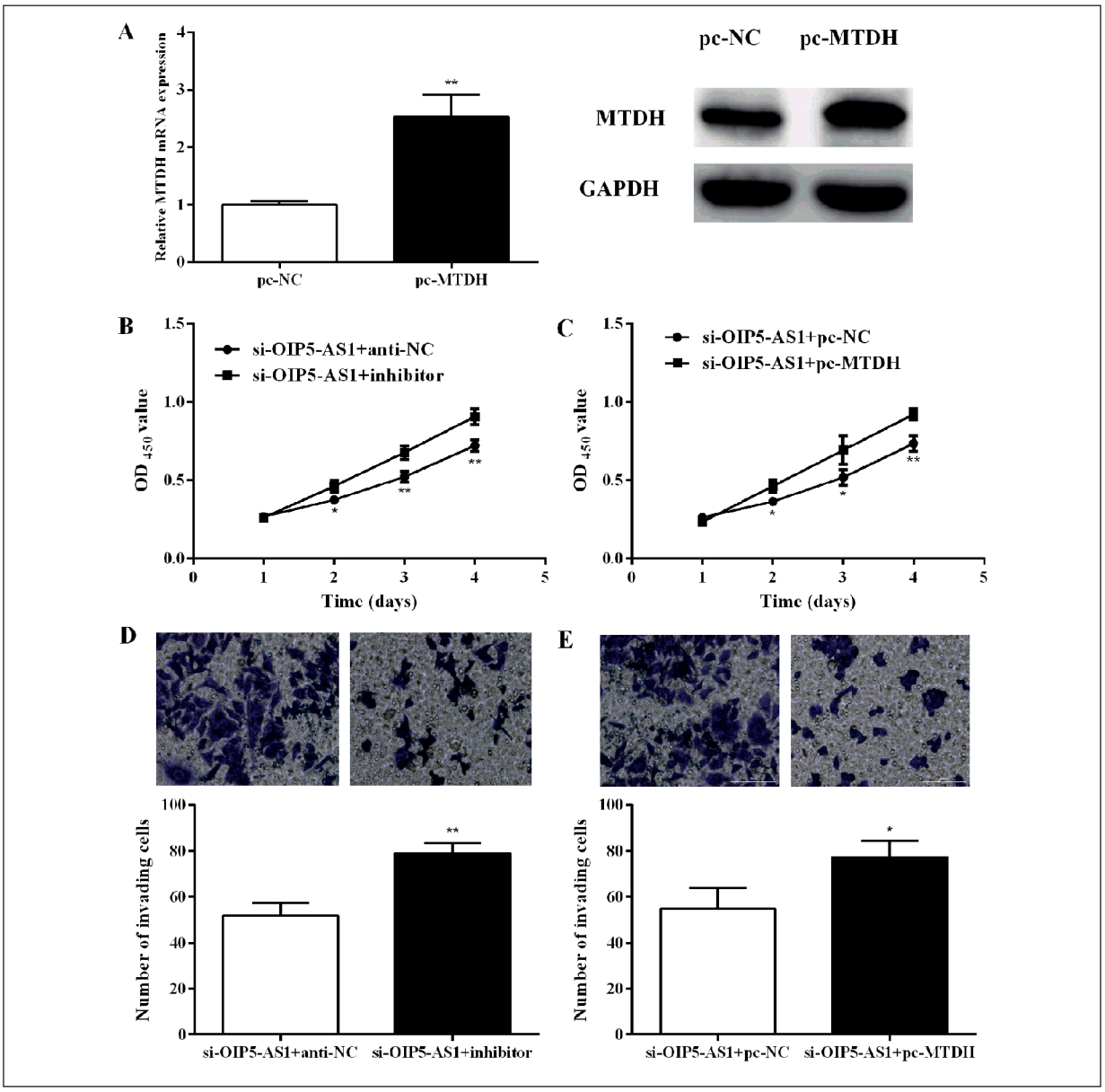


**Figure 5.** OIP5-AS1 regulated BCa cell proliferation and invasion through miR-217 and MTDH. **A**, MTDH expression was enhanced in T24 cells treated with pc-MTDH. **B, C**, Cell proliferation of T24 cells transfected with si-OIP5-AS1 and miR-217 inhibitor or pc-MTDH. **D, E**, Number of invaded T24 cells transfected with si-OIP5-AS1 and miR-217 inhibitor or pc-MTDH (200×). *$p < 0.05$, **$p < 0.01$.

poor prognosis of various tumors[31]. Zhang et al[32] reported that MTDH was upregulated in BCa and its knockdown suppressed cell proliferation and invasion. In our study, OIP5-AS1 downregulation signally increased miR-217 expression, and the miR-217 overexpression or OIP5-AS1 knockdown inhibited MTDH expression. Moreover, inhibition of miR-217 could reverse the suppression on MTDH expression induced by OIP5-AS1 knockdown. In BCa tissues, a negative correlation between the expression of OIP5-AS1 and miR-217, a negative correlation between miR-217 and MTDH expression and a positive correlation between MTDH and OIP5-AS1 expression were observed. It is suggested that OIP5-AS1 might downregulate miR-217 through "sponge action", which indirectly promoted MTDH expression. Moreover, rescue assays demonstrated that MTDH overexpression or miR-217 inhibition could reverse the suppression of OIP5-AS1 knockdown

on cell proliferation and invasion, suggesting that OIP5-AS1 axis may involve in BCa tumorigenesis through miR-217/MTDH.

Collectively, we explored the functional link between OIP5-AS1 and miRNA. Moreover, it was found that OIP5-AS1 could regulate MTDH expression through miR-217, thereby promoting the proliferation and invasion of BCa cells. The shortcoming of this study is that the effect of OIP5-AS1 on the proliferation and invasion of BCa has not been verified *in vivo*, which is the focus of further research. Besides, this study examined OIP5-AS1 expression in 30 pairs of BCa tumor tissues and adjacent tissues. The number of the sample is small. Therefore, the value of clinical tumor markers of OIP5-AS1 and its potential diagnostic and therapeutic value require more samples for further confirmation. In addition, we will expand clinical sample size at a later stage to further explore the possible relationship between OIP5-AS1 expression and the clinical prognosis of patients. The regulatory network of tumor cells is complex and diverse. We have only preliminary explored the possible regulation of OIP5-AS1 in BCa in one aspect. Moreover, OIP5-AS1 may also interact with more miRNAs in the regulation of miRNA molecular sponges. Therefore, a more and more in-depth research is needed to discover the underlying secrets.

## Conclusions

This study showed that OIP5-AS1 was up-regulated in BCa tissues and cells. Knockdown of OIP5-AS1 repressed the proliferation and invasion of BCa cells. Results first put forward OIP5-AS1 acts as an oncogene in BCa through regulating miR-217/MTDH expression. This newly identified the regulatory network of OIP5-AS1/miR-217/MTDH signaling in BCa progression. These findings provide a new understanding of the potential mechanisms, and novel therapeutic strategies for BCa. After continuous in-depth research on the entire lncRNA/miRNA/mRNA ceRNA network, we gradually clarified the role and regulatory mechanism of ceRNA in BCa and provided new clues for clinical diagnosis and treatment of BCa.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

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